Sleep Breathing and Sleep-Deprivation Physiology

Subjects: Respiratory System

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Sleep-disordered breathing is associated with sleep deprivation. This sleep disruption interferes with the normal restorative functions of NREM and REM sleep, resulting in disruptions of breathing and cardiovascular function, changes in emotional reactivity, and cognitive decline in attention, memory, and decision making. As the human body goes through the different stages of sleep, physiological changes in the breathing mechanism are present. Sleep disorders, such as obstructive sleep apnea-hypopnea syndrome, are often associated with sleep-disordered breathing and sleep deprivation. Hypoxia and hypercapnia coexist with lack of sleep and undermine multiple functions of the body (e.g., cardiovascular system, cognition, immunity). Among the general population, athletes suffer from these consequences more during their performance. This concept supports the beneficial restorative effects of a good sleeping pattern.

sleep deprivation sleep-disordered breathing

1. Sleep-Disordered Breathing Physiology

1.1. Respiratory Aspect

The mechanism of breathing includes air flow through the passages of the respiratory system due to pressure gradients that are formed by contraction of the diaphragm and the thoracic muscles. Air flows from a region of higher pressure to a region of lower pressure. Respiration involves the interplay between three different pressures: the atmospheric, the interalveolar, and the intrapleural pressure. Inspiration is the active phase of respiration and the result of muscle contraction, and expiration is the passive phase in calm state. Regulation of respiratory system is subconscious and determines rhythmic rotation between inspiration and expiration and ventilation (breathing frequency and depth) [1].

Sleep state is associated with significant changes in respiratory physiology, including ventilatory responses to hypoxia and hypercapnia, upper airway, and intercostal muscle tone, and tidal volume and minute ventilation. These changes are further magnified in certain disease states, such as chronic obstructive pulmonary disease, restrictive respiratory disorders, neuromuscular conditions, and cardiac diseases [2]. Sleep-disordered breathing (SDB), which causes sleep deprivation and intermittent hypoxia, encompasses a broad spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea (CSA), as well as sleep-related hypoventilation and hypoxemia. Relative hypotonia of respiratory muscles, body posture changes, and altered ventilatory control result in additional physiologic changes contributing to hypoventilation [3]. Hypercapnia,

hypoxemia, and negative intrathoracic pressure swings lead to increased sympathetic response in order to maintain the normal air flow followed by hyperventilation.

1.2. Neural Aspect

Breathing is an automatic function and is regulated, according to the metabolic demands, by the autonomic nervous system (ANS) and, more specifically, by the respiratory center (RC), a central pattern generator (CPG) located in medulla oblongata along with the other vital reflexes. Cortical–medullary circuits furthermore guarantee that voluntary control of breathing is possible [4]. Upon loss of cortical functions without the loss of the medullary CPG, however, control is maintained by the latter.

1.3. Input Sensors

Wakefulness, non-rapid eye-movement sleep (NREM), and rapid eye-movement sleep (REM) sleep represent three distinct states during the sleep–wake cycle [5]. Breathing is maintained during sleep, but its regulation differs from wakefulness [6]. The progression through sleep stages is accompanied by a sequence of physiological changes based on chemoreceptor and baroreceptor reflexes [7]. Chemoreceptors are divided into peripheral and central. Chemoreflex input consist of peripheral (carotid and aortic bodies), which reflect the concentrations of arterial O_2, and of central receptors, which are sensitive to CO_2 and H^+ changes in the CSF [8]. Consequently, the ventilatory feedback control system of the chemoreflex is vulnerable to rapid fluctuations of this input, similar to those that occur during NREM sleep [9].

Two additional respiratory control centers exist in the medulla: the vasomotor (VMC) that regulates blood pressure and the cardiac center (cardioinhibitory and cardioacceleratory centers) for the regulation of heart rate. The three centers are interconnected to function coordinately for the release not only of the chemoreflex but also for the baroreflex [10]. The baroreceptor reflex is activated when blood pressure is found increased by the baroreceptors in walls of carotid internal artery and of aorta and vasodilation occurs (inhibition of VMC) as well as decreased heart rate (stimulation of cardioinhibitory centers).

In sleep-disordered breathing, the circle of intermittent hypoxia–hypercapnia stimulates chemoreflex entirely, which in turn overstimulates SNS, attenuates baroreflex, and enhances hyperventilation after arousal [11]. Arousal occurs in order to increase the muscle tone and compensate for hypoventilation. Interestingly, the increased tone of SNS persists during daytime, too. As baroreflex is desensitized, the PNS is incapable of antagonizing the detrimental effects of SNS overstimulation, demonstrating mainly hypertension and tachycardia.

