Respiratory Physiology During Sleep

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KEYWORDS

• Ventilatory regulation • Respiratory motoneurons • Hypoxemia • Hypercapnia
• Pneumotaxic center • Apneustic center • Chemoreceptors

KEY POINTS

- Ventilatory regulation is conceptually best understood as a 3-part system consisting of a central controller, sensors, and effectors.
- The effectors of respiration include the respiratory motoneurons and muscles, which are involved in inspiration and expiration.
- Positional changes during sleep (ie, nonupright position) affect the mechanics of breathing significantly.
- Both hypoxemia and hypercapnia can develop during sleep in patients with chronic obstructive pulmonary disease.
- Upper-airway narrowing and excess weight, if present, can increase the mechanical load on the respiratory system as well as breathing work.

The respiratory system provides continuous homeostasis of partial pressures of arterial oxygen (Pa_{O_2}), carbon dioxide (P_{CO_2}), and pH levels during constantly changing physiologic conditions. This elegant system responds promptly to subtle variations in metabolism occurring in both health and disease. During wakefulness, volitional influences can override this automatic control. Modifications occur in the regulation and control of respiration with the onset of sleep. Furthermore, these changes differ significantly with specific sleep stages. These alterations in respiratory control can result in the pathogenesis of sleep-related breathing disorders and limit the usual respiratory compensatory changes to specific disease states. This article reviews the normal physiology of respiration in both awake and sleep states, and discusses the effects of common disease processes and medications on the respiratory physiology of sleep.

CONTROL OF RESPIRATION

Ventilatory regulation is conceptually best understood as a 3-part system consisting of a central controller, sensors, and effectors. *Sensors* primarily include central and peripheral chemoreceptors, vagal pulmonary sensors, and chest-wall and respiratory muscle afferents. Data from these sensors regarding dynamic oxygen and CO_2 levels, lung volumes, and respiratory muscle activity are continuously transmitted to the central controller. Within the medulla, the *central controller* generates an automated rhythm of respiration that is constantly modified in response to an integrated input from the various receptors. The controller modulates motor output from the brainstem to influence the activity of the *effectors*, namely respiratory motoneurons and muscles. These effectors then alter minute ventilation and gas exchange accordingly (**Table 1**).

The medullary ventilatory center consists of neurons in the dorsal respiratory group (DRG)

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Table 1
Control of respiration

Controllers/Effectors	Location	Afferents	Effects
Dorsal Respiratory group	Dorsomedial medulla, ventrolateral to the solitary tract	Upper airways, intra-arterial chemoreceptors, and lung afferents via the 5^{th}, 9^{th} and 10^{th} cranial nerves, respectively	Increased frequency of a ramping pattern of firing during continued inspiration
Ventral Respiratory Group	Ventrolateral medulla	Response to the need for forced expiration occurring during exercise or with increased airways resistance	Respiratory effectors muscles are innervated from the VRG via phrenic, intercostal and abdominal motoneurons.
Pneumotaxic center	Rostral pons consists of the nucleus parabrachialis and the Kolliker-Fuse nucleus.	Pontine input serves to fine tune respiratory patterns and may additionally modulate responses to hypercapnia, hypoxia, and lung inflation	Duration of inspiration and provide tonic input to respiratory pattern generator
Apneustic center	Lower pons	Pneumotaxic center and vagal input	Provide signals that smoothly terminate inspiratory efforts
Central Chemoreceptors	Ventrolateral surface of medulla	Extracellular fluid [H+] concentration	Respond to changes in brain extracellular fluid [H+] concentration
Peripheral Chemoreceptors	Carotid bodies and the aortic bodies	Afferent input to the medulla through the 9^{th} cranial nerve	Respond mainly to PaO_2, but also to changes in $PaCO_2$ and pH
Pulmonary Mechanoreceptors	1. PSRs are located in proximal airway smooth muscles. 2. J-receptors are located in the juxtacapillary area and appear to mediate dyspnea in the setting of pulmonary vascular congestion 3. Bronchial c-fibers		1. Respond to inflation, especially in the setting of hyperinflation 2. Mediate dyspnea in the setting of pulmonary vascular congestion 3. Affect bronchomotor tone and respond to pulmonary inflammation

and the ventral respiratory group (VRG) (**Fig. 1**).[1] Located in the dorsomedial medulla, ventrolateral to the solitary tract, the DRG was previously believed to be the site of rhythmic inspiratory drive. More recent research in animal models suggests that the respiratory rhythm is generated by a group of cells known as the pre-Bötzinger complex, a network of cells surrounding the Bötzinger complex in the ventrolateral medulla.[2]

