REVIEW

Sleep in the Critically ill Patient

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Abstract: Critically ill patients are known to suffer from severely fragmented sleep with a predominance of stage I sleep and a paucity of slow wave and REM sleep. The causes of this sleep disruption include the intensive care unit (ICU) environment, medical illness, psychological stress, and many of the medications and other treatments used to help those who are critically ill. The clinical importance of this type of sleep disruption in critically ill patients, however, is not known. This article reviews the literature on sleep disruption in the ICU, the effects of sepsis on sleep, the effects of commonly used ICU medications on sleep, the relationship between sleep and sedation, and the literature on the biological and psychological consequences of sleep deprivation specifically as it relates to the critically ill. Finally, an integrative approach to improving sleep in the ICU is described.

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INTRODUCTION

SLEEP LOSS AMONG MEDICAL PROFESSIONALS AS A POTENTIAL CAUSE OF MEDICAL ERRORS HAS RECEIVED A GREAT DEAL OF ATTENTION IN RECENT years in both the lay press and medical literature, and such information has been a driving force for change in the culture of medical training.[1,2] Ironically, the effects of poor sleep among patients, especially those who are critically ill and who may be most vulnerable to the effects of sleep deprivation, remain largely unknown and unexplored. Numerous studies over the past 30 years have consistently demonstrated that patients in the intensive care unit (ICU) sleep poorly, but few have addressed the consequences of poor sleep on the recovery of these patients, especially those with a prolonged illness. This article will critically review (1) sleep disruption in patients in the ICU, (2) the effects of sepsis on sleep, (3) the effects of commonly used ICU medications on sleep, (4) sleep and sedation, and (5) the literature on the biologic and psychological consequences of sleep deprivation specifically related to the critically ill patient.

Sleep Disruption in the ICU

Surveys have identified poor sleep as one of the most frequent complaints among patients who have survived a critical illness.[3-10] The poor sleep manifests during the patients' illness and can persist for an extended period after their ICU stay.[3-10] Medical professionals have been shown to vastly overestimate the amount of sleep that their patients achieve, as compared with objective polysomnographic data.[11] A number of studies investigating the characteristics of sleep in critically ill patients in a variety of ICU settings have shown remarkable consistency (see Table 1); patients in medical, cardiac, and surgical ICUs almost uniformly have fragmented sleep, with long sleep-onset and rapid eye movement (REM) latencies and poor sleep efficiencies.[11-16] The total number of hours of sleep over a 24-hour period may be relatively normal (7-9 hours), but approximately 50% of the sleep hours occur during the day in short bouts (this makes it more difficult for the patient to achieve REM and delta sleep).[11,16,17] In fact, an increased percentage of wakefulness and stage 1 sleep (40%-60%) and decreased amounts of stages 2 (20%-40%) 3/4 (10%), and REM sleep (10%) are consistently found among patients in the ICU.[12-16,18] Patients have increased arousals and increased arousals resulting in awakenings compared with normal healthy controls. In summary, patients in the ICU have been shown to have severely fragmented nonconsolidated sleep, which is weighted heavily in favor of "light" versus "deep" sleep. These observations may, in part, explain why 38.5% of patients in one study who survived a critical illness and spent at least 48 hours on mechanical ventilation recalled "not being able to sleep," 40% remembered awakening in the middle of the night, and 35% recalled having had trouble falling asleep during their ICU admission.[4] The vast majority of these patients were either moderately or extremely "bothered" by these problems.[4] Sleep disruption was the second most stressful condition reported by patients with cancer who were in an ICU (second to the inability to communicate, which was only reported by those who were mechanically ventilated).[5] Thus, a growing body of evidence suggests that sleep disruption may adversely affect a patient's experience both during the ICU admission as well as afterward for survivors.

Table 1—Characteristics of Sleep in Critically Ill Patients

Severely fragmented
Total sleep time over 24 hours may be normal
Sleep may be evenly distributed between day and night
Increased time in stage 1 sleep
Decreased time in stages 2, 3, 4, and REM
Increased arousals and awakenings

REM refers to rapid eye movement sleep.

