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Lecture 5

Ventilation control

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Control of ventilation occurs at different levels of the respiratory system through a negative feedback system that allows precise regulation of levels of arterial carbon dioxide and oxygen. Mechanisms for ventilatory instability leading to sleep-disordered breathing include changes in the genesis of respiratory rhythm and chemoresponsiveness to hypoxia and hypercapnia, cerebrovascular reactivity, abnormal chest wall and airway reflexes, and sleep state oscillations. One can potentially stabilize breathing during sleep and treat sleep-disordered breathing by identifying one or more of these pathophysiological mechanisms. This review describes the current concepts in ventilatory control that pertain to breathing instability during wakefulness and sleep, for alternative therapies to stabilize breathing during sleep, and proposes recommendations for future research.

Control of ventilation is orchestrated at different levels of the respiratory system and through the entire life span of the individual. Understanding the physiological and clinical aspects of ventilatory control during wakefulness and sleep and in health and disease is a prerequisite step toward developing therapies that stabilize ventilatory control. This review describes ventilatory control mechanisms during wakefulness and sleep, with an emphasis on mechanisms that pertain to sleep-related breathing disorders.

Respiratory Rhythm Pattern Generators: Inspiration and Expiration

Anatomy of the Respiratory Cycle

Breathing rhythm originates in the medulla and continues even after the medulla is separated from the forebrain and pons. During eupneic breathing, neuronal activity in the brain stem can be divided into three phases:

