REVIEW ARTICLE

Respiratory Failure and Sleep

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Introduction

Respiratory failure is a commonly encountered pathological entity. It is quite often seen that respiratory failure first manifests itself during sleep, much before it occurs during wakefulness. Also, sleep is impacted adversely by respiratory failure. This article attempts to summarize the interaction of respiratory failure and the sleep state.

Effects of sleep on respiration in normal subjects

The respiratory center is under the influence of chemical inputs from chemoreceptors responding to paO_2, $paCO_2$ and pH. It is also influenced by mechanoreceptors in the airway, lungs and chest wall as well as behavioral inputs from cortical centers via the reticular activating system [1]. Sleep onset is associated with a diminished responsiveness of the respiratory center to chemical and mechanical inputs, more so in REM sleep. The ventilatory responsiveness to hypoxia and hypercapnia is reduced and responsiveness of respiratory muscles to the respiratory center outputs is diminished (diaphragm is impacted less than the accessory muscles of respiration) [2] [3]. In adult men the hypoxic ventilatory response in NREM sleep is two-third of that in wakefulness, falling to one-third that level during REM sleep. In adult women, there is no change in hypoxic response between wakefulness and NREM but the response in REM is half that in other stages. The hypoxic ventilatory response in REM sleep is about 0.4 LPM/ percentage fall in SaO_2 [4].

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The hypercapneic ventilatory response in adults drops during NREM to about half the level in wakefulness and falls further during REM to one-third the level of wakefulness. Some gender differences, however, may exist [4]. During NREM sleep, breathing is regular in amplitude and frequency [5],[6]. A decrease in minute-ventilation due to a reduction in tidal volume is associated with an increase in end-tidal PCO_2 ($P_{ET}CO_2$) [7]. Part of this hypoventilation is due to a lower metabolic rate as VO_2 and VCO_2 diminish during sleep [8].

Both tidal volume and frequency of breathing are more variable in REM that in NREM. Minute ventilation is lower in phasic REM than in tonic REM sleep. No clinically significant deterioration in gas exchange occurs in normal subjects but significant hypoxemia is often seen in REM sleep in patients with respiratory insufficiency [9,10].

Airway resistance

Upper airway resistance increases during sleep as compared to wakefulness [11]. Lower airway patency may be compromised. Nocturnal broncho-constriction is seen in 50% asthmatics compared to only 8% amongst normal subjects [12]. Ventilatory compensation to resistive loading occurs during NREM sleep, but whether this compensation is as marked as during wakefulness is not clear. During REM phase, ventilatory compensation to resistive loading is markedly reduced. Added inspiratory resistance produces a similar percentage of increase in arousal frequency in stages 2, 3 and 4 NREM and REM sleep. Arousal from sleep following airway occlusion is far more rapid in REM than NREM sleep.

Arousal responses

Hypoxia is a poor stimulus to arousal in normal subjects but arousal sensitivity to hypoxia is reduced in REM sleep in obstructive sleep apnea (OSA). Hypercapnia

produces arousal at variable levels but awakens most subjects before the E_TCO_2 has risen by 15 mmHg above the level seen during wakefulness [4].

Rib cage and abdominal contribution to breathing

Breathing is predominantly a function of diaphragmatic contraction in supine position during the resting state[13]. An increased ribcage contribution is seen during NREM (as evidenced by rise in EMG activity) with no change in diaphragmatic activity [14]. Expansion of ribcage improves mechanical efficiency of diaphragmatic contraction (length and/or radius of curvature) leading to increase in diaphragmatic pressure (Pdi) [15,37]. During REM sleep, there is no ribcage contribution to breathing due to marked reduction in the activity of intercostals muscles. Also, during REM sleep, the diaphragmatic EMG is substantially increased while Pdi falls (reduced diaphragmatic efficiency). This change becomes clinically significant in conditions like COPD and diaphragmatic weakness [16],[17].