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The ICU Environment

Although illness, pain, and medications contribute to sleep disruption in ICU patients, the primary factor causing sleep disruption had been thought to be the ICU environment. Noise from various sources, including ventilators, alarms, television, phones, beepers, and conversation, have all been purported to disturb sleep in the ICU.[16,17] Patients have reported that noise, specifically talking, is a frequent cause of sleep disruption in the ICU.[19-21] Several studies have confirmed that peak noise levels in ICUs are far in excess of 45 dB during the day and 35 dB at night, which are the recommendations of the Environmental Protection Agency for peak noise levels in the ICU.[16,17,19-21] Noise levels in the ICU have been shown to range from mean levels of 53 to 65 dB to peak levels greater than 80 dB throughout a 24-hour period.[16,17,19] Two recent studies have specifically investigated the effect of noise on sleep architecture in ICU patients. Freedman et al imported data from a sound meter into 24- to 48-hour polysomnographic recordings in ICU patients in order to determine if noise resulted in frequent arousals or awakenings.[16] Their study of 22 patients in a medical ICU was able to attribute only 11.5% of arousals and 17% of awakenings to environmental noise. In a related study, Gabor et al compared the influence of environmental noise and patient-care activities (primarily nursing activities such as dressing care, adjustment of intravenous drips, medication administration) on the sleep of 7 mechanically ventilated ICU patients and 6 healthy volunteers.[17] Similar to the study of Freedman, environmental noise was measured by a sound meter while simultaneous polysomnography recordings were performed. Twenty percent of the arousals and awakenings in their study patients were directly attributable to noise, and only 7% of the disruptions to sleep were directly due to patient-care activities. Interestingly, noise was the primary cause of sleep disruption in the healthy controls; however, their overall sleep was not pathologically fragmented. Normal subjects slept in single ICU rooms with closed doors, and their sleep architecture was compared with that of subjects in open ICU rooms. The affect of noise reduction (doors closed) was to increase sleep quantity without affecting either sleep architecture or the arousal and awakening index.[17] It is not clear from this investigation if noise reduction is an appropriate intervention to improve sleep in ICU patients. Other studies, however, have demonstrated that the use of earplugs has successfully improved sleep in ICU patients, as measured by shortened sleep and REM latencies, increased REM duration, and decreased awakenings.[22-24]

In addition to noise, it has been proposed that light exposure, the primary zeitgeber responsible for setting the circadian clock, also can affect the sleep pattern of ICU patients. However, a survey of patients who had survived a critical illness revealed that light was not as disruptive to their sleep as were noise and patient-care activities.[7] Nocturnal light levels, in those ICUs in which it was measured, were variable, with mean maximum levels ranging between less than 5 lux to more than 1400 lux.[18,25] Light levels as low as 100 to 500 lux have been found to affect nocturnal melatonin secretion, and 300 to 500 lux may have an affect on the human circadian pacemaker.[26] Therefore, the importance of light as a disrupter of patients' sleep and circadian physiology may vary depending on the light level in each ICU. Noise and light levels, which were once thought to be among the most important variables in disturbing sleep in the ICU, have now been shown to be responsible for only a minority of sleep disruptions. It is likely that multiple factors, including the patient's primary illness (or the severity of that illness), pain, medications, and nursing and physician interventions such as vital signs, chest radiographs, and procedures disturb sleep in the ICU patient (see Table 2).

Table 2—Factors in the Intensive Care Unit That Adversely Affect Sleep

Noise
Light
Pain or illness and consequent psychosocial stress
Patient-care activities, ie vital signs, medication administration, diagnostic testing
Dyssynchrony with mechanical ventilation
Medications (many have adverse affects on sleep; see text and Table 4)

The relationship between sleep and severity of illness is somewhat controversial but may be very important. Parthasarathy and Tobin found that there was a significant increase in sleep disruption (combined arousals and awakenings per hour) in those patients with higher disease severity scores and in those patients who died, compared with survivors of critical illness.[27] But this relationship can be explained by many factors and does not necessarily imply causality. Similarly, Dohno et al found that patients in a coronary care unit in the higher severity-of-illness group, as judged by a cardiologist (although their criteria were not specified), had more nocturnal awakenings and more sleep-stage changes (consistent with greater sleep fragmentation) than a comparable group with less severity of illness.[28] Gabor et al found that patients (mean APACHE score 31, with a range of 7-61) slept more poorly than did healthy volunteers in the same ICU environment with a higher awakening index, shorter sleep time, and a lower percentage of slow-wave sleep.[17] Although these data are preliminary, severity of illness may turn out to be a very important cause of sleep disturbance in ICU patients.

