Sleep Neurobiology and Critical Care Illness

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KEYWORDS

• Sleep alterations • Neurobiology • Sleep EEG pattern • Sleep organization • Circadian rhythms

KEY POINTS

- Intensive care unit (ICU) patients experience severe sleep alterations, with reductions in several sleep stages, marked sleep fragmentation, low sleep continuity, and circadian rhythm disorganization.
- The numerous sources of these sleep alterations are associated with disruptions of sleep neurobiological processes and sleep dynamics that can alter sleep restorative functions.
- Understanding the neurobiology of sleep in the ICU is a major challenge for future sleep studies in critically ill patients.

INTRODUCTION

That critical illnesses and environmental factors in intensive care units (ICUs) are associated with sleep disturbances was recognized shortly after the first ICUs were created. Many studies documented objective lack of restorative sleep.[1–4] Sleep alterations in critically ill patients differ from sleep changes observed in ambulatory patients (such as patients with sleep apnea syndrome) in pathophysiology as well as the consequences of sleep loss.

The literature regarding consequences of sleep deprivation on health is growing rapidly but ICU patients are unlikely to avoid the biological and neurobehavioral repercussions of sleep loss. To appreciate all of the phenomena triggered by sleep loss in the ICU, it is important to understand the neurobiology of healthy sleep and the specific neurobiological derangements of sleep in critically ill patients.

NEUROBIOLOGY OF THE NORMAL SLEEP CYCLE

In human beings, sleep is composed of non–rapid eye movement (NREM) sleep, which can be light NREM (stages 1 and 2) or deep sleep (stages 3 and 4). The distinction between wake and NREM sleep is made by visual analysis of a 30-second portion of an electroencephalogram (EEG): during waking, the EEG shows a mix of fast oscillations (>16 Hz) and alpha rhythm (8–12 Hz) of low amplitudes (<10 μV). During light NREM sleep (stages 1 and 2), the background EEG is characterized by slow theta oscillations (frequency between 4 and 7 Hz) and sleep spindle and K complexes. These latter regularly occur and provide the landmark of stage 2. During deep NREM sleep (also called slow wave sleep; stages 3 and 4), the EEG shows slow waves (0.5–2 Hz) of high amplitude (>75 μV). Rapid eye movement (REM) sleep is a particular sleep stage in which the EEG shows theta and

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alpha rhythms. Identification of REM sleep is based on the presence of rapid eye movements identified on electro-oculograms and complete chin muscle atonia. During REM sleep, the brain is highly active, and most dreams and nightmares occur during this stage.

Human sleep is monophasic, and is programmed to occur during nighttime. The sleep-wake cycle is accurately organized and controlled. A sleep deficit elicits a compensatory increase in the intensity and duration of sleep, and excessive sleep reduces sleep propensity. This process could be represented as a sleep-pressure regulation, which would maintain this pressure between an upper and a lower limit. Sleep homeostasis can be represented by the interaction of 2 main physiologic processes. The first process is known as process S, which increases during waking and declines during sleep. Electroencephalographic slow wave activity (SWA) corresponds with an indicator of sleep homeostasis and the level of SWA is determined by the duration of prior sleep and waking. The timing and propensity to fall asleep are also modulated by a circadian process. This second process is driven by the internal clock. This circadian rhythm is sensible to external factors that help to keep the sleep-wake cycle synchronized with night-day alternation. The main external synchronizing factors are light, physical activities, meals, and social interactions.

The quantity of sleep is acutely regulated, and sleep deprivation has many neurobiological consequences. On the day following 1 night without sleep, brain performances are severely decreased. The most visible behavior is an increased tendency to fall asleep, even when the person fights to remain awake. The night following the sleep deprivation is modified and a sleep rebound usually occurs. This sleep rebound triggers a lengthening of nighttime sleep, an increase in slow wave sleep, and an increase in REM sleep.

METHODS FOR SLEEP STUDY IN INTENSIVE CARE UNIT PATIENTS

Sleep can be assessed in terms of quantity (total sleep time and time spent in each sleep stage), quality (fragmentation, sleep EEG patterns), and distribution over the 24-hour cycle.