1.4. Output Mediators

The mutable environment of respiratory regulation during sleep affects multiple systems and structures: the ANS as well as lungs, chest wall, and upper airway [12]. During wakefulness and REM, sympathetic tone is dominant, whereas during NREM sleep, parasympathetic tone prevails to create a state of reduced activity [13]. Therefore,

blood pressure and heart rate are reduced during NREM, whereas in REM sleep, the pulses of sympathetic activity induce tachycardia and relatively increase blood pressure [14].

During sleep, ventilation and functional residual capacity decrease slightly [15]. In stage I of NREM sleep, sufficient muscle tone is maintained, and frequent body posture changes occur. Respiratory pattern is more regular, while minute ventilation is progressively reduced, resulting in an increase of end-tidal carbon dioxide ($ETCO_2$) compared to a waking state. During REM, respiratory pattern varies while ventilation further drops, accompanied by a slight reduction in oxygen saturation [16].

These fluctuations of arterial blood pressure, heart rate, and respiration occur in NREM and REM sleep and during transitions between sleep and arousal [17]; they may explain the sensitivity differences in hypoxia–hypercapnia, a major pathophysiologic element in sleep-disordered breathing [5]. Pulmonary stretch receptors work in coordination with central and peripheral chemoreceptors as the corresponding reflexes affect upper airway and respiratory pump muscles. The relationship is displayed in detail in **Figure 1**. A reduction in respiratory muscle tone occurs during NREM sleep but is more prominent during REM [18], attenuating the occlusion pressure responses to both hypoxia and hypercapnia in REM sleep stage, a clinical phenomenon consistent with emerging even in normal people [19]. In this context, arousals emerge, fragmenting sleep architecture. A protective reflex is activated by local upper airway (UA) mechanoreceptors due to the negative pressure in the UA, preventing its collapse by enhancing activity of UA dilators [20]. This reflex re-establishes ventilation in an alternative-to-arousal manner.

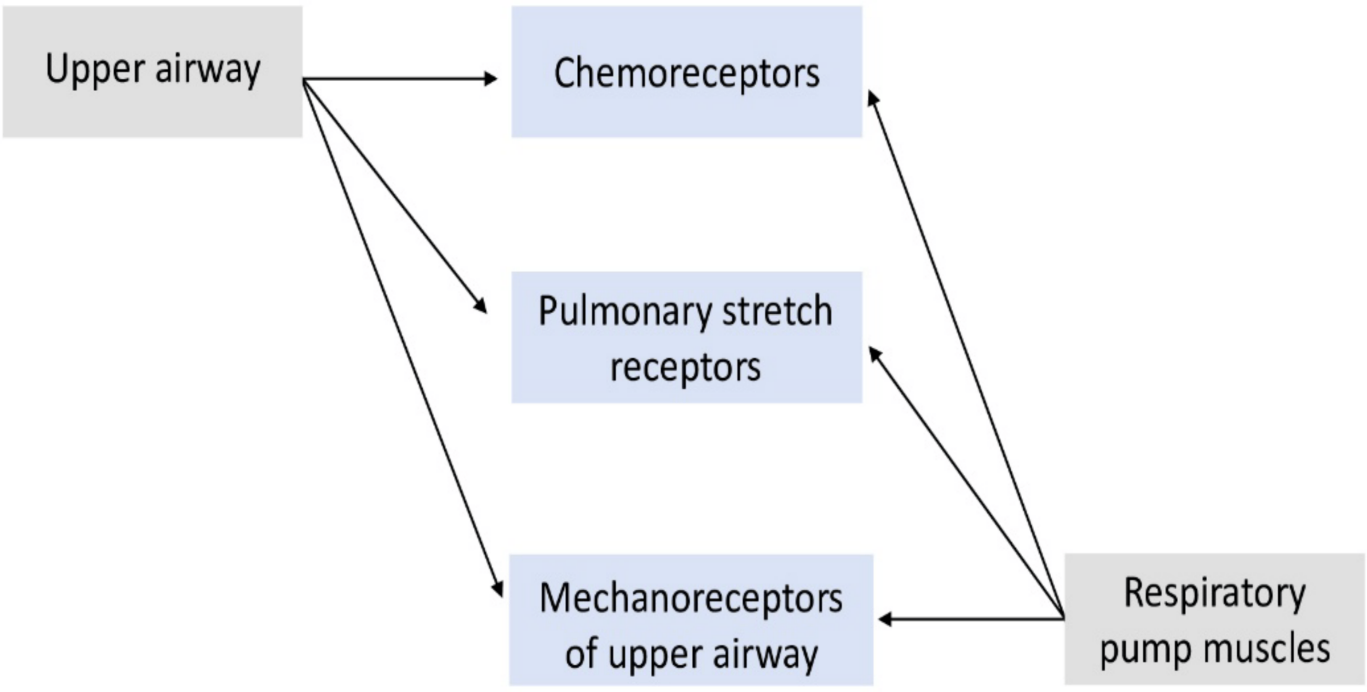

Figure 1. All the reflexes that take part in the control of respiratory rate during sleep. As inspiration occurs, upper airway muscles are activated by the mechanoreceptors, resulting in a protective reflex that prevents occlusion of airflow without arousals. However, inspiratory activation may become insufficient in terms of timing and magnitude

due to stronger activation of respiratory pump muscles that lead to inadequate compensation for the airway-collapsing effect of negative inspiratory pressure.