The medullary centers respond to direct influences from the upper airways, intra-arterial chemoreceptors, and lung afferents via the fifth, ninth and tenth cranial nerves, respectively. The DRG appears to be active primarily during inspiration, with increased frequency of a ramping pattern of firing during continued inspiration. The VRG, located within the ventrolateral medulla, contains both inspiratory and expiratory neurons. VRG output increases in response to the need for forced expiration occurring during exercise or with increased airways resistance. Respiratory effectors muscles are innervated from the VRG via phrenic, intercostal, and abdominal motoneurons.

Poorly understood pontine influences further regulate and coordinate inspiratory and expiratory control. The pneumotaxic center in the rostral

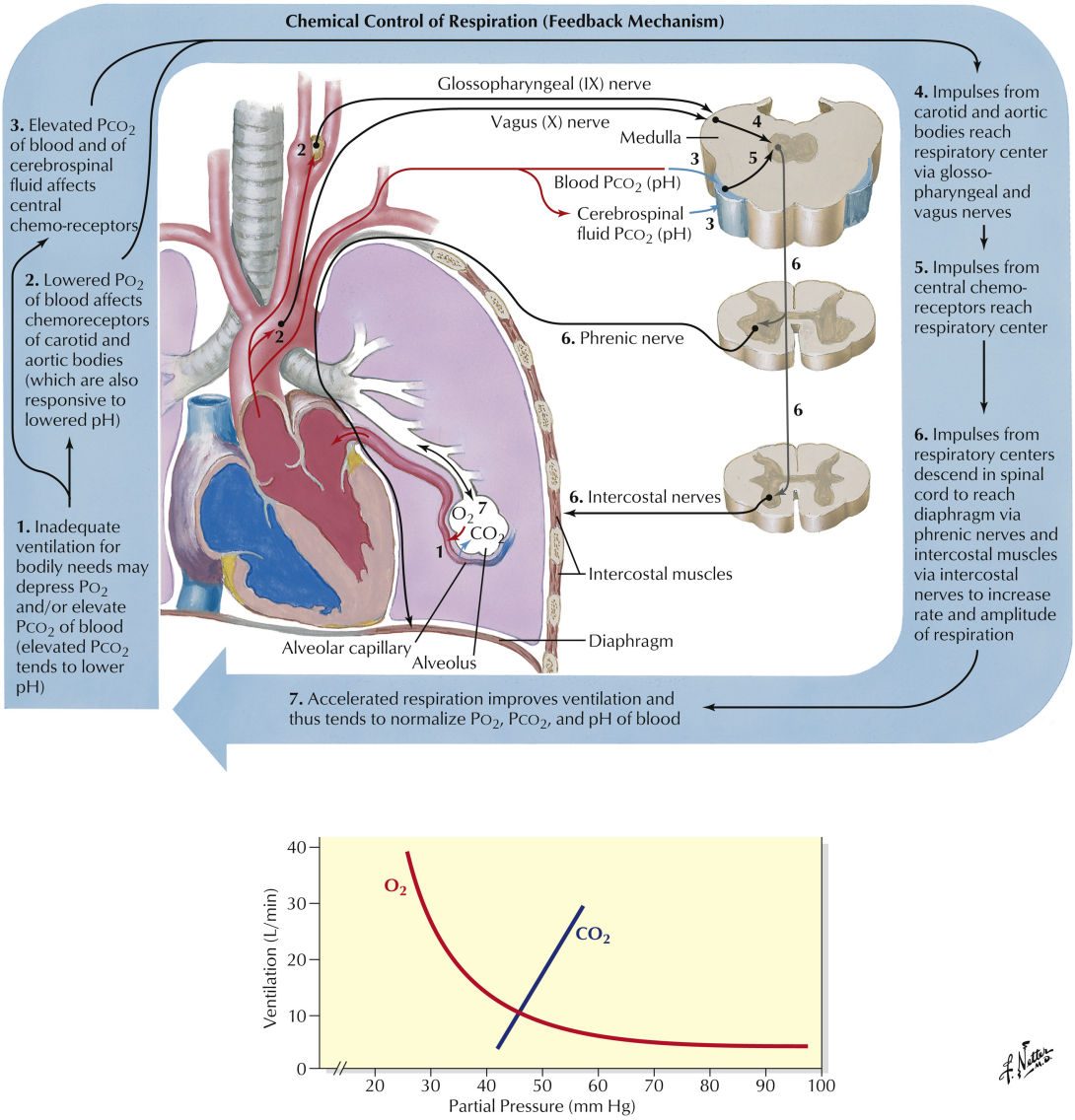

Fig. 1. A simplified diagram of the principal efferent (*left*) and afferent (*right*) respiratory control pathways. A section through the brain, brain stem, and spinal cord is shown (with pertinent respiratory areas indicated by *shading*), as are the central nervous system links with the respiratory apparatus. (Netter illustration from http://www.netterimages.com. © Elsevier Inc. All rights reserved.)

pons consists of the nucleus parabrachialis and the Kolliker-Fuse nucleus. This area appears to primarily influence the duration of inspiration and provide tonic input to respiratory pattern generators. Similarly, the apneustic center, located in the lower pons, functions to provide signals that smoothly terminate inspiratory efforts. The pontine input serves to fine-tune respiratory patterns and may additionally modulate responses to hypercapnia, hypoxia, and lung inflation.[3] The automatic central control of respiration may be influenced and temporarily overridden by volitional control from the cerebral cortex for a variety of activities, such as speech, singing, laughing, intentional and psychogenic alterations of respiration, and breath holding.

