Sleep in the ICU

Richard J. Schwab, M.D.
Professor of Medicine
Division of Sleep Medicine
Pulmonary, Allergy and Critical Care Division
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Sleep in the ICU - Disclosures

- NIH grants - PPG (Phenotyping and OSA)
- ResMed Grant/Registry to study OSA/CSA and CPAP in hospitalized patients
- Jazz clinical trial for EDS in OSA
- Consultant:
  - Apnicure
  - Foramis Medical Group
  - CryOSA

Sleep in the ICU
ATS Official Statement: The Importance of Healthy Sleep

• Sleep appears to be important for a number of vital functions:
  – Neural development
  – Learning
  – Memory
  – Cardiovascular and metabolic function
  – Cellular toxin removal


ATS Official Statement: The Importance of Healthy Sleep

• Major Conclusions of the Statement:
  – Short sleep duration (≤ 6 hours/ 24 hour period) is associated with adverse outcomes, including mortality
  – Long sleep duration (> 9-10 hours/ 24 hour period) may be associated with adverse health outcomes
  – Although individual variability exists, the optimal sleep duration for good health in an adult population is 7-9 hours


Sleep Deprivation in the ICU

Figure 1. Factors related to sleep deprivation in critically ill patients.

Sleep in the ICU

Table 1. Sleep Disturbances in Critically Ill Patients

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>ICU-related factors</th>
<th>PSG findings in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting sleep disorders</td>
<td>Pain</td>
<td>TST Unchanged/decreased</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Noise</td>
<td>TST occurring during daytime hours</td>
</tr>
<tr>
<td>ICU-related factors</td>
<td>Light</td>
<td>Sleep latency Unchanged/increased</td>
</tr>
<tr>
<td>Sleep care activities</td>
<td>Patient care activities</td>
<td>Sleep efficiency Decreased</td>
</tr>
<tr>
<td>PSG findings in critically ill patients</td>
<td>Noise</td>
<td>Sleep fragmentation Increased</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>Light</td>
<td>Arousals Increased</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>Patient care activities</td>
<td>NREM stage 1 (N1) Increased</td>
</tr>
<tr>
<td>Sleep fragmentation</td>
<td>Noise</td>
<td>NREM stage 2 (N2) Increased</td>
</tr>
<tr>
<td>Arousals</td>
<td>Light</td>
<td>NREM stage 3 (N3) Decreased</td>
</tr>
<tr>
<td>NREM stage 1 (N1)</td>
<td>Patient care activities</td>
<td>REM Decreased</td>
</tr>
</tbody>
</table>

Challenges with scoring PSG in critically ill patients

NREM stage 2

- Absence of K complexes
  - 20–44%
- Absence of sleep spindles
  - 20–44%
- Use of sedating medications

Alternative PSG scoring strategies

Pathologic wakefulness

- Visual assessment of EEG
  - Absence of K complexes and sleep spindles
  - High-amplitude continuous theta frequency
  - No fast frequencies, no EEG slow artifacts

Atypical sleep

- Absence of K complexes and sleep spindles
- High-amplitude continuous theta frequency

Potential Physician/Nursing Factors Causing Sleep Disruption in the ICU

- Diagnostic testing and invasive procedures
  - Chest radiographs, phlebotomy (4 AM to 6 AM)
  - Intravenous or central catheters
  - Nursing interventions
  - Vital signs
  - Administration of medications
Potential Environmental Factors Causing Sleep Disruption in the ICU

- Lighting
- Noxious odors
- Noise (75 dB is as loud as a cafeteria at noon)
  - Mechanical devices and alarms, including ventilators, infusions pumps, telemetry and oximetry (45 - 76 dB)
  - Background noise (55 - 72 dB)
  - Nursing or respiratory care (55 - 83 dB)
  - Hospital staff conversations (60 - 74 dB)
  - Beepers (70 - 84 dB)

Freedman N, Schweb RJ. Sleep in the ICU. The Intensive Care Unit Manual; 511-519, 2001

