Review Article

Sleep and mechanical ventilation in the intensive care unit

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Abstract. Sleep is essential to a patient's well-being. The importance of sleep is highlighted by the adverse effects in the wake of its absence both physically and mentally. Sleep is difficult to achieve in the intensive care unit due to noise, patient care activities, illness, and mechanical ventilation. Activities related to mechanical ventilation such as suctioning, discomfort of the essential tremor, alarms, treatments and sedation effects can all alter sleep architecture. However, mechanical ventilation itself especially as it relates to asynchrony may also play a larger role than previously thought. This paper aims to review sleep in the intensive care unit and the relationship of mechanical ventilation.

Keywords: Sleep, mechanical ventilation, sedation, delirium

1. Introduction

Sleep is a vital physiologic process. Sleep represents a reversible change in our awareness of the environment, which in the animal kingdom is a dangerous event. Therefore, sleep must be worth the risk even in critically ill patients. According to the American Academy of Sleep Medicine's new criteria, normal sleep is a series of stages alternating between non-rapid eye movement (NREM), N1 (light sleep), N2, N3 (deep sleep, previously stage 3 and 4 in the Rechtschaffen staging system), and rapid eye movement (REM) [1]. Each stage has its own

electroencephalography, electromyography and electrooculography patterns. N1 represents the transition from wakeful state, predominantly alpha waves, to light sleep with more theta waves. N2 is characterized by slower waves with higher amplitude, and the appearance of K complexes and sleep spindles. Deep sleep, N3, is often referred to as restorative sleep. This stage is comprised of high voltage, low frequency delta waves. REM is marked by rapid eye movement, atonia, variations in heart rate and respirations, and absence of thermoregulation. Throughout the night, NREM and REM stages cycle 4–6 times [2]. The proportion of sleep spent in each stage differs as we age, possibly reflecting the function of each stage in physical restoration, memory consolidation, and our ability to learn new tasks [3]. Many studies have shown alterations of normal sleep structure in intensive care unit (ICU) patients with decreased sleep efficiency, total sleep time occurring throughout the day, and suppressed slow wave and REM phases of sleep [4–6].

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Sleep-wake cycles are an orchestra of neurobiological pathways and neurotransmitters. Orexin, histamine and acetylcholine are excitatory neurotransmitters involved in wakefulness along pathways in the hypothalamus and brainstem, while gamma-aminobutyric acid and adenosine promote sleep state. The most accepted conceptual model of this complex interplay of neurophysiologic sleep processes proposes two processes working independently to control our sleep-wake cycle, process S and process C [7]. Process S, the homeostatic process, represents the drive to sleep and increases linearly as a person is awake longer. Therefore, the longer a person is awake, the stronger the drive to sleep. On the other hand, process C, a circadian rhythm, has an oscillating pattern during the day that promotes alertness. As a person becomes deprived of sleep, these processes become less coordinated.

While the exact function of sleep is unknown, human and animal studies uphold its requirement for normal homeostasis. NREM deep sleep (N3), or slow wave sleep, is thought to be needed for physical restoration and declarative memory consolidation, and REM may be important for procedural and emotional memory consolidation [8]. Children spend more time in slow-wave sleep compared to adults and demonstrate the immense capacity to learn new skills [9]. Whereas, the elderly have overall less sleep efficiency, slow-wave sleep, and total sleep time. These patterns of sleep and learning coincide due to a causal relationship rather than by coincidence according to most studies. Gómez et al. [10] demonstrated that 15 mo old infants had improved recognition of non-linguistic word patterns after napping compared to non-napping controls. Children and adults show improved learning and memory consolidation after rest. However, there are some studies that suggest different types of learning respond equally well to quiet rest as compared to sleep [11]. Sleep must have more importance than just consolidation of tasks, memories, and visual/auditory learning.

2. Sleep disruption in the intensive care unit

Although all of sleep's purposes are unknown, sleep deprivation has serious consequences. Rats subjected to prolonged sleep restriction died as a result [12]. In humans, sleep deprivation has been associated with problems with memory, cognitive impairment, decreased endurance, decreased insulin sensitivity, increased gastric acid secretion, and increased cytokine production [3–5]. All of these disruptions could

negatively impact critically ill children even more than the healthy subjects in which they were discovered. Sleep disturbances in the ICU are well documented. Many events in the ICU attribute to sleep disturbances observed in patients including noise, light, patient care activities, procedures, illness itself, pain, anxiety, sedation and mechanical ventilation [6–13].