Afferent input to the central controllers is mediated primarily by central chemoreceptors, peripheral chemoreceptors, intrapulmonary receptors, and chest-wall/mechanoreceptors. Chemoreceptors provide a direct feedback to central controllers in response to the consequences of altered respiratory efforts. Central chemoreceptors, located primarily within the ventrolateral surface of medulla, respond to changes in brain extracellular fluid $[H^+]$ concentration. Other receptors have been recently identified in the brainstem, hypothalamus, and the cerebellum. These receptors are effectively CO_2 receptors, as central $[H^+]$ concentrations are directly dependent on central P_{CO_2} levels. Central $[H^+]$ may differ significantly from arterial $[H^+]$, as the blood brain barrier prevents polar solute diffusion into the cerebrospinal fluid (CSF). This isolation results in an indirect central response to most peripheral acid-base disturbances mediated through changes in partial pressure of arterial carbon dioxide (Pa_{CO_2}). Central responses to changes in P_{CO_2} levels are also slightly delayed for a few minutes by the location of receptors in the brain only, rather than in peripheral vascular tissues.

Peripheral chemoreceptors include the carotid bodies and the aortic bodies. The carotid bodies, located bilaterally at the bifurcation of the internal and external carotid arteries, are the primary peripheral monitors. These highly vascular structures monitor the status of blood about to be delivered to the brain and provide afferent input to the medulla through the ninth cranial nerve. The carotid bodies respond mainly to Pa_{O_2} but also to changes in Pa_{CO_2} and pH. Of importance, they do not respond to lowered oxygen content from anemia or carbon monoxide (CO) toxicity. Their mechanisms are integrated, and acute hypoxia induces an increased sensitivity to changes in Pa_{CO_2} and acidosis. Conversely, the response to low Pa_{O_2} is markedly attenuated in the setting of low Pa_{CO_2}.

Respiratory responses to increases in central Pa_{CO_2} levels above 28 mm Hg are linear with increases in respiratory rate, tidal volume, and minute ventilation.[4] Peripheral Pa_{CO_2}-driven responses also vary with differences in levels of Pa_{O_2}. By contrast, the slope of the ventilatory response to Pa_{O_2} varies based on sensitivity and threshold. The response to hypoxia is nonlinear and appears to be minimal above Pa_{O_2} levels of 60 mm Hg.