<table>
<thead>
<tr>
<th>Unit</th>
<th>n</th>
<th>Gender (M/F)</th>
<th>Mean Age (yr)</th>
<th>Ventilated Patients (count)</th>
<th>Mean ICU Stay (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCU</td>
<td>60</td>
<td>49/20</td>
<td>61.1 ± 11.6</td>
<td>1</td>
<td>7.2 ± 14.9</td>
</tr>
<tr>
<td>ICU</td>
<td>39</td>
<td>23/16</td>
<td>62.6 ± 12.4</td>
<td>0</td>
<td>12.6 ± 22.3</td>
</tr>
<tr>
<td>MICU</td>
<td>55</td>
<td>28/28</td>
<td>51.4 ± 17.0</td>
<td>20</td>
<td>11.3 ± 24.6</td>
</tr>
<tr>
<td>SICU</td>
<td>48</td>
<td>30/18</td>
<td>61.4 ± 15.4</td>
<td>11</td>
<td>8.3 ± 11.8</td>
</tr>
<tr>
<td>Total</td>
<td>209</td>
<td>121/88</td>
<td>66.6 ± 15.4</td>
<td>32</td>
<td>8.6 ± 17.5</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: CCU = coronary care unit; ICU = intensive care unit; MICU = medical intensive care unit; SICU = surgical intensive care unit.
* Mean ± SD, range in parentheses.

Freedman et al, AJRCCM 159:1155-1262, 1999

Perceived Sleep Quality between Home and ICU (N = 203; p = 0.0001)

Freedman et al, AJRCCM 159:1155-1262, 1999
Studied 22 (20 ventilated) MICU patients with continuous polysomnography and environmental noise measurements over a 24 - 48 hour period

- To determine the underlying mechanisms of altered sleep/wake patterns in ICU patients
- To objectively determine the effect of ICU environmental noise on sleep fragmentation
  - Simultaneous real time recordings of environmental noise (Quest 1900 portable sound level meter) and polysomnography
Sleep/Wake Cycles in the ICU
(Freedman et al, AJRCCM 163, 451-457, 2001)

- Mean total sleep time per 24 hr period: 8.8 ± 5.0 hrs
- Sleep typically occurred in short bouts (41 ± 18 bouts/24 hrs) with 57% of total sleep during daytime
- Abnormal sleep architecture with a predominance of stage 1 sleep and decreased or absent stages 2, 3, 4 and REM sleep
  - Stage 1 (mean 59 ± 33%)
  - Stage 2 (mean 26 ± 28%)
  - Stage 3/4 (mean 9 ± 18%)
  - REM sleep (mean 6 ± 9%)
- Twelve of the patients demonstrated no REM sleep
Sleep in Mechanically Ventilated Patients

- The sleep of a mechanically ventilated ICU patient suffers from all the problems known to affect the sleep of non-ventilated patients plus:
  - Dyssynchronous breathing
  - Ventilator mode
  - Discomfort from the endotracheal tube
  - Stress related to increased difficulty communicating
  - Possibly a greater severity of illness


Hypnograms of 8 ventilated ICU patients
  - Sleep fragmented with frequent awakenings
  - Distribution of sleep over the 24 hour period
  - Prolonged wake

Ventilator Mode and Sleep Disruption
Parthasarathy et al (AJRCCM 2002;166:1423-1429)

- More apneas per hour with pressure support ventilation compared to assist control
- Addition of dead space reduced the number of apneas
Sleep in Mechanically Ventilated Patients - Ventilator Synchrony

- Mechanical ventilator settings may also worsen sleep continuity by causing dysynchronous breathing or by being set to a range of respiratory frequencies to which the patient cannot entrain (Weinhouse and Schwab (Sleep 29: 707-716, 2006))
- Sedated individuals are believed to entrain to a wide range of respiratory frequencies
- Optimizing ventilator settings for patient comfort and sleep and the role of pharmacologic sedation is an area that needs active investigation

Effect of Medications on Sleep

<table>
<thead>
<tr>
<th>Medications (Examples)</th>
<th>Sleep Alterations</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td></td>
<td>Sedating properties may worsen SDB</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td>Drowsiness, CNS depression enhanced by alcohol intake</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td>Severe sedation, extensive drug interactions</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td></td>
<td>Drowsiness, fatigue</td>
</tr>
<tr>
<td>Antiparkinsonian drugs</td>
<td></td>
<td>Sedating effects common</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td></td>
<td>Drowsiness, weakness, syncope</td>
</tr>
<tr>
<td>Insomnia, NA</td>
<td></td>
<td>Sedating effects common</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; SDB, sleep-disordered breathing; SWS, slow wave sleep; TST, total sleep time.

Redeker, NS, et al. Sleep Disorders and Sleep Promotion in Nursing Practice: Springer Publishing Company; 2011.
Effect of Medications on Sleep

<table>
<thead>
<tr>
<th>Medications (Examples)</th>
<th>Sleep Alterations</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone, cortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2 Antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does Sleep Deprivation Impair Clinical Performance?