The ICU environment is not conducive to sleep. Noise, light, patient care activities, and procedures could understandably prevent normal sleep architecture. These aspects have been studied to determine their effect on overall sleep disturbance. Gabor et al. [13] found noise and patient care activities only explained 28% of sleep disruption which was similar to previous studies that had examined noise. Therefore, the majority of sleep disturbance must be due to other factors including illness itself, sedation and mechanical ventilation.

The immune system is intimately tied to the central nervous system. Illness and sleep deprivation have had interesting effects on the interplay between the two systems [14]. Neurons that are immunoreactive for IL-1 and TNF are located in brain regions that are implicated in the regulation of sleep-wake behavior, notably the hypothalamus, the hippocampus and the brainstem [15,16]. IL-1 and TNF increase NREM sleep in several species (rat, mouse, monkey, cat, rabbit and sheep) irrespective of the route of administration [17]. In other studies, cytokines seem to play a role in normal sleep as well as recovery from sleep loss [16,18]. In accordance, loss of sleep seems to alter the normal immune response. Lange et al. [19] demonstrated decreased antibody formation toward hepatitis A immunization following a night of sleep deprivation compared to rested controls. This underscores the importance of sleep on the immune response.

During illness, the normal sleep architecture is often altered. However, it is often difficult to discern whether the illness itself, the immune response to the illness, or an aspect of the ICU environment contribute to this observance most greatly. For example, Mundigler et al. [20] studied septic ICU patients against non-septic ICU patients and healthy controls. They followed urine 6-sulfatoxymelatonin, a metabolite of melatonin, every 4 h over a 24 h period to evaluate the effects of infection and ICU environment on circadian rhythms. The normal circadian fluctuation of melatonin was blunted in the patients with sepsis compared to the non-septic critically ill adults as well as the healthy adults. Interestingly, all of the septic critically ill patients were mechanically ventilated while only 3 of 7 in the non-septic group were

mechanically ventilated [20]. Therefore, it is possible that mechanical ventilation itself played a large role in the decrease in circadian fluctuation of melatonin. Healthy children sedated, paralyzed and ventilated in the ICU after tracheoplasty demonstrated significant sleep alterations [21]. These patients would be expected to lack the disturbances of the immune response and cytokine release that are believed to alter sleep in sepsis. Although there were only two patients in this observation, it does suggest that sedation and mechanical ventilation must have a more significant influence on sleep architecture than previously thought.

3. Role of sedation in sleep disruption

Sedation is frequently required to alleviate the discomfort and psychological distress related to mechanical ventilation. Alterations of sleep have been shown to occur in intermittent and continuous sedation strategies [22,23]. Most sedative medications used in the ICU cause some disturbance of normal sleep architecture [24]. Benzodiazepines may induce stage 1 and 2 of sleep, but have been shown to reduce stage 3, even at small doses. Borbély and Achermann [25] found that one dose of versed caused severe reduction of REM that lasted even the following night. Another study found an independent association between lorazepam dose, REM suppression and the development of delirium [23]. REM abnormalities involve the same serotonergic pathways related to the psychotic manifestations of delirium. Other medications that exert effects on the gamma-aminobutyric acid receptor, such as propofol, demonstrate similar patterns of altered sleep stages like Benozzo's [26–28]. Opiates are also frequently used as sedatives for ventilated patients. Morphine and fentanyl suppress stage 3 and REM. A newer sedative, such as dexmedetomidine, provides sedation and analgesia through activation of alpha 2 receptors at the locus coeruleus and along the spinal column. Dexmedetomidine was studied in an animal model and was found to support N3. The MENDS trail found infusions of dexmedetomidine to provide target sedation with a reduced incidence of delirium in adult ICU patients [29]. While the relationship between sleep disruption and ICU delirium has yet to be established, the role of sedation involves both. More research needs to be conducted, but dexmedetomidine may provide improved sleep architecture and less delirium [30]. ICU delirium symptoms and the symptoms of sleep deprivation are strikingly similar

[31]. It stands to reason that since sedation has been shown to be a causative factor in both ICU delirium and sleep deprivation that sleep disruption may have a causative relationship to ICU delirium, but this has not been studied. ICU delirium has been shown to lengthen hospital stay, increase morbidity and mortality in ICU patients, and increase costs by 31% [32–36]. If sleep disturbance does in fact attribute to ICU delirium, then improving sleep would have clinical importance. Withdrawal from sedation also has overlapping symptoms with sleep disruption and is a known cause of ICU delirium [37].

