Circadian Dysrhythmias in the Intensive Care Unit

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KEYWORDS

• Critical care • Mechanical ventilation • Circadian rhythm • Melatonin

KEY POINTS

- Circadian abnormalities are widespread because of uniform sleep disruption and aberrant sleep architecture in the intensive care unit (ICU).
- Circadian dysrhythmias develop due to critical illness as well as the ICU environment and therapies (mechanical ventilation [MV], sedation).
- Sleep and circadian rhythms should be addressed by ICU providers as an aspect of care to restore health and physiologic homeostasis.
- Changes to the ICU environment, use of natural light, and administration of melatonin in the evening may improve circadian alignment.

INTRODUCTION

Circadian Physiology

All physiologic functions have an endogenous rhythm, which is modulated by neuroendocrine signals and is regulated by the circadian clock. The rhythms are entrained to their natural environment by light, feeding, and other social cues with light being the most important factor. The principal clock resides in the suprachiasmatic nucleus (SCN) within the hypothalamus and serves as the master pacemaker for the individual. The SCN not only determines the timing of sleep and wakefulness but also regulates other circadian rhythms that are independent of sleep such as cortisol levels, core body temperature (CBT), and melatonin release.[1] The SCN coordinates the peripheral oscillators found in every organ and tissue via neurohormones and aligns these peripheral clocks to the central rhythm (**Fig. 1**).[2] On the cellular level, approximately 15% of gene expression as well as protein and lipid production are under circadian control, which are highly conserved across species.[3]

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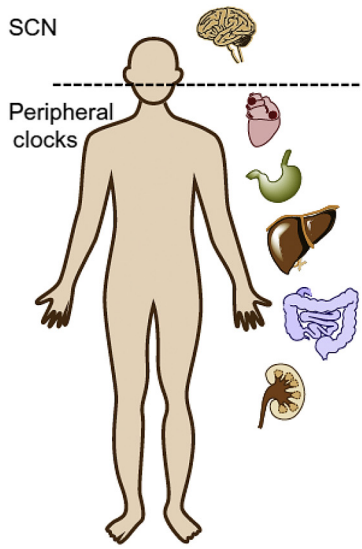

SCN input	Light
SCN output	Sleep/wakefulness Feeding & energy expenditure Glucose homeostasis Hormonal regulation Body temperature regulation Blood pressure & respiratory changes
Peripheral clocks input	Feeding/fasting Signals from SCN
Peripheral clocks output	Lipogenesis Insulin secretion Glucose clearance Food absorption Fat accumulation

Fig. 1. The SCN is the master clock that regulates peripheral clocks in other organ systems and sets the circadian rhythm of temperature, sleep/wake, and metabolic, neuroendocrine and cardiovascular regulation via the peripheral clock output. (*From* Griffett K, Burris TP. The mammalian clock and chronopharmacology. Bioorg Med Chem Lett 2013;23:1929–34; with permission.)

Although circadian variation in blood pressure, CBT, urine output, lung function, metabolism, coagulation, and immune response is well established,[4] the clinical implications of this on disease manifestation and monitoring have been overlooked. The circadian pattern in heart attacks and asthma flares may reflect circadian changes in immune parameters such as cytokine release, leukocyte tissue migration, and T-helper response. Disease onset may also be timed by increases in sympathetic nervous system output resulting in bronchial constriction and higher blood pressure.[5] Asthmatic airways have greater circadian variability in peak flow. Lung inflammatory response to viruses and antigens may also be influenced by circadian factors.[6]

The circadian nature of physiology has profound implications for critical care. Circadian abnormalities can lead to derangements in physiologic homeostasis and affect critical illness. Patient assessments of temperature, blood pressure, metabolism, and lung function are often made disregarding circadian time, which limits comparability. Drug efficacy may differ depending on the timing of administration because immune response, metabolic function, hormones, and pharmacokinetics have circadian variation.[7] The developing field of chronopharmacology addressing this has not yet translated into the ICU. Furthermore, a patient with circadian abnormalities may be at greater risk for delirium, prolonged ICU stay, and morbidity.[8] Awareness of the intrinsic circadian rhythm of the patient in ICU has clinical relevance.

Circadian Disruption in the Intensive Care Unit

Sleep in the ICU is aberrant in timing, architecture, and amount. Studies using polysomnography (PSG) monitoring in the ICU show an absence of circadian sleep pattern with 50% of sleep in the daytime.[9] Perception of sleep by staff is inaccurate and typically grossly overestimated.[10] Sleep architecture is aberrant with rapid eye movement (REM) and slow wave (N3) sleep lacking and severe sleep fragmentation common.[11,12]