- Data are not definitive but:
  - Anesthesiologists take longer to intubate
    - Gaba et al, Anesth 1998
  - Affects hand-eye coordination in surgeons performing laproscopy
    - Taffinder et al, Lancet 1998
  - Medical errors in ICU (NEJM October 28, 2004)
  - Professionalism is compromised/increased risk of depression
  - No procedures post call

Potential Deleterious Effects of Sleep Deprivation in the ICU

- Respiratory System
  - ? Adversely affect weaning
- Immune Function
  - ? Adversely affect healing
- Neuroendocrine System
- ICU syndrome/Delirium
Effects of Sleep Deprivation on the Respiratory System

- Decreased forced vital capacity
- Decreased maximum voluntary ventilation
- Decreased hypercapnic ventilatory response by 20% - 24%
- Decreased hypoxic ventilatory response by 29%
- Decreased inspiratory muscle endurance by 24%
- Decreased genioglossal EMG activity
- Increased upper airway collapsibility


Poor Sleep Quality is Associated with Late Non-Invasive Ventilation Failure

- Prospective observational cohort of 27 patients requiring non-invasive ventilation
- Hypercapnic respiratory failure
- Proportion of patients with abnormal sleep (abnormal EEG, disrupted circadian rhythm and decreased REM) in non-invasive ventilation failure verses success: 50% vs. 8% (P=0.03)
- Non-invasive ventilation failure was associated with delirium (64% vs. 0%)

Roche Campo et al; Crit Care Med 38:477-485, 2010

Effects of Sleep Deprivation on the Immune System

- Poor sleep is thought to increase susceptibility to illness; however, this association is controversial
- Sleep deprivation in rats leads to death in 2-3 weeks
- Studies of humans undergoing total or partial sleep deprivation have shown non-specific changes in immune response and decreases in aspects of cellular immune function
  - Sleep deprivation (4 hours) in 30 healthy adults increased monocyte production of interleukin 6 and tumor necrosis factor alpha
  - Irwin et al, Arch Int Med 166; 1756-1762, 2006
Effect of Sleep Deprivation on Neuroendocrine System

- Studies have shown that partial sleep deprivation is associated with high sympathetic tone
- Cortisol levels have been found to increase on the night following one night of sleep loss
- Neuroendocrinologic changes may be much greater in critically ill patients

Interventions to Improve Sleep in the ICU

<table>
<thead>
<tr>
<th>Table 20.1</th>
<th>Interventions to Promote Sleep During Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td>Interventions</td>
</tr>
<tr>
<td>Goal: Reduce Effects of Environmental Disturbance</td>
<td>Monitor noise, light at night; normal lighting during the day</td>
</tr>
<tr>
<td></td>
<td>Quiet patient care interactions; &quot;Quiet Time&quot; for patients/visitors</td>
</tr>
<tr>
<td></td>
<td>Music, music, white noise</td>
</tr>
<tr>
<td>Activity: Modify patient and Treatment Related Effects on Sleep</td>
<td>Reduce drug interactions affecting sleep patterns; evaluate sleep effectiveness on all hospital patients; ingested medications</td>
</tr>
<tr>
<td></td>
<td>Prevent delirium using anxiolytics; anti-anxiety drugs</td>
</tr>
</tbody>
</table>

Redeker, N.S. et al. Sleep Disorders and Sleep Promotion in Nursing Practice: Springer Publishing Company; 2011.
Relationship Between Sleep Deprivation and Delirium?

Factors Affecting Circadian Rhythms in the ICU

• Altered sleep architecture
• Sleep deprivation
• Aberrant light/dark cycles and social cues
• Severity of illness
• Affect on respiratory muscle strength
  • Implications for weaning

Circadian Rhythms in the ICU

• To investigate circadian rhythms in the ICU, we recorded core body temperature over a 48-hour period in 21 ventilated patients (59 ± 11 years; 8 males vs. 13 females)
• Core body temperature was measured with a swan-ganz catheter or bladder catheter
• A circadian rhythm was detected in the temperature records of every patient
• Substantial variability among patients in the timing (phase) of the circadian rhythm
• Circadian phase position for 17 of the 21 patients fell outside a previously established reference interval for variability among healthy normals
Subject Demographics and Clinical Information