Sleep In the Mechanically Ventilated Patient

Another cause of sleep fragmentation in the ICU patient is mechanical ventilation. Cooper et al described severe sleep fragmentation in 20 mechanically ventilated patients with lung injury.[12] The relationship between ventilator mode and sleep disruption was subsequently investigated in a study by Parthasarathy and Tobin.[29] In that study, pressure support ventilation and assist control ventilation were compared in 11 mechanically ventilated patients by a protocol involving sequential ventilator changes on 1 study night. Five of their 6 patients with left-ventricular ejection fraction < 50% or a history of congestive heart failure developed central apneas on pressure support ventilation with resulting awakenings, leading to increased sleep fragmentation, compared with ventilation on assist control mode. For those patients in whom apneas did not develop (4 of the remaining 5 patients), there were no differences in awakenings or arousals between the modes of ventilation. The authors also found that the addition of dead space, with a resultant mean increase in end-tidal CO_2 of 4.3 mm Hg, decreased the frequency of central apneas and sleep disruption. This study raises the possibility that the mode of nocturnal ventilation may have an adverse effect on the sleep of mechanically ventilated patients and, therefore, that there may be an optimal ventilator setting that would facilitate sleep.

The mechanical ventilator settings may also worsen sleep continuity by causing dyssynchronous breathing or by being set to a

Table 3—Effects of Sepsis on Sleep

Increased NREM sleep
Decreased REM sleep
Increased sleep promoting cytokines TNF, IL-1β
Altered EEG: low-voltage, mixed-frequency waves with variable theta and delta ("septic encephalopathy")
Loss of normal circadian melatonin secretion

NREM refers to non-rapid eye movement sleep; REM, rapid eye movement, sleep; TNF, tumor necrosis factor; IL, interleukin; EEG, electroencephalogram.

range of respiratory frequencies to which the patient cannot entrain (entrainment is the phenomenon in which the neural impulses that normally initiate inspiration adjust to the presence of mechanical breaths by establishing a fixed temporal [i.e., synchronized] relationship). The range of respiratory frequencies to which a normal healthy person can entrain to mechanical inflations is less during non-REM sleep than wakefulness but is enhanced by vagal feedback; this does not occur in animals that have had a vagotomy.[30-32] When individuals are awake, forebrain influences are believed to override autonomic control to optimize comfort, i.e., synchronous breathing. Sedated individuals are believed to entrain to a wide range of respiratory frequencies both because sedatives may decrease respiratory drive and because the drugs may also decrease mechanoreceptor activity from pulmonary stretch receptors.

The sleep of a mechanically ventilated ICU patient, therefore, suffers from all the problems known to affect the sleep of non-ventilated patients but, in addition, may be further worsened by dyssynchronous breathing, ventilator mode, discomfort from the endotracheal tube, stress related to increased difficulty communicating, and possibly a greater severity of illness (see above). Thus, it is not surprising that mechanically ventilated patients have severely fragmented sleep. Optimizing ventilator settings for patient comfort and sleep and the role of pharmacologic sedation are areas that need active investigation.

Effect of Sepsis on Sleep

Although it seems intuitive that sepsis can adversely affect sleep, the pathogenesis of this relationship remains poorly understood. Table 3 summarizes some of the findings of the affects of sepsis on sleep in humans.

Freedman et al found that the 5 of their patients who either developed sepsis or positive blood cultures during electroencephalogram (EEG) monitoring had a characteristic EEG pattern of low-voltage, mixed-frequency waves with a variable amount of theta and delta activity.[16] These investigators suggested that these EEG changes could be an early marker for sepsis. The EEG changes occurred with eyes both open and closed, making it impossible to determine the subjects' state of consciousness based on the EEG. The patients in Freedman's study were not on continuous infusions of sedatives. Similar findings of "septic encephalopathy" have been described by others, but the EEG findings associated with sepsis need to be validated in larger ICU populations.[33-35]