Full polysomnography (PSG) is the only reliable tool for measuring sleep, especially in patients with marked sleep disturbances. Accurate sleep scoring requires the recording of at least 3 EEG signals (preferentially F4-A1, C4-A1, O2-A1), 2 electro-oculography signals, and a submental electromyography (EMG) signal. Additional signals are usually recorded, such as nasal and oral airflow, thoracic and abdominal belts, electrocardiogram, and pulse oximetry. Sound and light levels should be measured, although these data are not obtained routinely.

SLEEP ELECTROENCEPHALOGRAM PATTERNS IN THE INTENSIVE CARE UNIT

Sleep scoring using either the system of Rechtschaffen and Kales[5] or the recently modified rules[6] poses a specific problem in critical care patients. A variable portion of the brains of critically ill patients does not generate the usual sleep EEG patterns and habitual markers of sleep.[7–11] The presence of theta and delta EEG activities during wakefulness, rapid fluctuations between EEG features of wake and NREM sleep, rapid eye movements during stage 2, and low-amplitude fast frequencies caused by sedation and delta burst arousal pattern are often observed.[8,12,13] In a study in conscious patients (Glasgow score >8) without neurologic disease who required mechanical ventilation for lung injury, 12 of 20 patients had abnormal sleep patterns[8]; among them, 7 patients showed EEG features of coma with reactive theta-delta activity and 5 had atypical sleep with virtually no stage 2 sleep and the presence of pathologic wakefulness (a combination of EEG features of slow wave sleep and behavioral correlates of wakefulness such as saccadic eye movements and sustained EMG activity). These 5 patients had worse acute physiology scores and received a higher mean benzodiazepine dose than the patients with disrupted but recognizable sleep patterns. In a similar group of 22 patients without sedation or neurologic disease,[9] only 17 patients (77.3%) had PSG recordings that could be scored. The remaining 5 patients had an EEG pattern of low-voltage mixed-frequency waves and variable amounts of theta-delta activity; all 5 developed sepsis during the study period, suggesting that sleep abnormalities were related to sepsis encephalopathy.[9]

In a recent study, Watson and colleagues[13] found major dissociations between EEG patterns and behavior in a group of 37 ICU patients. These dissociations consisted of abnormally slow EEG frequency in the theta range (3–7 Hz), a frequency that normally indicates sleep, or even delta range in some awake patients; In contrast, they observed low-amplitude, high-frequency beta EEG activity in patients who were in coma. Some patients who were awake and interactive with research personnel showed predominately theta activity (3–7 Hz), a frequency that normally indicates sleep. One patient, awake and able to follow simple instructions, was documented to have

important delta activity, a finding that is normally associated with slow wave sleep. In contrast, unresponsive comatose patients were noted to have alpha activity present on PSG, which is an EEG frequency typically seen in the wake state. These observations led Cooper and colleagues[8] to propose new sleep states called pathologic wakefulness and atypical sleep.

Atypical Sleep and Pathologic Wakefulness

Several teams have deal in depth with the concept of atypical sleep and pathologic wakefulness. Drouot and colleagues[11] proposed a new classification based on the reports of Cooper and colleagues.[8] Drouot and colleagues'[11] study focused on ICU patients admitted for respiratory failure, treated with noninvasive ventilation, and who were not sedated nor taking drugs interfering with sleep physiology. The investigators proposed that atypical sleep and pathologic wake have to be used when patients clearly show alternation between 2 distinct vigilance states. Atypical sleep was defined as non-REM sleep without spindle or K complexes. In contrast, pathologic wakefulness was defined by the association of a global slowing of EEG frequencies (with a peak frequency $\leq$7 Hz) and an impaired EEG reactivity.[11] Watson and colleagues[13] emphasized Drouot and colleagues'[11] new classification by extending their findings in patients with higher severity of illness and receiving sedation. Investigators also incorporate the judicious EEG classification for coma developed by Young and colleagues.[14] In a similar way, Watson and colleagues[13] proposed a new algorithm that includes, as a first step, a comparison between patients' behavior and EEG patterns.