(1) inspiratory

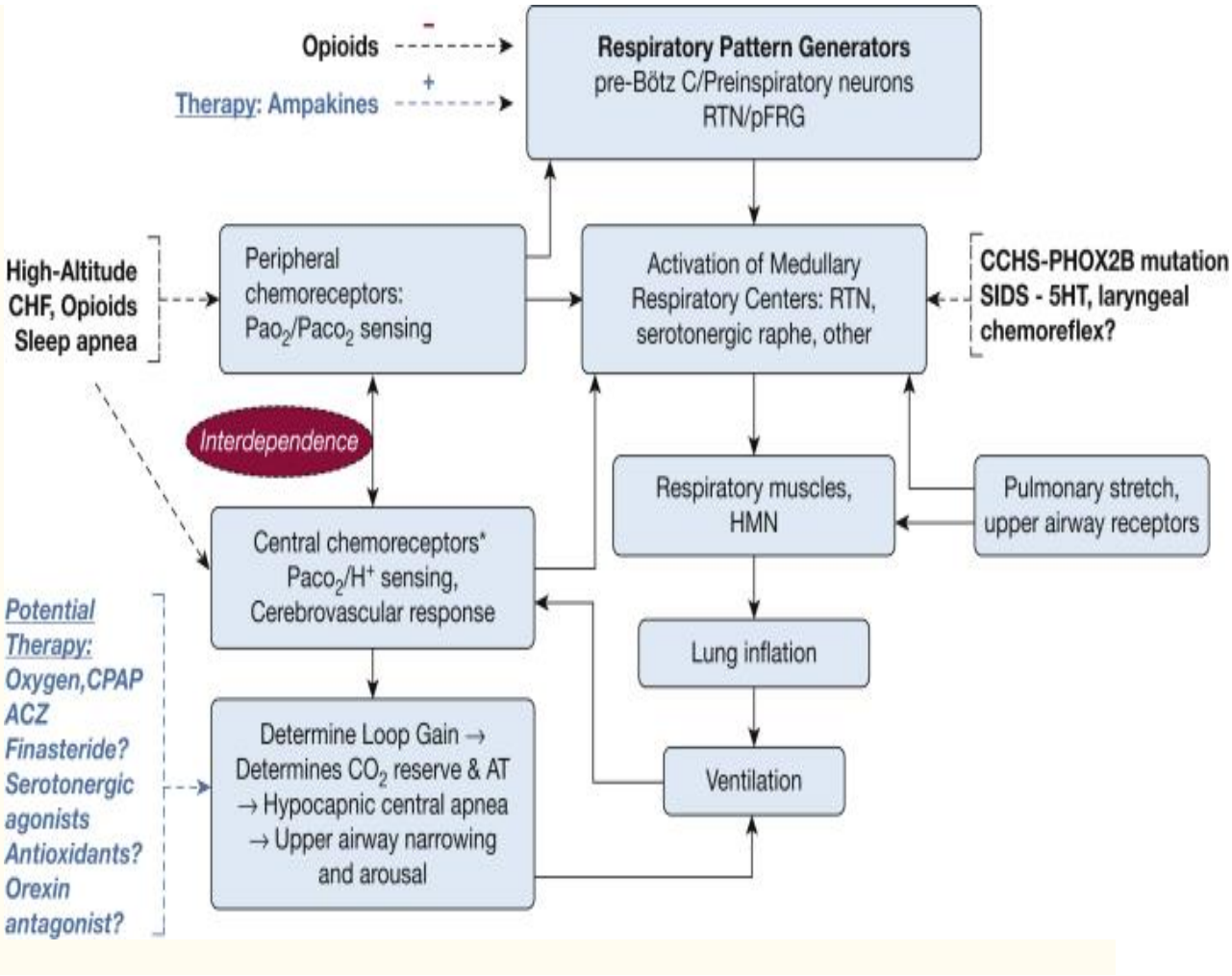
(2) postinspiratory

(3) late expiratory (or preinspiratory) neural activity.[1] Inspiration starts with the synchronized onset of neuronal discharge that increases to a maximum level but suddenly ends activity. This is followed by a secondary declining burst called postinspiratory "after discharge" that represents the active phase of the "passive" exhalation from the lungs.[2] Classically, two clusters of nuclei in the medulla were thought to regulate respiration: the dorsal respiratory group, which was activated immediately prior to inspiration, and the ventral respiratory group, which modulated phase switching to expiration. However, data from neonatal rat studies identified an oscillating respiratory-pattern generator (RPG), the Pre-Bötzinger complex (pre-Böt C), located in the ventral medullary respiratory column caudal to the Bötzinger nucleus[3] that consists of voltage-dependent neurons with rhythmic discharge patterns. The pre-Böt C is thought to be the primary RPG that provides inspiratory rhythm, whereas another group of neurons, the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG),[4,5] provides rhythmic expiratory drive. An opposing view is that preinspiratory neurons in the pFRG periodically trigger the inspiratory-pattern generator, the pre-Böt C.[6] Rostrally in the pons, the Kölliker-Fuse (KF) and parabrachial nuclei are relay nuclei for reflex and higher-order CNS control of breathing, including control of postinspiratory activity.[2] The KF area also regulates the inspiratory-expiratory phase transition and the dynamic control of upper airway patency during the respiratory

cycle[7]; the KF area receives input from various visceral sensory afferents through the vagal and glossopharyngeal nerves.[7] Respiratory rhythm generation is controlled by multiple modulators, including noradrenergic, serotonergic, peptidergic, acetylcholine neurons, and long-term synaptic plasticity.[8,9] Moreover, the RTN/pFRG, with its chemosensitive neurons, provides tonic excitation to the pre-Böt C and Böt

Control of Ventilation

Ventilatory control is regulated by a feedback system that allows only small changes in arterial P_{O_2}, P_{CO_2}, and pH under physiological states such as rest, exercise, and sleep. Likewise, reflexes from the airways and lung also influence respiration. The respiratory system maintains homeostasis by integrating chemical, metabolic, and mechanical input during complex physiological states and adjusting ventilatory motor output to meet ventilatory demands (Fig 1).



Chemical Control of Ventilation

Chemical ventilatory control monitors afferent input (P_{CO_2} and P_{O_2}) through the peripheral and central chemoreceptors to maintain P_{CO_2} and P_{O_2} within a specific range. The central chemoreceptors modulate ventilation in response to changes in the carbon dioxide/H+ detected within the brain, whereas the faster-acting peripheral chemoreceptors respond to changes in P_{O_2} and P_{CO_2} in the periphery. Moreover, oxygen sensing also occurs in the pons.

Major *central chemoreceptor* sites are distributed throughout the lower brain stem The central chemoreceptors are responsible for

approximately two-thirds of the ventilatory response to carbon dioxide/pH.[12] The response is linear until very high levels of carbon dioxide are reached. The *peripheral chemoreceptors* are located in the carotid body, at the bifurcation of the carotid artery, and to a smaller extent, at the aortic arch. The carotid bodies are highly vascular and are the major chemoreceptor site for hypoxia, sensing Pa_{O_2}, but not oxyhemoglobin saturation or oxygen content. The carotid bodies are also very sensitive to changes in P_{CO_2} and $[H^+]$. The carotid bodies' hypoxic response is curvilinear, increasing in slope once Pa_{O_2} drops to < 60 mm Hg. The steeper slope leads to higher ventilation for a given change in Pa_{O_2} and hence more pronounced hypocapnia. The changing gain of the hypoxic ventilatory response may explain the destabilizing effect of hypoxia on ventilation through hypocapnia.