Sepsis has also been associated with the loss of normal circadian melatonin secretion.[36] Normally, melatonin or its metabolite 6-sulfatoxymelatonin (6-SMT) is found at low levels during daylight hours and peaks between 1 am and 3 am.[37] Its release from the pineal gland is inhibited by light. Mundigler et al demonstrated the loss of periodic 6-SMT excretion in septic, awake patients in the ICU in favor of more-continuous stimulation of melatonin production.[36] In this investigation, ambient light was excluded by covering patients' eyes with an eye mask from 10 pm until 6 am and by turning off artificial lights during the night except during nursing rounds. Melatonin excretion remained abnormal for several weeks after recovery from sepsis. Their results demonstrated normal circadian excretion of melatonin in their nonseptic patients in the ICU.[36] In contrast, Shilo et al described a loss of the normal nocturnal rise in melatonin secretion in nonseptic, critically ill patients, but their results may have been influenced by the effects of continuous ambient light exposure.[38] These investigators did not describe any attempt to control or measure ambient light levels. Melatonin has been shown to have a protective effect in animal models of sepsis due to its free-radical scavenging and antioxidant properties and, in fact, has been successfully used to treat septic pediatric patients.[39-41] The importance of melatonin to the sleep of the critically ill patient is unknown; however, administration of melatonin to critically ill patients with chronic obstructive pulmonary disease has been shown to improve sleep measured by actigraphy in 1 study.[42]

Sepsis, therefore, is associated with altered sleep, possibly by an affect on the neurohormonal milieu of the central nervous system (alterations in melatonin) or perhaps by a more direct affect on the electrical activity of the central nervous system manifested by the EEG changes described. It has been proposed that these changes, particularly a reduction in REM sleep, may be an appropriate adaptation to the stress of sepsis;[43] REM sleep is the time of greatest cardiopulmonary variability and oxyhemoglobin desaturation, and, therefore, a patient's already unstable hemodynamic status may be further compromised in this stage of sleep.

Effect of ICU Medications on Sleep

Many of the medications used in the treatment of critically ill patients have effects on sleep patterns of healthy adults.[44-49] Table 4 lists some commonly used ICU medications with their effects demonstrated by polysomnography. However, for most of these medications, their affects on sleep and sleep patterns of the critically ill have not been studied. Benzodiazepines, antipsychotics, and opiates are all associated with REM suppression and, conversely, REM rebound if these medications are withdrawn abruptly.[44,45,50,51] Although there are no objective measures of sleep quality for critically ill patients, 1 study compared patients' reports of subjective sleep quality when sedated with midazolam versus propofol and found these medications to be comparable regardless of their affect on anxiety or depression.[52] The sleep of patients sedated with both propofol and benzodiazepines, which enhance the affinity of GABA for its receptors, differs from "natural" sleep[53,54] in several ways: (1) norepinephrine release from the locus coeruleus continues during anesthesia with GABAergic anesthetics[55]; (2) naturally occurring sleep is characterized by a cyclic progression through EEG stages, whereas this normal sleep architecture is variably affected by sedatives; (3) natural sleep is characterized by complete reversibility with external stimuli; and (4) natural sleep subserves a putatively restorative function, whereas there is little to suggest a similar role served by sedation. In contrast, however, the α_2-agonist dexmedetomidine, a sedative-analgesic infusion approved for use in the ICU for patients on mechanical

Table 4—Effect of Medications Used in the Intensive Care Unit on Sleep

Medication	Total sleep time	Wakefulness after sleep onset	Stage 2 %	SWS %	REM %	Sleep-onset latency
Sedative/hypnotics						
Benzodiazepines	+	-	+	-	-	-
Zolpidem	+	-	+/-	+	+/-	-
Chloral hydrate	+	NA	NA	NA	NA	-
Dexmedetomidine	NA	NA	NA	+	-	-
Propofol	+	-	NA	NA	No effect	-
Eszopiclone	+	-	+	+/-	+/-	-
Ramelteon	+	+/-	+/-	+/-	+/-	-
Analgesics						
Opiates	-	+	NA	-	-	NA
Antipsychotics						
Haloperidol	+	-	NA	+	-	-
Atypical antipsychotics i.e., risperidone	+	-	NA	+	-	-
Stimulants						
Methylphenidate	-	+	-	NA	-	NA
Antidepressants						
Trazadone	NA	-	NA	+	-	-
SSRI	-	+	NA	NA	-	+
Tricyclics	NA	NA	NA	NA	-	NA
Cardiovascular						
β-blockers	NA	+	NA	NA	Variable	+
Epinephrine/ norepinephrine	NA	NA	NA	-	-	NA
Dopamine	NA	NA	NA	-	-	NA
Respiratory						
Xanthines i.e., theophylline	-	+	NA	-	-	+
Miscellaneous						
Corticosteroids	NA	+	+	-	-	NA