Pathophysiology of Atypical Sleep and Pathologic Wakefulness

Several factors may explain the EEG abnormalities seen in patients with atypical sleep. The first factor could be hypercapnia. In the Drouot and colleagues[11] study, several patients had hypercapnic respiratory failure, which is known to induce various abnormalities in brain function, ranging from mild hypovigilance to encephalopathy.[15–18] Similar EEG alterations have been reported in healthy awake individuals during hypercapnia.[19] However, arterial P_{CO_2} values did not differ between the group with atypical sleep/pathologic wakefulness and the group with normal sleep, suggesting that other factors could be involved in atypical sleep.[11] Sleep deprivation per se is known to alter EEG patterns during prolonged wakefulness and also during the subsequent recovery sleep. Sleep deprivation experiments showed linear decreases in alpha activity and increases in theta and delta activities on wakefulness EEGs.[20] The background EEG activity alterations in patients with atypical sleep/pathologic wakefulness were similar to those reported in healthy individuals subjected to sleep deprivation for 24 hours.[21,22] Recovery sleep following sleep deprivation is characterized by significantly decreased spindle[23] and K-complex densities.[24] Because ICU patients are exposed to sleep deprivation for several consecutive days or weeks,[25,26] atypical sleep may constitute a compensatory mechanism in which deep sleep predominates over light (stage 2) sleep to maximize sleep debt recovery. The association of hypercapnia and sleep deprivation in the genesis of atypical sleep has been suggested because spindle density (a marker of atypical sleep) decreases with increase of both SWA and arterial CO_2 levels.[27] Some patients with atypical sleep (with no spindle or very low spindle density) showed normal levels of arterial P_{CO_2}. These patterns could have turned into atypical sleep because of a severe sleep deprivation.[27] However, whether hypercapnia inhibits spindle circuitry and K-complex generators or favor sleep stage associated with low spindle densities, such as slow waves sleep,[28] remains unknown.

Rapid Eye Movement Sleep in the Intensive Care Unit

Most of studies have reported that REM is commonly lacking in ICU patients.[3] However, REM sleep scoring can be difficult when submental muscle atonia, a hallmark of REM sleep, is lacking. REM sleep without atonia and dissociated REM sleep seems uncommon in ICU patients,[29] but these conditions have not been extensively studied. Whether loss of muscle atonia is related to pre-existing disease, medications, or the ICU environment remains to be established.[29] A study of ICU patients with Guillain-Barré syndrome showed a higher incidence of REM sleep abnormalities (including loss of atonia, short REM latency, and daytime REM sleep episodes) compared with ICU patients with paraplegia.[30]

Furthermore, hypercapnia can also produce a REM deficit. The amount of REM sleep was decreased in patients with hypercapnic respiratory failure.[31] However, contrasting results have been reported in experiments in rodents, which showed that hypercapnia increased the amount of REM sleep.[32]

In addition, most studies are transversal experiments and have performed a single PSG at a defined time during an ICU stay. Few studies

have been published with longitudinal and repeated PSG, so the initial course of REM deprivation, and the presence and the timing of a potential REM rebound, are unknown, at least in medical ICUs. Some rare reports performed in surgical ICUs have shown an initial, severe REM sleep deficit, followed by an important rebound of REM sleep in the first week after surgery.[33–36]

SLEEP ORGANIZATION IN THE INTENSIVE CARE UNIT

Sleep Architecture

As mentioned in earlier, better analysis of sleep quantity and quality disturbances in ICU patients requires prolonged PSG that lasts at least 16 to 24 hours. Severe sleep-wake disorganization is a major characteristic of sleep in ICU patients. Loss of light/dark circadian synchronization and the prolonged inactive decubitus favor daytime sleep. Studies using long-duration recordings consistently showed abnormal sleep distribution over the 24-hour cycle, with as much as 50% of sleep occurring during the day.[8,9,25,37,38] All the studies found considerable interindividual variability in TST. For instance, TST ranged from 1.7 to 19.4 hours in one study.[9] Nevertheless, the results indicate that quantitative sleep deprivation is not consistently present.