2. Sleep Deprivation

2.1. Sleep Deprivation and CO_2 Retention

Disordered breathing is commonly associated with hypercapnia, which is followed by sufficient CO_2 retention. This phenomenon leads to various impairments due to dangerous levels of hypercapnia. Acute responses to CO_2 affect breathing primarily via central chemoreceptors [21]. Retention of CO_2 not only contributes to chemoreflex via hypercapnia and acidosis but also serves as a powerful stimulus to increase respiration. Hypoxia potentiates the effects of CO_2, resulting in a stronger ventilatory response. Through various mechanisms, retention of CO_2 can persist during daytime, too [22].

Carbon dioxide retention is related to oxidative stress and increased sympathetic activity with subsequent effects, such as hypertension. Recent evidence has now implicated a role for oxidative stress in sleep and sleep loss [23]. Oxidative stress is defined by increased oxygen reactive species (ROS) production and inability of the cell to alienate them. Prolonged wakefulness/sleep deprivation activates an adaptive stress pathway termed the unfolded protein response, which temporarily guards against the deleterious consequences of reactive oxygen species [21][23]. The elevated sympathetic response also triggers a generalized inflammatory cascade that is associated with the pathophysiology of multiple comorbidities, including insulin resistance, hypertension, diabetes, atherosclerosis, and metabolic syndrome [24]. Epidemiologic studies in adults and children and laboratory studies in young adults indicate that sleep deprivation may be associated with several relevant impairments: decreased glucose tolerance, decreased insulin sensitivity, increased evening concentrations of cortisol, increased levels of ghrelin, decreased levels of leptin, and increased hunger and appetite. Nevertheless, the current epidemic of obesity could be partly attenuated by better sleep regulation [25]. In healthy adults who are chronically sleep restricted, a simple, low-cost intervention, such as sleep extension, is feasible and is associated with improvements in fasting insulin sensitivity [26]. In the matter of inflammatory system, sleep loss triggers signaling pathways in the brain and periphery. The Toll-like receptor 4 (TLR4) activates inflammatory signaling cascades in response to endogenous and pathogen-associated ligands known to be elevated in association with sleep deprivation. TLR4 is therefore a possible mediator of some of the inflammation-related effects of sleep loss [27]. Furthermore, total sleep loss produces significant increases in plasma levels of sTNF-alpha receptor I and IL-6, messengers that connect the nervous, endocrine, and immune systems [28].

2.2. Sleep Deprivation and Exercise: Cognitive Implications

A sleep-deprived brain fails to recuperate neurons, undermining cognitive performance. General cognitive assessment tests unveil the cognitive phenotype of SD, especially in attention and short-term memory, as they anatomically overlap [29][30]. Furthermore, SD, in the context of sleep apnea, affects learning and memory [31][32]. Furthermore, other daytime consequences, such as excessive sleepiness and fatigue, coexist and interact with

cognitive impairment [33]. These are linked with various effects on exercise, including athletic performance, reaction time, accuracy, strength and endurance [34]. Alertness, judgment, and decision making suffer due to SD, shifting motivational behaviors towards sleep-promoting goals [35][36].

Sleep deprivation of 30 to 72 h consecutively does not affect cardiovascular and respiratory responses to exercise of varying intensity or the aerobic and anaerobic performance capability of individuals. Muscle strength and electromechanical responses are also not affected. Time to exhaustion, however, is decreased by sleep deprivation [37]. Research indicates that some maximal physical efforts and gross motor performances can be maintained. Effects on cognitive function consist of slower and less accurate cognitive performance. Reduction in sleep quality and quantity could result in an autonomic nervous system imbalance, simulating symptoms of the overtraining syndrome [38]. The integrity of sleep architecture seems to determine subjective sleep quality and waking performance. The effects of insufficient sleep primarily concern subjective and objective sleepiness as well as attention, whereas performance on higher cognitive functions appears to be better preserved albeit at the cost of increased effort [39]. All in all, sleep deprivation induces a vulnerability in various domains of cognition, leading to overall suboptimal performance.

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