4. Mechanical ventilation and sleep disruption

Mechanical ventilation is an intervention vital for many critically ill patients during their treatment course. Activities related to ventilation contribute to sleep disturbance including suctioning, pain of endotracheal tube, noise of alarms, over ventilation, and patient-ventilator asynchrony. Apneas and asynchrony lead to increased arousals, awakenings, and decreased sleep efficiency. Parthasarathy and Tobin [38] demonstrated increased sleep fragmentation in patients ventilated in pressure support ventilation (PSV) compared to assist control. These patients experienced more central apneas in PSV, most likely due to over ventilation in PSV during sleep. Apneas and the resulting sleep fragmentation was alleviated by introducing dead space during PSV. It is important to understand the role that mechanical feedback plays in the patient's response to a mechanically delivered breath. The mechanical feedback is related to the delivered lung volume (length of muscular contraction) and flow (velocity of the contraction) delivered. Thus, when lung volume and flow are greater, muscle pressure will be less. The exact role of mechanical feedback is not well understood and may play only a small role in patient-ventilator interactions, but in a situation of high ventilator demands with hypercapnic hyperventilation, muscle pressure may underestimate neural output to respiratory muscles and can be reduced by up to 15% [39]. Central apneas during PSV were also seen in a study that found increased sleep fragmentation due to central apneas that could be improved with adjustments to the level of support [40]. These findings support that central apneas during sleep are the result of lowered PCO_2 below a stimulating level. Ventilation triggering during sleep, when cortical triggers are absent, is dependent on $PaCO_2$. Mode of ventilation may not affect sleep as previously thought. When comparing

assist control, automatically adjusted PSV and clinically adjusted PSV no differences were found in sleep fragmentation. Minute ventilation was similar in all three modes suggesting the level of support, not the mode of ventilation, determines the effect on sleep through the effects of ventilation on PaCO_2 during sleep [40]. In the study of Parthasarathy and Tobin [38], most of the patients that experienced central apneas had congestive heart failure. Heart failure results in higher left ventricular filling pressures, which causes pulmonary edema then subsequent increased chemo-sensitivity, hyperventilation, lowered CO_2 and finally central apnea.

The intricate relationship between ventilator synchrony and sleep quality requires a greater understanding of this relationship in pediatric patients. Patient ventilator asynchrony is the failure of two controllers to act in harmony. When a patient is being ventilated with a mechanical ventilator, there are two controllers: the clinician controlled mechanical pump of the ventilator, and the patient's own respiratory muscle pump. We have previously identified a high rate of asynchrony in pediatric patients who are mechanically ventilated. In patients with bronchiolitis, we found evidence of asynchrony in 72% of studied breaths (Heulitt et al. *Neurally triggered breaths have reduced response time and work of breathing compared to pneumatically triggered breaths in a recovering animal model of lung injury* Pediatric Critical Care Medicine 2011 [submitted]). Patients during this study were sedated and asleep, but the exact stage of sleep and role of sleep in the asynchrony is unclear. Our preliminary data in a pediatric animal model identifies a higher level of arousal during periods of asynchrony. Conversely, the animals have deeper sedation/sleep when asynchrony is absent. This preliminary data begins to describe the relationship of patient ventilator interactions more accurately.

5. Conclusions and future directions

Perhaps an even more important question is whether normal sleep matters for the critically ill patient and should improvement of sleep in the ICU be a goal for physicians. Some studies suggest that the maintenance of sleep architecture during illness improves recovery and survival. Toth et al. [14] retrospectively analyzed data derived from long-term studies of sleep disruption in infected rabbits. A cumulative sleep-quality score was calculated for each animal that included duration and the intensity of NREM sleep. Sleep quality differed among animals with higher inoculation dose; sicker

animals had more sleep disruption. Also, animals with the same inoculation dose, higher sleep scores had better survival than those with low scores. Although infection alters sleep, better sleep correlated with improved survival. This result implies that appropriate sleep may indicate appropriate immune response and vice versa. In humans, Valente et al. [41] found patients with traumatic brain injury had improved survival and functional outcome related to better sleep architecture. Maintenance of sleep wake cycles in these 24 comatose adult traumatic brain injury patients was more predictive of outcome than neuroradiologic imaging and initial Glasgow coma scale. In this case, sleep may be representative of a brain with less injury and therefore the ability to achieve sleep, or that sleep is reparative or at least sparing of vulnerable but not lost neurons. Either way, sleep seems to be a factor of value in the critically ill patient that should be supported by the clinician. Sleep data in intensive care patients has largely been reported in adults. Investigated sleep-ventilator interactions have never been observed in children. By having a better understanding of the apnea and asynchrony events that occur during periods of sleep, we can continue to pursue further research in reducing events and improving sleep quality of mechanically ventilated patients.

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