<table>
<thead>
<tr>
<th>Demographics and Clinical Information</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>21</td>
</tr>
<tr>
<td>Male (female)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Age, mean ± SD, min-max, y</td>
<td>59 ± 11, 33-75</td>
</tr>
<tr>
<td>APACHE III score, mean ± SD, min-max</td>
<td>49 ± 22, 20-95</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
<td>17</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>10</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>3</td>
</tr>
<tr>
<td>COPD-exacerbation</td>
<td>6</td>
</tr>
<tr>
<td>ARDS</td>
<td>5</td>
</tr>
<tr>
<td>First day of CBT recording, mean ± SD, min-max</td>
<td>19.9 ± 18.9, 5-45</td>
</tr>
</tbody>
</table>

Data are presented as No. subjects unless indicated otherwise.
APACHE = Acute Physiology and Chronic Health Evaluation. CBT = core body temperature; max = maximum, min = minimum.
*Relative to day of ICU admission.

Subjects’ Circadian Phase Position

- Each triangle indicates an individual patient’s clock time of the estimated CBT minimum, plotted against clock time (in hours).
- In 10 patients, circadian phase position (CPP) fell earlier than the reference interval; in 7 patients, the CPP fell later.
- The gray bar indicates the reference interval for healthy normal subjects (04:38-06:45), taken from a database of healthy extreme morning- and evening-type individuals studied under constant-routine conditions.
- The vast majority of healthy normal subjects would be expected to have circadian phase positions inside this relatively narrow reference interval.
- In contrast, the circadian phase positions of patients in the ICU were distributed over the entire 24 h of the day.
- The mean ± SD of circadian displacement in either direction (advance or delay) was 4.44 ± 3.34 h.

Circadian Rhythms in the ICU

- Stepwise linear regression was performed to determine if age, gender, APACHE III score, or day in the ICU could predict the patient-specific magnitude of circadian displacement.
- APACHE III score was the only variable found to be significantly predictive of circadian displacement.

Discussion

• Our findings suggest that the severity of illness may directly or indirectly contribute to changes in the circadian rhythms in ICU patients
• Altered circadian phase positions in patients in the ICU may also result from abnormal temporal cues (zeitgebers) in the ICU environment, which can cause desynchronization of the circadian pacemaker
• Light patterns, in particular, appear to be different for ICU patients compared with normal control subjects
• Ambient light is a relatively potent zeitgeber in human beings, but if ICU patients receive insufficient and/or improperly timed light, it may result in changes in the circadian rhythmicity


Discussion

• Knowledge of the circadian phase position in critically ill patients may also have direct physiologic and therapeutic implications
• Patients with COPD show circadian fluctuations in pulmonary function, with circadian differences between peak and trough values of FEV1 and peak expiratory flow rates of 25% to 50%
• This time may be predictable based on the temporal relationship between the pulmonary function rhythm and the CBT rhythm
• Healing may be impacted by circadian rhythms, and alignment of central and peripheral oscillators by zeitgebers, such as feeding regimes, may benefit patients


Discussion

• Drug efficacy and half-life depend on circadian timing
• Chronotherapy may benefit patients in the ICU by potentially enhancing drug efficacy and/or decreasing toxicity
• CBT recordings may be useful as a circadian marker in future research to evaluate the efficacy of circadian-based drug delivery strategies

Conclusions about Circadian Rhythms
(Gazendam et al. Chest. 2013;144:483-9)

- Circadian rhythm of CBT in critically ill ICU patients to be considerably shifted relative to normal control subjects
- Patients with higher APACHE III scores showed greater circadian phase displacement
- Increased knowledge and consideration of patients’ circadian rhythmicity may have a positive impact on therapeutic interventions and the quality of sleep in the ICU
- The finding of abnormal circadian rhythms in the ICU strongly suggests that appropriately timed patient care and treatment strategies aimed at realigning circadian rhythms may be beneficial for clinical recovery in critically ill patients

Sleep and Circadian Rhythms Disturbances in the ICU

- Patients sleep in the ICU but they sleep in short bouts throughout the 24 hour period
- Delta/REM sleep are difficult to achieve in the ICU
- Human ICU interventions appear to be more disruptive to sleep than noise
- The ventilator can disturb sleep in the ICU
- Sleep deprivation may adversely affect immune, respiratory function, neuroendocrine, and cause (?) delirium
- Circadian rhythms are present but displaced in ICU patients
- Consider nonpharmacologic approaches initially

Sleep in the ICU

Thank you for your attention!
Any Questions?
rschwab@mail.med.upenn.edu