A modest fall in FRC takes place in healthy adults in NREM and REM [18]. This may result in a significant V/Q mismatch in chronic lung disease [19]. The reduction in FRC is mainly attributable to respiratory muscle hypotonia, a cephalad displacement of diaphragm and a decrease in lung compliance.

Neuromuscular changes in sleep

A marked loss of tonic activity in tongue, pharyngeal, laryngeal and intercostal muscles takes place in REM sleep. There is supra-spinal inhibition of α-motoneurones (and to a lesser extent γ-motoneurones) in addition to pre-synaptic inhibition of afferent terminals from muscle spindles. The diaphragm escapes this reduction during REM as it is driven by α-motoneurones and has far fewer spindles than the intercostals muscles.[1]

In summary, there is an overall trend towards reduction in ventilation during sleep. There is no change in the arterial blood gas values in normal subjects. In those patients who have an underlying respiratory disease & daytime hypoxemia, life-threatening hypoxemia may occur as the changes take place on the steep part of the oxygen dissociation curve.[20] The overall effects of sleep on respiration are depicted in Figure 1.

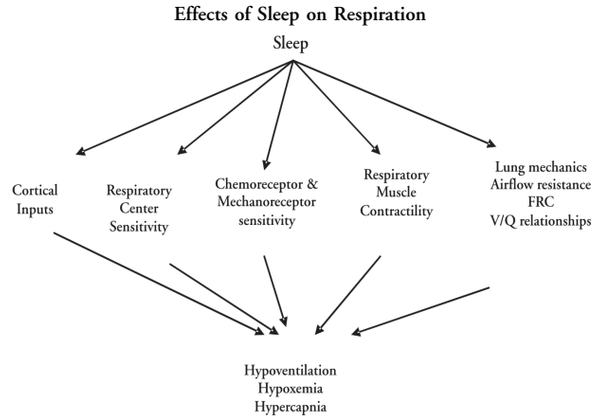

Figure 1: Overall effects of sleep on respiration

Effects of sleep on respiration in disease states:

Nocturnal oxygen desaturation in COPD [21-26]

There are four basic mechanisms that result into nocturnal oxygen desaturation in patients with COPD.

a. Hypoventilation occurs due to the loss of contribution of accessory muscles to breathing; particularly from the ribcage, consequent to loss of muscle tone during REM sleep.

b. Hypoxemic patients show a proportionately greater fall in SaO2 with hypoventilation than normoxemic individuals as changes occur in the steep portion of the oxygen dissociation curve.

c. A larger fall in PaO2 occurs among major desaturators as compared to minor desaturators, in conjunction with similar rise in P tc CO2 in both patient groups. This suggests that V/Q mismatch also plays a role in addition to simple hypoventilation in such patients in bringing about nocturnal desaturation during sleep.

d. There is co-existing sleep apnoea (overlap syndrome) in 10-15% of COPD patients.

Unlike patients with Interstitial Lung Disease, COPD patients desaturate more than twice as much during sleep than during exercise. The demand for coronary blood flow during episodes of nocturnal hypoxia can be transiently as great as during maximal exercise. Nocturnal desaturation, even in the absence of significant awake hypoxemia, can cause pulmonary arterial hypertension.[27]

Nocturnal asthma

There are several circadian influences that bring about changes during sleep in nocturnal asthma. Irrespective of sleep stage, pulmonary function falls and airway resistance rises proportionately throughout night.[28,29] Circadian rhythm in circulating hormones and mediators, like decrease in catecholamines and increase in histamine, predispose to nocturnal broncho-constriction.[19] Cholinergic tone also increases at night, thus leading to bronchoconstriction. Other factors like gastro-esophageal reflux, airway cooling, snoring and sleep apnea, and allergens in bed also contribute to desaturation in nocturnal asthma.[30]