[a]Medication effects described were tested in normal healthy individuals.[44-49,62,122-125]

+refers to an increased effect; -, decreased effect; +/-, no significant effect; NA, information not available; SWS, slow-wave sleep; REM, rapid eye movement sleep; SSRI, selective serotonin reuptake inhibitors.

ventilation, has been shown to inhibit release of norepinephrine by the locus coeruleus.[56] Dexmedetomidine has been shown to enhance slow-wave sleep—unlike benzodiazepines, which decrease slow-wave sleep—and, perhaps not coincidentally, has been shown to exhibit a trend toward reducing the incidence of delirium in a cohort of cardiac surgery patients, compared with those sedated with propofol or midazolam.[57] Dexmedetomidine is currently approved only for use in patients initially mechanically ventilated; however, its lack of respiratory depression and its opiate-sparing effects, a result of having receptors on the dorsal horn of the spinal cord, makes it an attractive option for a broad range of critically ill patients.

Finally, it is important to consider the importance of drug withdrawal on sleep. Abrupt cessation of sedatives and alcohol will cause worsening of sleep fragmentation.[44] Abrupt cessation of barbiturates, nicotine, and short-acting benzodiazepines can lead to withdrawal insomnia.[44] Even abrupt withdrawal of a short-acting β-blocker or α-agonist (clonidine) will lead to increased sympathetic activity that may worsen sleep continuity.[58] Thus, a thorough review of medications is indicated for all ICU patients who have difficulty sleeping.

Sleep and Sedation

Sedation is commonly used in ICU patients; however, the relationship between sleep and sedation has not been well studied. Both diurnal and nocturnal sedation have been advocated as a means to help minimize the typically high levels of agitation and pain in critically ill patients and possibly to facilitate sleep. Sedation may have both negative affects on sleep, by its affect on the normal characteristics of the sleep EEG, and positive affects, by increasing total sleep time and sleep continuity.[46,49] Tung et al demonstrated that, after rats were sedated with propofol during their normal sleep phase, they did not demonstrate the expected manifestations of sleep deprivation; specifically, there was neither an increased sleep tendency nor a sleep-stage rebound after propofol sedation.[59] These results suggest that propofol does not interfere with the normal restorative effects of naturally occurring sleep. In healthy human volunteers, propofol given for 1 hour, 8 hours prior to nocturnal sleep was associated with increased sleep latency, raising the possibility that sedation with propofol subserves a function that overlaps with sleep.[60] In fact, studies in animal and human models have suggested that propofol, barbiturates, dexmedetomidine, and benzodiazepines share neurophysiologic pathways involved in sleep.[56,61-64] Furthermore, some medications such as the opiates affect cholinergic transmission in parts of the central nervous system important to the natural sleep pathway, especially REM sleep.[63] REM sleep and sedation share many clinical similarities, including motor hypotonia, temperature dysregulation, disconjugate eye movements, altered sensorium and mentation, and respiratory depression.

In summary, naturally occurring sleep and pharmacologic sedation and anesthesia share many similarities. Their differences, however, are equally important. Naturally occurring sleep, in contrast with pharmacologic sedation, is spontaneously occurring, circadian, reversible with external stimuli, associated with discrete EEG patterns, and perhaps most importantly an essential biologic function. Sedation is a nonphysiologic nonessential state, which is not spontaneous, circadian, or fully reversible with external stimuli (see Table 5). Although sleep and sedation share similar neurobiologic and phenotypic properties, the ultimate measure of their similarity, whether they subserve similar biologic functions, can only be determined when the essential function of sleep is elucidated. The biologic need for sleep and the therapeutic need for sedation almost universally coexist in critically ill patients; therefore, the interaction between them is important and requires further study.

Biologic and Psychological Effects of Sleep Deprivation

Sleep is an essential biologic function. The importance of sleep to the recovery of the critically ill patient, however, has not been directly evaluated. Decades of research on the biologic and psychologic affects of sleep deprivation, however, offer some insights. Although few of these studies have been performed on critically ill subjects, we will review the relevant available data of the effect of sleep deprivation on immune function, catecholamines, hormones, metabolism, pulmonary mechanics, control of breathing, psychological or neurocognitive function, and quality-of-life measures.