Peripheral and central chemoreceptors are anatomically linked.[10] Following bilateral carotid body resection in humans, peripheral chemoresponsiveness was absent, but there was an associated reduction in central carbon dioxide sensitivity, indicating that the carotid bodies exert a tonic drive or tonic facilitation on the output of the central chemoreceptors.[17] Other studies have also demonstrated that the responses of the central chemoreceptors are markedly influenced by the magnitude of sensory input from the carotid chemoreceptor. Thus, chemoreceptor *interdependence* determines the normal drive to breathe in eupnea and in acute hypoxia.

Mechanical Influences

Afferent input from chest wall, lungs, and airways predominantly affects the pattern of breathing and is most apparent when increased demands are placed on the ventilatory control system and is mediated by receptors in the chest wall and muscles. The Hering-Breur reflex, elicited by inflation of slow-adapting chemically insensitive pulmonary stretch receptors, causes a decrease in the frequency of inspiratory effort following inflation. It

is strong in cats, dogs, and rabbits but is almost absent in humans; it is more powerful at birth than it is in adult mammals.[22, 23] Whether the proprioceptive chest wall receptors play a role in irregular breathing in neonates is unclear. Additionally, the laryngeal chemoreflex is a protective reflex initiated by chemical stimulation in the laryngeal lumen that results in a series of reactions including respiratory inhibition, closure of the glottis, and bradycardia, and it may be implicated in the sudden infant death syndrome (SIDS).

Metabolic Rate

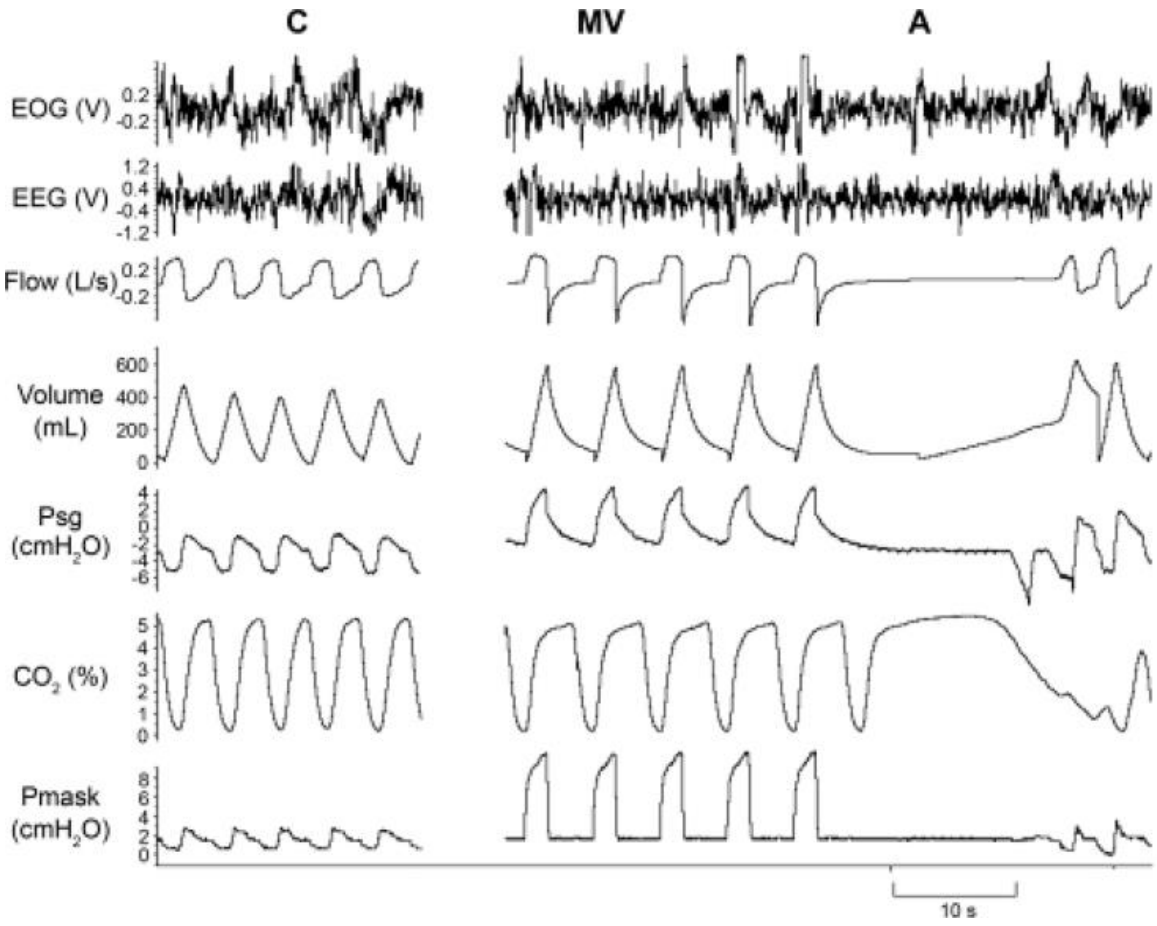
Oxygen consumption and carbon dioxide production effect alveolar ventilation by mechanisms that are not well understood. The tracking of ventilation to metabolic rate is very precise. For example, during exercise, ventilation increases in a linear manner related to metabolic rate. When an animal was placed on a membrane oxygenator, which allowed the removal of metabolic carbon dioxide production, ventilation was reduced to apnea by removing increasing amounts of carbon dioxide.

