PERSPECTIVE

Effect of sleep on breathing – Why recurrent apneas are only seen during sleep

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In the past four decades, respiration during sleep has intrigued clinicians and basic scientists, probably owing to a better recognition of the clinical significance of sleep apnea syndrome. Sleep apnea syndrome is characterized by repetitive episodes of cessation of airflow at the nose and mouth lasting at least 10 seconds during sleep in association with one or more of the following symptoms: habitual snoring, restless sleep, morning headache, excessive daytime sleepiness and intellectual impairment (1). Although the phenomenon of sleep disordered breathing (SDB) has long been noticed (2,3), the first polysomnographic recording of frequent respiratory pauses during sleep in humans dates back to 1965 (4).

As the term suggests, sleep apnea involves two control systems, i.e., those controlling consciousness and respiration. What interests us is that recurrent apneas occur predominantly, if not entirely, during sleep. This phenomenon raised a fundamental question: how the sleeping state itself can permit - or even provoke - apneas in an otherwise healthy respiratory system, which is precise and mechanically efficient in wakefulness?

It has long been known that sleep generally depresses respiration, circulation and other vital activity mainly due to the reduced metabolic rate and sympathetic activity. However, SDB reveals more complex effects of sleep on ventilation than merely depression. In general, sleep may disturb breathing via the following mechanisms: (I) functional changes in the central nervous system, such as the loss of the wakefulness stimulus; (II) the state related fluctuation of excitatory and inhibitory impact on respiration; (III) decline of skeletal muscle tone; (IV) attenuation of ventilatory response to chemical and mechanical loads; and (V) reduction in functional residual capacity (FRC) and mismatch of ventilation/blood ($\dot{V}/\dot{Q}$) ratio related to recumbent position. The follow discussion will examine the implications of the aforementioned factors on breathing stability and respiratory pattern during sleep.

Loss of wakefulness drive to breathing control

Like all oscillators, the respiratory rhythm generator requires tonic inputs to keep oscillations between inspiration and expiration, which is mainly provided by chemical drive and wakefulness stimulus. The wakefulness stimulus, a non-specific drive, might arise from suprapontine regions or the reticular activating system (5). During wakefulness, the tonic input from the wakefulness stimulus to the respiratory center is sufficient to compensate for reductions in chemical stimuli and sufficient to overcome other inhibitory factors, so that apnea rarely occurs in awake humans even in the presence of substantial hypocapnia such as vigorous and long-lasting singing or crying. In contrast, a sleep-related loss of the wakefulness stimulus leaves ventilation under metabolic control, making the respiration control system very sensitive to any transient reduction of $PaCO_2$ and predisposing those sleepers with low CO_2 reserve or high upper airway collapsibility to apnea. (6,7). Furthermore, the loss of wakefulness stimulus, coupled with the reduced respiratory muscular tone during sleep may exacerbate alveolar hypoventilation in some diseases, making marginal ventilation during wakefulness become inadequate during sleep. Hence, the withdrawal of the wakefulness stimulus has the most important impact on ventilatory control and probably plays a critical role in the pathogenesis of SDB (5).

Neurophysiologic changes with sleep state modifies respiration

Sleep is not a homogeneous state and can be subdivided into two distinct neurophysiological states based on behavioral and electrographic characteristics: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. Dynamic changes of

sleep state with alterations in the degree of alertness are also potential factors in destabilizing breathing.

Slow wave NREM sleep is featured by the stability of autonomic regulation with an absent waking neural drive and a quiescent behavioral system (8). Therefore, respiration is relatively stable in slow wave sleep (9). In contrast, light sleep stages, especially stage I sleep and transition periods are characterized by unstable autonomic regulation. The alpha/theta-state-specific alterations may lead to ventilatory instability at or even before sleep onset (10,11).

Rapid eye movement sleep is constituent of tonic motor inhibition and bursts of phasic events. In the tonic phase, breathing is still under chemical-metabolic control as it is in NREM sleep. However, in the phasic phase, the breathing pattern is mainly affected by the behavioral system through the REM sleep processes, fluctuating with ponto-geniculo-occipital (PGO) driven excitatory and inhibitory influences (5,12). Although breathing is often irregular in REM sleep, central apneas are rarely seen in this stage. That is probably because the apneic threshold for hypocapnia is masked by non-chemical PGO-related inputs during REM sleep (13). Indeed, periodic breathing in REM sleep is mainly composed of obstructive apneas and hypopneas. Recent research suggests that REM-related withdrawal of excitatory noradrenergic and serotonergic inputs to upper airway (UAW) motoneurons may reduce pharyngeal muscle activity, predisposing to OSA (14).

Moreover, sleep is fragmented by arousals, awakenings and state-transitions. All of these events may affect breathing stability (15). Arousal, a state of heightened brain stem activity, is a brief awakening (3-15 seconds) from sleep induced by various external or internal influences, including chemical as well as mechanical stimuli arising from respiratory effort. This protective mechanism is often triggered by apneas and hypopneas, helping to terminate them. On other hand, the transition from sleep to arousal provides excitatory drives to the respiratory system, enhancing chemoresponsiveness and causing a surge of ventilation and transient hypocapnea (16). These changes, in turn, tend to destabilize breathing. Consequently, arousal often plays dual roles in SDB as it terminates the existing apnea, but also triggers new ones.