Resultant interactions of chemoreceptor inputs regulate normal Pa_{CO_2} levels in humans to between 37 and 43 mm Hg at sea level. In effect, respiratory control is primarily dependent on Pa_{CO_2} with modulation by other factors. Sensitivity of peripheral receptor responses to hypercapnia and hypoxia also increases with a reduction in arterial pH. Whereas acute hypoxia stimulates increased sensitivity to Pa_{CO_2} peripherally, it might depress central respiratory drive.[5]

Additional feedback to the central controller is transmitted from the lung directly from pulmonary stretch receptors (PSRs) and other afferent pathways. PSRs are located in proximal airway smooth muscles, and respond to inflation, especially in the setting of hyperinflation. PSRs mediate a shortened inspiratory and prolonged expiratory duration. Additional input is also provided by rapidly adapting receptors that sense flow and irritation. J-receptors are located in the juxtacapillary area and appear to mediate dyspnea in the setting of pulmonary vascular congestion. Bronchial c-fibers also affect bronchomotor tone and respond to pulmonary inflammation.

Afferent activity from chest-wall and respiratory muscles additionally influences central controller activity. Feedback information regarding muscle stretch, loading, and fatigue may affect both regulatory and somatosensory responses. Upper-airway receptors promote airway patency by activation of local muscles including the genioglossus. These receptors may also inhibit thoracic inspiratory muscle activity. Thus, afferent activity enables an appropriate response by central regulation.

The effectors of respiration include the respiratory motoneurons and muscles, which are involved in inspiration and expiration. Descending motoneurons include two anatomically separate groups, the corticospinal tracts and the reticulospinal tracts. The phrenic nerve, arising from C3 to C5, innervates the diaphragm as the primary muscle of respiration. Accessory muscles that assist inspiration include the sternocleidomastoid,

intercostal, scalene, and parasternal muscles. These muscles serve to collectively stabilize and expand the ribcage. Abdominal muscles are active in expiration and may also assist with inspiration during exercise, or in the setting of chronic obstructive pulmonary disease (COPD) or diaphragm weakness. Upper-airway muscles active in inspiration include the genioglossus, palatal muscles, pharyngeal constrictors, and muscles that pull the hyoid anteriorly. Collectively, these muscle groups and motoneurons effect responses generated from central control centers based on input from multiple receptors. This elegant system operates through the complex coordination and interaction of these subcomponents to continuously adapt to changing metabolic needs.

RESPIRATION DURING SLEEP

Regulation of respiration differs significantly between sleep and wakefulness. With sleep onset, important changes occur in the various processes that regulate respiratory control. Behavioral influences on respiration terminate with cessation of input from the waking state. Positional changes typically associated with sleep also result in significant alterations in respiratory mechanics. Sleep is a dynamic physiologic state with further varying effects on respiration seen in specific sleep stages, particularly in rapid eye movement (REM) in comparison with non–rapid eye movement (NREM) sleep.

Minute ventilation falls with the onset of sleep in response to decreased metabolism and decreased chemosensitivity to oxygen (O_2) and CO_2.[6,7] Ventilation during NREM sleep demonstrates an inherently more regular respiratory pattern than wakeful breathing, without significant reductions in mean frequencies. The nadir of minute ventilation in NREM sleep occurs during NREM stage 3 (N3) sleep (ie, slow-wave sleep), primarily as a result of reductions in tidal volume. As a result, end-tidal carbon dioxide ($ETCO_2$) during NREM sleep increases by 1 to 2 torr compared with the waking state.[8] During REM sleep, respiratory patterns and control vary more significantly. REM sleep respiration is typically characterized by an increased frequency and a reduced regularity. Tidal volume is reduced further in comparison with that of NREM sleep, resulting in the lowest level of normal minute ventilation. Accordingly, $ETCO_2$ increases of an additional 1 to 2 torr, often associated with a reduction in oxygen saturation, are seen with the onset of REM sleep. Metabolic reductions seen in sleep demonstrate sleep-stage variations with increased rates in REM compared to NREM sleep.