Sleep stage distribution is substantially altered in ICU patients. Sleep stage 1, which normally constitutes less than 5% of TST, accounts for up to 60% of TST in critically ill patients.[8,9,25,33,34] Marked deficits in slow wave sleep (sleep stages 3 and 4) were documented in medical ICU patients and postsurgical patients.[25,33–36] REM sleep is often reduced or abolished,[8,25,39] especially during the first night following surgery.[33–36] Data on sleep stage 2 are conflicting. Sleep stage 2 was normal or increased in some studies[25,34,35,40] and decreased in other studies.[9,36,39] The discrepancies across studies preclude general conclusions.

In addition, differences in the time point of sleep recording may contribute to interindividual variability of sleep parameters. Surgical ICU patients best illustrate this fact because PSG can be performed at baseline (before surgery) and after anesthesia using a standardized regimen. The results showed marked reduction or elimination of slow wave sleep and REM sleep during the first 2 postoperative nights, with a significant rebound of REM sleep in the third or fourth postoperative night,[33–36,41] contrasting with little[35] or no rebound of slow wave sleep.[34,36] These results also highlight the need for longitudinal studies describing changes in sleep over time according to the reason for ICU admission and to disease severity.

Sleep Fragmentation

Concomitantly with sleep stage disorganization, ICU patients experience severe sleep fragmentation with arousals or awakenings. Studies of mechanically ventilated patients showed up to 79 arousals and awakenings per hour of sleep, leading to interruption of sleep every 46 seconds.[8,25,42]

Sleep Continuity

Based on Bonnet's[43] sleep continuity theory, which posits that at least 10 minutes of uninterrupted sleep are needed to serve a recuperative function, several investigators have deemed quantification of sleep continuity to be of interest. Recently, Drouot and colleagues[44] showed that, in nonsedated patients admitted for hypercapnic respiratory failure treated with noninvasive ventilation (NIV), the percentage of TST spent in short naps (ie, sleep episodes lasting between 10 and 30 minutes) was higher and the percentage of sleep time spent in sleep bouts (ie, sleep episodes lasting <10 minutes) was lower in patients with successful NIV compared with patients with NIV failure. Usual sleep quantification, such as TST, sleep stages composition, and sleep fragmentation, were not different between patients with good outcome compared with patients with poor outcome.

CIRCADIAN RHYTHMS AND MELATONIN IN INTENSIVE CARE UNIT PATIENTS

Not only sleep is disturbed, but more generally circadian rhythm. The latter can be assessed indirectly by measuring the oscillations in core body temperature, or directly by melatonin and melatonin metabolite assays.

In a study of 15 ICU patients, the circadian rhythm of core body temperature persisted, but the time of the acrophase showed marked intraindividual variability with shifts of several hours from day to day.[45] In a recent study, Gazendam and colleagues[46] found that acrophases were shifted (advanced or delayed) in 81% of patients, but that this shift was stable across days in each individual. In contrast, in a large cohort of 137 patients investigated after thoracic or vascular surgery, core body temperature showed no circadian rhythmicity in most patients during the first 3 postoperative days.[47]

The circadian rhythm generator, located in the suprachiasmatic nucleus, triggers melatonin production and release by the pineal gland. Melatonin levels start to increase around bedtime and peak at about 3 AM. The onset of melatonin secretion is a robust marker of circadian rhythms.[48] It can

be investigated either by assaying serum melatonin concentrations or by determining the urinary 6-sulfatoxymelatonin (6-SMT) level, a surrogate marker for plasma melatonin in healthy subjects. Following the first report by Shilo and colleagues[49] of altered 6-SMT rhythm in ICU patients, several groups investigated melatonin production. One study showed striking abnormalities in urinary 6-SMT excretion in 16 of 17 ICU patients with sepsis, contrasting with normal excretion in 6 of 7 ICU patients without sepsis and in 18 of 23 controls.[50] In another study, the circadian rhythm of urinary 6-SMT concentration was altered in 12 of 16 ICU patients, and 6-SMT excretion was lower during periods with ventilation than during periods of spontaneous breathing.[51] In a recent study, a circadian rhythm of 6-SMT excretion was present in most (81%) patients, but only 4 subjects had normal timing, the others being phase delayed.[52] In addition, the circadian melatonin rhythm was altered in 7 of 8 ICU patients, with no correlation between melatonin levels and levels of sedation.[53]