Central hypoventilation syndrome

Initially, this condition often presents during respiratory infection. It occurs perhaps due to abnormalities in brain-stem and peripheral chemoreceptors resulting in inadequate afferent input to brainstem respiratory center. There is an impaired response to hypoxia and hypercapnia. It often accompanies stroke, acoustic neuroma & neurofibrormatosis.[31]

Neurological & neuromuscular disorders

This group comprises disorders of the brain stem (stroke) and peripheral nervous system. Stroke, poliomyelitis, multiple sclerosis, traumatic paralysis and motor neurone disease are some of the examples. Hypoventilation, occurring in the above-mentioned disease states, is aggravated by sleep. Sleep related hypoxemia in muscular dystrophy occurs predominantly in REM sleep and mainly due to the loss of accessory muscle contribution to breathing in the setting of diaphragmatic weakness. Sleep apnea may co-exist in obese patients.[32]

Thoracic cage disorders

Conditions like kyphoscoliosis and thoracoplasty are included in this group of disorders. Desaturation is most pronounced during REM sleep Causes of respiratory insufficiency include V/Q inequality, alveolar hypoventilation, increased work of breathing and a reduction in surface area for gas exchange[20].

Obstructive sleep apnea (OSA)

OSA, as is well known, occurs in the anatomically small or collapsible upper airway. During wakefulness, the neuromuscular compensatory system increases the activity of pharyngeal dilator muscles. This tonic pre-motor input (plus neuro-muscular compensation) and augmented reflex driven muscle activity is lost at sleep onset; thus leading to pharyngeal collapse.[33]

The influence of chronic disorders on control of breathing is outlined in Figure 2.

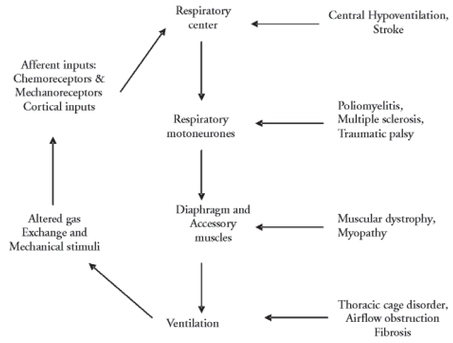

Figure 2: Influence of chronic disorders on control of breathing

Breathing during sleep in patients with nocturnal desaturation

Hypoventilation, most pronounced during REM sleep, is found in sleep related desturators irrespective of underlying disease. A reduction in tidal volume is the major cause of hypoventilation in such patients. In one report, a reduction in minute ventilation (V_E) persisted despite correction of upper airway obstruction by nCPAP, thus pointing towards a reduction in postural neural drive as one of the underlying causes.[34] The mechanism by which nocturnal desaturation in sleep is gradually perpetuated in a twenty-four hours state is depicted in the flow-chart outlined in Figure-3.

Arousal protects against dangerous hypo-ventilation & respiratory failure during sleep → arousal also leads to sleep disruption → sleep disruption results in daytime hypersomnolence → **multiple episodes of microsleep & macrosleep during day** → advanced disease is associated with multiple sleep-wake-sleep phenomena throughout day & night → sleep no longer remains nocturnal event but is fragmented into a 24 hr sleep-wake phenomenon → respiratory failure thus becomes a 24 hour state

Figure 3: Mechanism by which nocturnal desaturation in sleep is gradually perpetuated in a twenty-four hours state

An improvement in daytime respiratory muscle function in such patients can be brought about by non-invasive ventilation (NIV) mainly due to the following factors.[35]

a. NIV rests chronically fatigued respiratory muscles

b. NIV rests chronically fatigued respiratory muscles thus diminishing daytime work of breathing

c. NIV prevents nocturnal hypoventilation thereby reducing arousals that lead to sleep fragmentation and excessive daytime sleepiness (EDS)

d. NIV lowers respiratory center "set point" for CO2 by ameliorating chronic hypoventilation.

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