Ventilatory responses to CO_2 and O_2 differ in sleep in comparison with wakefulness, with important distinctions between REM and NREM sleep. The linear increases in ventilatory responses to $Paco_2$ persist during NREM sleep, albeit with a reduced slope compared to wakefulness. These changes appear more evident in males than in females, who demonstrate reduced CO_2 responses while awake with less apparent reductions during NREM sleep.[9] In addition, the threshold of the response to CO_2 is shifted upward, with a higher $ETCO_2$ required to drive respiration in sleep. Responses to increases in $ETCO_2$ are further reduced during REM sleep. Respiratory output in sleep, particularly NREM sleep, is significantly reduced in response to hypocapnia. Respiratory responses to hypoxia appear attenuated during NREM sleep as well, without significant gender-related differences; hypoxia-induced drive is reduced further in REM sleep.

Of importance, both hypoxia and hypercapnia may trigger arousals from sleep, resulting in a return to the more tightly regulated ventilatory control associated with wakefulness. Arousal thresholds for hypercapnia range between 56 and 65 torr, and vary among the different sleep stages. The threshold for arousal in response to hypoxia is more variable and seems less reliable. Severe oxygen desaturations in some individuals do not uniformly result in arousals.

In addition to the changes in controller responses during sleep, the effectors also demonstrate significant sleep-related functional variation. Of the various effectors of respiration, the upper-airway muscles appear to be the most dramatically affected by changes occurring with sleep. As described previously, these muscles function to maintain patency and prevent collapse of the upper airways during inspiration. These muscles primarily include the genioglossus, tensor palatini, and the sternohyoid, which are active during inspiration during wakefulness and are reduced activity during sleep. The genioglossus responds briskly to increases in $Paco_2$ during wakefulness; this response markedly diminishes during sleep. Indeed, the modest increase in $Paco_2$ seen with sleep onset does not appear to produce a significant increase in genioglossus activity. Human studies of upper-airway responses during REM sleep are limited, with most studies demonstrating that muscle activity is eliminated by generalized REM-sleep–associated skeletal muscle atonia; this effect is most prominent during phasic REM sleep. Upper-airway responses to hypoxia generally parallel the responses to hypercapnia. Studies consistently demonstrate more striking sleep-related reductions in muscle activity of the upper

airways than of the diaphragm or accessory muscles of respiration.

Positional changes during sleep (ie, nonupright position) affect the mechanics of breathing significantly. Anatomic structures of the upper airways may be more predisposed to collapse, particularly with the concurrent reductions in upper-airway muscle tone. Redundant soft-tissue–related airway compromise and retroglossal narrowing of the upper airways may be significantly increased in the supine position. Subtle increases in vascular congestion of the airways in response to positional changes may also augment airways resistance. In the supine position, the contribution of chest-wall expansion does not exceed the effect of increased abdominal distention, and functional residual capacity is thus reduced. Intercostal muscle activity is significantly increased during NREM sleep compared with wakefulness, and results in proportional increases in the contribution of the chest wall to respiration. With REM-sleep–associated atonia, skeletal muscles associated with respiration are significantly impaired and ventilation is accomplished by the diaphragm alone. Chest-wall compliance is increased with this decreased intercostal tone, and paradoxic collapse of the chest during inspiration may occur. REM sleep is, therefore, associated with relative hypoventilation from both reduced respiratory mechanical capacities and decreased sensitivity of the respiratory drive to hypercapnia and hypoxia.

There are significant differences in the responses to increased airways resistance between sleep and wakefulness. During the waking state, increased ventilatory responses to both elastic loading and airways-resistance loading are present; this prompt compensation maintains appropriate ventilation and prevents development of hypercapnia. Load compensation is significantly reduced during sleep. During NREM sleep, moderate levels of elastic loading (18 cm H_2O/L) results in decreases in minute ventilation and increases in $ETCO_2$.[10] Ventilatory effort is then increased without normalization back to preload levels of ventilation. Lower levels of loading (12 cm H_2O/L) result in significant ventilatory changes over a few breaths resulting in full compensation without arousals.[11] Waking responses to resistance loads include an increase in the duration of respiration, an increase in tidal volume, and a decrease in respiratory rate. Minute ventilation is reduced. Responses to increased resistance during NREM sleep demonstrate a different pattern of reduced tidal volumes and increased respiratory rates, and no significant change in inspiratory time ratio. Reductions in minute ventilation in response to resistance loading are more evident during NREM sleep than in waking states.