Factors Interfering with Circadian Rhythms and Melatonin

Melatonin secretion can be influenced by numerous factors,[48] such as age, benzodiazepines, adrenergic compounds, β-blockers, opiates, light exposure, sedation, mechanical ventilation,[51] and sepsis.[50] The contribution of each of these factors in the melatonin release disturbances documented in ICU patients remains unclear.[54]

FACTORS RESPONSIBLE FOR SLEEP DISRUPTION IN THE INTENSIVE CARE UNIT

Numerous factors contribute to sleep disruption in ICU. Some of them are not specific to the ICU (eg, noise and light), although they are intense and frequent in the ICU. Some other conditions are more specifically met in the ICU and interfere with sleep neurobiology, such as continuous lighting, continuous bed rest, and sedation.

The Intensive Care Unit Environment

The level of noise is more than the World Health Organization recommendations in many ICUs,[55] making sleep difficult, and it was rated by patients as one of most sleep disruptive factors.[55,56] In a study involving completion of a questionnaire by patients recently discharged from the ICU, patients reported that vital sign assessments and phlebotomy were more disruptive than noise.[57] In a subsequent study using PSG and synchronized recordings of environmental noise in 22 ICU patients, episodes of noise were related to only 11.5% of all arousals and 17% of all awakenings.[9] Similarly, in another study, noise and patient-care activities explained only 30% of all arousals and awakenings; no causative factors were identified in the other cases.[25] However, because of the large number of peak sounds in the ICU (36.5 per hour of sleep in one study),[25] as well as the large number of arousals and awakenings in ICU patients (from 22 to 79 per hour of sleep),[8,25,42] a causal relationship between noise and arousal/awakening is difficult to ascertain.

Light Exposure

Continuous light exposure and the disappearance of the natural day-night rhythm in the ICU may alter the circadian clock. Nocturnal light intensities vary across ICUs but can exceed 1000 lux.[58,59] Because 100 lux is sufficient to affect melatonin secretion, nocturnal light exposure may modify circadian rhythms. In one recent study, light exposure at night was appropriate (median, <2 lux) but low during the day (median, 74 lux), further reducing day-night contrast.[40]

Loss of Physical Activity

Physical activity is a powerful zeitgeber (time cue), and greater diurnal activity is associated with larger variations in body temperature oscillations.[60] In bed rest experiments in which healthy individuals were asked to stay in bed for 36 hours, daytime naps were common, and sleep-onset REM occurred in up to 43% of naps and 80% of individuals.[61] In an elegant study[25] in which healthy volunteers stayed in bed in an ICU, most of the volunteers lost their circadian organization of sleep and slept during the day, suggesting that loss of activity per se may disrupt circadian rhythms and the sleep-wake cycle.

Effects of Drugs on Sleep

Many drugs used for light sedation or analgesia in the ICU influence sleep in healthy individuals and therefore could be causes of sleep disturbances.[62] Benzodiazepines are used to shorten sleep latency and facilitate sleep continuity. In healthy individuals, benzodiazepines lengthen sleep stage 2, increase TST, and decrease both slow wave sleep duration and REM sleep.[63,64] Tricyclic antidepressants and serotonin reuptake inhibitors increase slow wave sleep and block REM sleep.[65] In addition, tricyclic antidepressants and serotonin reuptake inhibitors may disrupt REM muscle atonia,[66] making this sleep stage difficult to recognize. Antipsychotics induce various sleep changes. Although haloperidol does not modify

sleep architecture, olanzapine increases TST, slow wave sleep, and REM sleep, and risperidone only decreases REM sleep.[67] Anticonvulsants may alter the sleep architecture.[68–70] It should be emphasized that all neurotropic molecules may affect EEG patterns during sleep and wakefulness. Opioids reduce slow wave sleep and REM sleep.[71] In addition, abrupt drug discontinuation may elicit withdrawal reactions such as insomnia after discontinuation of sedatives.[72]