It appears paradoxical that sleep predisposes patients to SDB via removal of the wakefulness stimulus, while arousal facilitates SDB although it restores the wakefulness stimulus. The explanation for this paradox lies in the transient nature of arousals and the short-lived nature of this state-related excitatory respiratory drive (16). When transient arousal yields to sleep, the quick abolition of excitatory input makes the respiratory control system very sensitive to the transient hypocapnia that results from prior arousal-provoked hyperpnea. This effect is exaggerated when arousal occurs at the end of apneas or hypopneas. The strong chemical stimuli built up during apnea,

plus the sudden release of upper airway resistance (R_{UAW}), enhances the arousal-provoked hyperpnea, driving $PaCO_2$ even lower. Therefore, frequent transitions between sleep and arousal/wakefulness exaggerates breathing instability.

What is more, ventilation and diaphragm activities show some dynamic changes throughout the night, and ventilatory response to CO_2 is subject to modulation by the circadian rhythm (17). Further investigation is needed to figure out how the circadian rhythm and sleep state interact to affect breathing when one is superimposed on the other.

Reduction of respiratory muscle tone

There is usually a progressive fall in the activity of skeletal muscles with both respiratory and nonrespiratory functions from wakefulness to NREM to REM sleep. The motor neurons are only slightly hyperpolarized during NREM sleep, but this change becomes more substantial during REM sleep. Therefore, a marked motor inhibition prevails during REM sleep. Likewise, postsynaptic inhibition occurs during REM sleep, which is also responsible for the REM-related hypotonia/atonia of the somatic musculature (18). More interestingly, the influence of sleep on the chest wall muscles and UAW muscles does not appear to be uniform or parallel. The UAW dilator muscle activity demonstrates a progressive depression during the night. As a result, RUAW undergoes a small increase in the early sleep period but continues to rise with the deepening of sleep (19). In contrast, the principal inspiratory muscles are relatively spared from the direct inhibitory influence of NREM sleep (20). For instance, diaphragm electromyographic (EMGdi) activity is only reduced at the onset of sleep with the transition from alpha to theta (19), and then gradually recovers to the same or an even slightly higher level than the resting awake values during stable NREM (21). The recruitment of the chest wall muscle activity as sleep progresses may at least partly result from the enhanced chemosensory stimulation of CO_2 retention in the face of increased R_{UAW}. However, EMGdi often undergoes intermittent and brief inhibition and fractionation coincident with PGO waves or eye movements (22), causing a reduction of airflow during REM sleep.

Reduced protective reflexes and compensatory mechanisms

The sleep state imposes a variety of loads on the respiratory system, for instance, the increased airflow resistance and increased $PaCO_2$. Unfortunately, the ability of the respiratory control system to compensate for chemical and/or mechanical loads declines, and the response thresholds for many modalities of stimulation increases during sleep (23). Among them, the

reduction of protective reflexes involving pharyngeal muscle dilators has more clinical significance because it may cause pharyngeal collapse. Moreover, the low sympathetic neural tone in sleep may desensitize the carotid bodies, reducing the chemosensitivity to CO_2 and hypoxia. The reduced compensation ability for these spontaneously occurring chemical/mechanical loads, in turn, permits UAW occlusion and CO_2 retention.

Position related alterations in lung function

As one assumes the supine position for sleep, the lung volume, especially FRC, decreases slightly in healthy humans, but largely in obese individuals and asthma patients (24), probably because of diaphragm cephalad displacement resulting from the abdomen content pressure. During deep sleep and REM sleep, respiratory muscle hypotonia, relative hypoventilation and the low lung compliance will further reduce end-expiratory lung volume. These postural related and sleep-associated reductions in FRC would decrease pharyngeal airway caliber and predispose the UAW to collapse (25). Moreover, distribution of air and blood within the lungs changes in the supine posture, worsening the V/Q mismatch, probably due to atelectasis and less uniform distribution of air and blood in the lung bases. This effect is more significant in obese subjects. The reduced gas exchange and gas storage in supine position likely disturb breathing by increasing the plant gain (i.e. $PaCO_2$ response to alveolar ventilation) and contribute to the rapid fall in SaO_2 during apneas in obese patients.

The combination and interaction of the above changes during sleep introduce the following alterations in ventilatory parameters: (I) UAW impedance and total airway resistance could increase more than twofold compared to the resting wakefulness (26) whereas no alteration of the elastic properties of the respiratory apparatus occurs. If these normal changes in UAW mechanics are exaggerated by any other factors, then the airflow limitation, snoring or OSA may occur; (II) A 10-15% of reduction in minute ventilation, mainly through a decrease in tidal volume as a result of respiratory muscle hypotonia, often causes an increase in $PaCO_2$ and slight oxygen desaturation, regardless of the reduction in the metabolic rate with sleep state (18); (III) under the background of a relatively low ventilation, there are several sighs (large tidal volume) sporadically occurring during sleep. These sighs help to open collapsed alveoli but often trigger periodic breathing through the post-hyperventilation hypocapnia (9); (IV) ventilatory response to CO_2 is attenuated during NREM and tonic REM sleep, which allows $PaCO_2$ to rise to a small extent during sleep.

In conclusion, sleep has a significant impact on breathing mainly through withdrawal of the wakefulness stimulus; alteration of chemical/non-chemical responses; and reduction of muscular tone, lung volumes, and metabolic rate. Even so, the effect of sleep on breathing is usually of minor physiological consequences in most healthy human subjects, and only predisposes those with compromised UAW patency or inappropriate ventilatory control systems to SDB (7).

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