MEDICATIONS AND BREATHING DURING SLEEP

There are several drugs that can impair respiration during sleep, including alcohol, anesthetics, narcotics, and sedative hypnotics. Conversely, some agents, such as almitrine, acetazolamide, some antidepressants, nicotine, progesterone, theophylline, and thyroid hormones, can stimulate breathing during sleep.

Drugs that can Impair Respiration

Alcohol, when ingested while awake, can lead to reduction of both hypoxic and hypercapnic ventilatory responses. Irregular breathing with transient apneas can develop. When ingested close to bedtime, it depresses the upper-airway muscle tone and may precipitate obstructive sleep apnea, or aggravate a preexisting one; the latter is generally most evident during the first 1 to 3 hours of sleep when alcohol levels are at their highest. Hypercapnia and significant hypoxemia can occur with severe intoxication. The risk of sleep-disordered breathing remains elevated in some abstinent alcoholics following long-term habitual alcohol use, possibly caused by residual upper-airway muscle dysfunction or damage to the central nervous system.[12]

Anesthetics can impair the hypoxic ventilatory response, decrease lung volumes, and decrease upper-airway muscle tone, all of which can lead to significant deterioration of respiratory status in patients with an existing obstructive sleep apnea or advanced COPD.[13]

Narcotics are potent respiratory depressants which, when ingested at bedtime, can diminish upper-airway muscle tone, give rise to hypoxemia, and decrease the hypercapnic ventilatory response.[14]

Sedative hypnotics (eg, benzodiazepines or barbiturates) are mild respiratory depressants. Depression of breathing is be more pronounced during coingestion with other central nervous system depressants, such as alcohol, or in individuals with an underlying respiratory impairment (eg, severe COPD, neuromuscular weakness, or hypoventilation syndromes). Both agents can decrease upper-airway muscle activity and worsen sleep-disordered breathing; they have variable effects on central apneas. Whereas they may increase the frequency and prolong the duration of hypercapnic forms of central apneas (eg, neuromuscular disorders), sedative hypnotics may be beneficial for patients with certain types of

nonhypercapnic form of central apnea, such as those that occur periodically at sleep onset.[15]

Drugs that can Stimulate Respiration

Almitrine is a respiratory stimulant that enhances peripheral chemoreceptor sensitivity. Although it can potentially improve nighttime oxygenation, this effect is generally mild and inconsistent.[16,17]

Acetazolamide administration induces metabolic acidosis from bicarbonate diuresis; this, in turn, can stimulate respiration.[18] Although it is beneficial for the treatment of high-altitude–related periodic breathing, its usefulness for patients with obstructive sleep apnea is limited, inconsistent, and unpredictable.

Certain *antidepressants*, such as protriptyline, a tricyclic antidepressant, and fluoxetine, a selective serotonin reuptake inhibitor, can decrease the frequency and duration of apneas-hypopneas by increasing upper-airway muscle tone and decreasing percentage of REM sleep, during which sleep-disordered breathing tends to be worse than during NREM sleep.[19]

Nicotine is a respiratory stimulant. Notwithstanding its effect of enhancing upper-airway muscle activity, it has no role in the treatment of obstructive sleep apnea.[20]

Progesterone can increase hypoxic and hypercapnic respiratory responses as well as minute ventilation; it can improve ventilation in patients with obesity-hypoventilation syndrome and decrease apnea-hypopneas in post-menopausal women.[21,22]

Theophylline can reverse the bronchospasm of nocturnal asthma, increase sleep-related oxygen saturation in patients with COPD, and improve Cheyne-Stokes crescendo-decrescendo periodic breathing.[23]

SLEEP PHYSIOLOGY AND RESPIRATORY DISORDERS

Nocturnal Asthma

Patients with nocturnal asthma often present with repetitive arousals and awakenings during the night accompanied by complaints of breathlessness, coughing, and wheezing secondary to bronchoconstriction.[24] A variety of factors may contribute to the worsening bronchial reactivity that occurs during sleep, including a relative increase in parasympathetic tone and decrease in nonadrenergic, noncholinergic discharge; comorbid gastroesophageal reflux or obstructive sleep apnea; circadian changes in levels of endogenous hormones (eg, catecholamines, cortisol, or histamine); or reduction of lung volumes and airway size. If severe, nocturnal asthma may give rise to significant hypoxemia.