Table 5—Relationship Between Sleep and Sedation

Similarities
Overlapping neurophysiologic pathways
Muscle hypotonia
Temperature dysregulation
Disconjugate eye movements (REM)
Altered sensorium and mentation
Respiratory depression
Differences
Sleep is spontaneous; sedation is not
Sleep is circadian; sedation is not
Sleep is an essential biologic function; sedation is not
Sleep is completely reversible with external stimuli; sedation is not
Sleep is associated with decreased release of norepinephrine from locus coeruleus; norepinephrine release continues during sedation
Sleep is associated with cyclic progression of EEG stages; sedation variably alters normal sleep architecture

REM refers to rapid eye movement; EEG, electroencephalogram.

There are 3 models of experimental sleep deprivation: total sleep deprivation, partial sleep deprivation, and specific sleep-stage deprivation. The sleep of the ICU patient, however, is not well represented by any one of these models, and no relevant experimental model has been developed.

Immune Function

It is thought that sleep deprivation is associated with an increased susceptibility to illness; however, the nature of this association is a subject of considerable controversy. It is generally accepted that there is a relationship between sleep and the immune system.[65,66] Studies of humans undergoing total or partial sleep deprivation have demonstrated a nonspecific modulation of the immune response and decreases in aspects of cellular immune function.[67] The clinical relevance of these findings, however, remain speculative. In fact, it is unclear whether the observed changes in cellular immunity with sleep deprivation are strictly immunosuppressive. Animal studies, for example, have suggested both an enhanced and suppressed immune response to sleep loss.[68,69] Human studies directed at determining a clinically important relationship between sleep loss and illness are lacking.

The ability of a critically ill patient to mount a robust immune response to an antigenic challenge may be crucial to survival; it is possible that the sleep quality of a critically ill patient may have some effect on the strength of this immune response. Spiegel, for example, demonstrated that sleep-deprived subjects had an attenuated response to immunization.[70] It has been proposed that chronic sleep loss is detrimental to immune function, as opposed to acute sleep loss, which may (transiently) enhance the immune system.[65] Sleep loss most likely affects the immune response by a direct effect on the central nervous system acting through the neuroendocrine axis.[65] It is clear, however, that further studies are needed to definitively determine how sleep deprivation affects the immune system and what, if any, clinical relevance it has to the critically ill patient.

Catecholamines, Hormones, and Metabolism

Sleep loss presents a stress to an ICU patient; however, it is not characterized by the same physiologic parameters as are seen with the prototypic "fight-or-flight" response. A small elevation in thyroid activity is seen in healthy individuals after sleep loss and likely reflects the augmented energy requirement associated with increased wakefulness.[71,72] Critically ill patients, however, are often found to have low measured levels of thyroid hormone, the so-called "sick euthyroid syndrome." Sleep loss is also associated with loss of the normal circadian variance of norepinephrine, prolactin, and growth-hormone levels in control subjects.[73,74] Many acutely critically ill subjects have been found to have high levels of catecholamines, growth hormone, and prolactin.[75] Prolonged critical illness, however, is associated with impairment of the normal pulsatile secretion of growth hormone, thyroid-stimulating hormone, and prolactin.[76] Cortisol levels have also been found to increase on the night following 1 night of sleep loss and are typically elevated in critically ill patients.[77,78]

Table 6—Metabolic and Hormonal Effects of Sleep Deprivation Compared with Critical Illness

	Sleep Deprivation	Critical Illness
Thyroid hormone	Increased	Decreased
Norepinephrine	Increased	Increased
Growth hormone	Decreased	Acute illness: increased; prolonged illness: decreased
Cortisol	Increased	Increased
Insulin resistance	Present	Present
Hyperglycemia	Absent	Present
VO_2	No change	Increased
VCO_2	No change	Increased
Nitrogen balance	Negative	Negative