Sedation and Sleep Function

Some experiments suggested that propofol may subserve a function that overlaps with sleep function. In an elegant study, Tung and colleagues[73] showed that rats sedated with propofol during their habitual sleep period did not show signs of sleep deprivation (such as sleep rebound) in the following hours. In a second experiment, the restorative effect of natural sleep and 6-hour propofol anesthesia were compared in sleep-deprived rats. No differences were found between natural sleep and anesthesia regarding delta power, REM sleep, or NREM sleep, suggesting that sleep and anesthesia provided similar recovery from sleep deprivation.[74]

However, although propofol may mimic some NREM sleep functions, this does not extend to all sleep functions because propofol consistently suppresses REM sleep in humans.[75]

CONSEQUENCES OF SLEEP DISRUPTIONS ON SLEEP NEUROBIOLOGY

Prolonged Sleep Privation

Regarding the severity of sleep disruptions in the ICU, it is important to note that the sleep regimens imposed on ICU patients is different from those experienced by ambulatory patients, such as patients with sleep apnea syndrome. The critical illness and the environment trigger a severe state of prolonged sleep deprivation. Studies conducted in healthy volunteers have shown that chronic restriction to 4 hours of sleep per night produced a cumulative cognitive performance deficit.[76]

Biological Effect of Sleep Deprivation

The immune system has long been regarded as vulnerable to sleep deprivation. Numerous studies have established that sleep deprivation impairs cellular and humoral immune responses and alters cytokine production.[77] Sleep deprivation was followed by decreases in natural killer (NK) cell and lymphocyte counts in some studies[78] and by increases in others.[79] Counts of T-helper cells and NK cells decreased after 1 night, but increased after 2 nights without sleep.[78] Sleep restriction (4 hours of sleep for 6 nights) in healthy volunteers was followed by a blunted response to immunization after influenza vaccination.[80] These data suggest that sleep loss in ICU patients may decrease the strength of immune responses.

Sleep and Sepsis

There have been few studies of the relationship between sleep deprivation and sepsis. In rodents, Friese and colleagues[81] reported that the experimental fragmentation of sleep after sepsis was associated with an increased mortality. These data suggest that loss of natural increase of sleep triggered by severe infection could be detrimental to health. Whether this is also the case in humans remains to be investigated.

Neurophysiologic Consequences of Sleep Loss

Sleep deprivation may affect pulmonary mechanics and respiratory muscles. In several studies, sleep deprivation for 24 hours reduced both hypercapnic and hypoxic ventilatory responses by 19% in healthy individuals.[82–84] Inspiratory muscle endurance and maximal voluntary ventilation were decreased after 30 hours without sleep.[85] All these data were obtained in healthy individuals, and no study has investigated the effects of sleep deprivation on respiratory function in critically ill patients. If the physiologic alterations seen in healthy individuals also occur in critically ill patients, they may adversely affect weaning from assisted ventilation.

Neuropsychological and Behavioral Effects of Sleep Alterations

Sleep deprivation affects cognitive functions. Many experiments have shown that specific neurocognitive domains, including executive attention, working memory, and concentration, are particularly vulnerable to sleep loss, the result being cognitive slowing and response perseveration.[86] Prolonged sleep deprivation over several days have been shown to trigger perceptual distortions and hallucinations in healthy individuals.[87] All these effects may play a role in the occurrence of delirium in ICU patients.[88]

SUMMARY

ICU patients experience severe sleep alterations with reductions in several sleep stages, marked sleep fragmentation, low sleep continuity, and circadian rhythm disorganization. The numerous sources of these sleep alterations are associated with disruptions of sleep neurobiological

processes and sleep dynamics that could alter sleep restorative functions. A crucial issue is how to objectively quantity this particular sleep, which is the step before imaging sleep protection strategies. Understanding the neurobiology of sleep in the ICU is a major challenge for future sleep studies in critically ill patients.

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