Chronic Obstructive Pulmonary Disease

Both hypoxemia and hypercapnia can develop during sleep in patients with COPD. Respiratory impairment is more severe during REM sleep than during NREM sleep. Hypoxemia, the extent of which is related to the percentage of REM sleep in relation to total sleep time as well as daytime levels of Pa_{CO_2}, Pa_{O_2}, and oxygen saturation (Sa_{O_2}), can result from hypoventilation, ventilation/perfusion mismatching, and/or reduction of lung volume (eg, functional residual capacity). COPD can also occur concurrently with obstructive sleep apnea; referred to as the overlap syndrome; this is associated with worse hypoxemia and greater pulmonary artery pressures compared with patients with isolated COPD.[25,26]

Restrictive Lung Disease

Sleep of patients with *interstitial lung disease* is often accompanied by frequent arousals. Sleep disruption appears to be more pronounced in those with nocturnal oxygen desaturation, the extent of which is influenced by levels of awake Pa_{O_2}, lung compliance, and age of the patient.[27] The increase in respiratory drive that is present in patients with interstitial lung disease may reduce the prevalence of apneas-hypopneas.

Kyphoscoliosis, by blunting ventilatory drive due to a greater mechanical load of displacing the thoracic cage, can lead to a number of sleep-related breathing disorders, such as central and obstructive apnea-hypopneas, periodic breathing, hypercapnia and hypoxemia.

Obesity is associated with increased work of breathing and greater metabolic demands. Lower functional capacity, less efficient respiratory muscles, and increased mass loading of the thoracic cage (ie, decrease in compliance) can all give rise to hypoxemia, which is generally worse during sleep than during wakefulness because of the lower functional residual capacity of a supine position, relative hypoventilation, and the development of sleep-related apneas-hypopneas. If severe, obesity can lead to the development of the obesity hypoventilation syndrome with its associated reductions in hypoxic and hypercapnic ventilatory drives.

Pregnancy, like obesity, can reduce lung volumes (eg, functional residual capacity and residual volume), especially during the third trimester when weight gain and uterine displacement are maximal. Pregnancy may also be associated with an increase in the prevalence of snoring, owing to structural changes and increased compliance of the upper airways. However, apnea-hypopnea frequency and sleep-related hypoxemia tend to be less affected

because of the augmented ventilatory drive produced by higher levels of progesterone.

Neuromuscular Disorders

Patients with *Duchene muscular dystrophy* can develop hypoventilation and oxygen desaturation during sleep. *Myotonic dystrophy* can involve the pharyngolaryngeal and diaphragm muscles; obstructive and central apneas-hypopneas, hypoventilation, and oxygen desaturation occurring during sleep has been described. *Poliomyelitis* is often associated with a defective central control of respiration and can give rise to apneas and hypopneas during sleep. *Diaphragm paralysis*, especially if bilateral, can lead to increases in $Paco_2$ and reductions in Pao_2; these derangements in arterial blood gases are generally worse during REM sleep in comparison with waking and NREM sleep, because of the REM-sleep–related inhibition of the intercostal and accessory respiratory muscles.

Obstructive Sleep Apnea

Upper-airway narrowing and excess weight, if present, can increase the mechanical load on the respiratory system as well as breathing work. Oxygen desaturation can result from repetitive episodes of apneas-hypopneas, the latter being more common during REM sleep than during NREM sleep. Episodes of oxygen desaturation, therefore, tend to more frequent and last longer during REM sleep. Hypoxemia and, to lesser extent, hypercapnia can also arise from the reduction in lung volume related to the supine sleep position and is made worse by comorbid obesity resulting in augmented respiratory muscle activity generated to compensate for the diminished or absent airflow secondary to upper-airway narrowing or collapse (ie, Müller maneuver).

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