Several investigators have sought to characterize metabolic changes in normal subjects deprived of sleep. Studies of multiple physiologic parameters, however, such as VO_2 max (maximum O_2 consumption), VCO_2 max (maximum CO_2 production), lactate levels, and heart rate fail to show consistent changes after variable amounts of sleep deprivation.[79] Critically ill patients, however, are often found to have higher VO_2, VCO_2, and heart rate, likely as part of their stress response and higher catecholamine levels.[80] Several investigators have also found evidence that sleep deprivation is associated with insulin resistance and "prediabetic" muscle metabolism; however, plasma levels of glucose in sleep-deprived subjects at rest have generally been found to be normal.[81-84] Insulin resistance in critically ill patients has been found to be both common and clinically important, with glucose control a predictor of mortality.[85,86] Finally, although there has been some evidence of an association between sleep deprivation and negative nitrogen balance, there has been no difference in measured clinical parameters, such as wound healing, between sleep-deprived subjects and those achieving a normal amount of sleep.[87,88] Critically ill patients are typically found to be catabolic, which is believed to be an impediment to patients' recovery.[89]

In summary, there have been a number of changes found in subjects' metabolic and hormonal profiles under conditions of experimental sleep loss (see Table 6), but it has not been determined whether these changes have any relation to the critically ill or an effect on clinical outcomes.

Pulmonary Mechanics and the Control of Breathing

It had traditionally been thought that sleep loss reduces the hypercapnic ventilatory response.[90,91] More recently, however,

Spengler et al concluded that 24 hours of total sleep deprivation did not have a significant impact on either the sensitivity of the central chemoreceptors or resting ventilation.[92] These results may not apply to the ICU patient whose total sleep time may be normal but severely fragmented.

It has also been believed that some measures of pulmonary mechanics are adversely affected by sleep loss.[93,94] It is known that the FEV_1 (the amount of air exhaled in the first second with maximal effort) and FEV_1/FVC (the ratio of the amount of air exhaled in the first second to the total amount of air exhaled), which are both used to measure expiratory airflow obstruction, have a diurnal variation.[93-97] In addition, inspiratory-muscle endurance and maximal voluntary ventilation have been shown to decrease in healthy men after a period of 30 hours without sleep, but measures of respiratory muscle strength are unaffected.[98] No studies have specifically investigated the relationship between sleep loss and pulmonary function and respiratory drive in critically ill patients; such physiologic alterations could have important implications for weaning from mechanical ventilation.

Psychological or Neurocognitive

Sleep loss has been associated with irritability, memory loss, inattention, delusions, hallucinations, slurred speech, incoordination, and blurred vision.[99] Even healthy subjects may be unable to complete simple repetitive tasks after a period of sleep loss.[99] In short, all criteria for the diagnosis of delirium may be caused by sleep loss.[100,101] The results of neuroimaging studies, lesion studies, and task-performance studies in humans suggest that sleep deprivation and delirium have effects on overlapping regions of the central nervous system, specifically the thalamocortical axis.[101-104] The anterior thalamus and the prefrontal cortex are among those areas affected and that are important to the integration of sensory information and consequent goal-directed action, so-called executive function.

It is known that sleep deprivation is a common phenomenon in critically ill patients and that delirium occurs frequently (80%) in groups at high risk, but the relationship between sleep deprivation and delirium remains a subject of debate.[105] It is not known if sleep deprivation is a cause of delirium in the ICU, if it contributes to ICU delirium by lowering patients' thresholds for developing delirium, or whether it has any relationship to delirium in the ICU at all. However, there is a growing body of evidence suggesting that the development of delirium in the ICU is an independent predictor of higher morbidity and mortality, increased length of stay, disposition to an institutional setting from the hospital, and cognitive impairment at hospital discharge.[106-108] Therefore, if a relationship between sleep deprivation and delirium were established, it would more closely link the poor sleep of the critically ill patient with the poor outcome of the delirious patient.

Quality of Life

Several studies have demonstrated that sleep loss has a negative impact on the subjective quality of patients' ICU life both during their hospitalization and for a variable period of time after discharge.[3-10] Long-term consequences of prolonged critical illness are beginning to be recognized and include continued poor sleep, memory deficits, depression, and symptoms consistent with posttraumatic stress disorder.[6,109-111] It has been hypothesized that the sleep loss suffered by ICU patients may be related to prolonged neurocognitive dysfunction now being recognized in survivors of critical illness, but rigorous data to support this hypothesis do not yet exist. Recent sleep fragmentation and chronic partial-sleep-deprivation studies have demonstrated neurocognitive deficits that accumulate with time, despite some adaptation to the subjective sense of sleepiness.[112-115] Studies of patients with obstructive sleep apnea, who also suffer from sleep fragmentation sometimes associated with hypoxia and hemodynamic variability, have also demonstrated abnormalities in a broad range of neurocognitive performance,[116,117] some of which may last for months even after initiation of treatment with continuous positive pressure.[118,119]

Table 7—An Integrative Approach to Improving the Sleep of Patients in the Intensive Care Unit

Environmental controls
Control noise exposure
Earplugs
Music therapy
Control light exposure (open blinds during the day; decrease light levels at night in the entire intensive care unit)
Nonpharmacologic measures
Minimize unnecessary interruptions during the patients' normal sleep hours
Review patients' medications both for adverse effects on sleep as well as for withdrawal phenomena that may affect sleep
Review settings of mechanical ventilation to guard against dyssynchronous breathing and central apneas
Review patients' history for symptoms that might suggest preexisting sleep disorders
Pharmacologic measures
Anxiolytics/hypnotics
Benzodiazepines. Short half-life (alprazolam, oxazepam) and medium half-life (lorazepam, temazepam) preferred to long half-life.
Benzodiazepine receptor-agonists, such as zolpidem, zaleplon, eszopiclone
Buspirone
Trazadone
Ramelteon
NOT recommended: chloral hydrate, diphenhydramine (except during pregnancy)
Antipsychotics with sedating properties
Atypical (olanzepine, quetiapine, risperidone)
Haloperidol
NOT recommended: chlorpromazine
Analgesics
Opiates
Nonsteroidal anti-inflammatory drugs
For intubated patients
Midazolam
Propofol
? Dexmedetomidine

An Integrative Approach to Improving Sleep in the ICU

To improve the sleep of critically ill patients, a multifaceted approach is recommended.[120] A summary of such measures and a list of recommended pharmacologic options may be found in Table 7. The choice of hypnotics, if deemed necessary, should be individualized and based on what is thought to be most responsible for disturbing the patient's sleep (i.e., anxiety, pain, or delirium). In general, the short-acting benzodiazepines and the nonbenzodiazepine hypnotics (such as zolpidem, zopiclone, eszopiclone, ramelteon) are reasonable options if pharmacologic

therapy is desired because they have less hangover effect then the longer-acting benzodiazepines.[46] Tolerance to some hypnotics may develop within days, however, and the benzodiazepines have also been implicated in ICU delirium.[121] There are no data on the effectiveness of sedating antidepressants as hypnotics in the ICU; however, trazadone is generally well-tolerated, its use is infrequently associated with respiratory depression and delirium, and it has some desirable pharmacokinetic properties such as a quick onset of action and an elimination half-life of 7 to 8 hours and, therefore, may be a reasonable alternative. A study on a small number of psychiatric inpatients concluded that the use of trazadone promoted longer, subjectively deeper sleep but was associated with daytime residual side effects.[122] The use of chloral hydrate is not recommended because it is less effective than benzodiazepines and is highly associated with daytime hangover.[46] Chlorpromazine and the older sedating antihistamines (such as promethazine and diphenhydramine) have undesirable antimuscarinic affects and, in the case of the antihistamines, have also been associated with ICU delirium and daytime hangover.[46] Finally, some of the newer atypical antipsychotic agents (such as risperidone and olanzapine) may be effective but have not been well studied for this indication; they may be most appropriate to consider for use when delirium interferes with sleep. Haloperidol, although not a sedative or hypnotic, may be effective for patients with delirium or agitation. However, the use of haloperidol can cause prolongation of the QT interval and, rarely, the neuroleptic malignant syndrome.

CONCLUSION

Critically ill patients consistently demonstrate sleep fragmentation with a predominance of wakefulness and stages 1 and 2 sleep at the expense of the deeper, putatively more restorative, stages 3, 4, and REM sleep. More than 40 years of investigation into the effects of sleep loss, usually in healthy adults, has demonstrated effects on immune function, metabolism, regulation of the central nervous system, and subjects' psychological state; the clinical significance of these findings as they relate to critically ill patients, however, is not well known. The relationship between patients' poor sleep, their ICU course, and their ultimate recovery has not been definitively proven. However, it seems likely that sleep is important to the recovery process as an integral homeostatic mechanism, but it remains to be determined if improving sleep will have an impact on patient outcome in the ICU.

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