Factors Modulating Control of Ventilation

Sleep State

The loss of the wakefulness stimulus to breathe renders ventilation dependent on chemoreceptor and mechanoreceptor stimuli. In addition, reduced activity of upper airway dilators and upper airway narrowing with increased upper airway resistance are normal physiological events during sleep. In extreme cases of upper airway narrowing, complete closure may occur, leading to OSA. There is also a loss of load compensation during sleep as “loads” are not perceived; thus, ventilation decreases and $Paco_2$ increases.

Nonrapid eye movement (NREM) sleep removes the wakefulness drive to breathe and renders respiration critically dependent on metabolic control and chemical influences, especially P_{CO_2}. Transient breathing instability and central apnea often occur during the transition from wakefulness to sleep.



Concept of Loop Gain

Ventilatory control during sleep operates as a negative-feedback, closed-loop cycle to maintain homeostasis of blood gas tensions within a physiological range. Loop gain, an engineering term, is used as a measure of ventilatory stability and represents the overall response of the plant (representing the lung and respiratory muscles), the controller (representing the ventilatory control centers and the chemoreceptors), and the delay, dilution,

and diffusion inherent in transferring the signal between the plant and the controller.

Cerebrovascular Responsiveness

Cerebrovascular responsiveness (CVR) to carbon dioxide is an important determinant of eupneic ventilation and hypercapnic ventilatory responsiveness in humans, primarily through its effects on the central chemoreceptors.[47] Changes in cerebral blood flow (CBF) regulation modify breathing stability in healthy young adults a decrease in CBF allows accumulation of carbon dioxide that stimulates the medulla, whereas an increase in CBF allows carbon dioxide removal and depresses ventilation. In young healthy adults, CBF and CVR to hypocapnia[52] were reduced by indomethacin, leading to increased AT and narrowed carbon dioxide reserve, that is, increased ventilatory instability. With an approximate 25% reduction in CBF, the subjects had increased alveolar ventilation (arterial P_{CO_2} decreased by 2-3 mm Hg) and increased ventilatory response to carbon dioxide of 40%. Thus, reductions in the normal cerebral vascular response to carbon dioxide may contribute to breathing instability during wakefulness and sleep.

Age

CSA is more prevalent in older individuals than in middle-aged adults. Sleep state oscillations may precipitate central apnea in older adults. Additionally, CBF regulation and CVR are reduced in elderly adults. However, investigations into the effect of aging on chemoresponsiveness during wakefulness have yielded conflicting results. We demonstrated that during NREM sleep, older adults, when compared with young adults, had increased chemosensitivity, with increased isocapnic hypoxic ventilatory responsiveness and hyperoxic suppression of ventilation (Dejours' effect) despite an absence of ventilatory long-term facilitation (plasticity) following acute intermittent hyopoxia. Increased chemosensitivity, unconstrained by respiratory plasticity and

reduced CVR, may explain the increased propensity for central apnea in elderly individuals during sleep.

Sex

The effect of sex on ventilatory control could be due to genetic or environmental factors; the latter is supported by studies demonstrating increased prevalence of sleep apnea after menopause, but there are no data in humans regarding the former. Hormonal influences on ventilatory control are also supported by experimental evidence demonstrating that the hypocapnic AT during sleep is altered by manipulations of sex hormones. There is evidence that women are less susceptible to the development of hypocapnic central apnea during NREM sleep compared with men following noninvasive mechanical ventilation. Physiologically, the hypocapnic AT was higher in men compared with women

Disorders With Dysfunctional Regulation of Ventilation During Sleep

Congenital Central Hypoventilation Syndrome

Children affected by the rare condition CCHS experience sleep-related hypoventilation and ventilatory failure, requiring ventilatory support during NREM sleep, although a milder degree of hypoventilation may also be present during REM and wakefulness.

Sudden Infant Death Syndrome

Autonomic dysregulation, prolonged laryngeal chemoreflex, blunted chemoreflexes and arousal reflexes, sleep apnea, and genotypic polymorphisms are some of the intrinsic factors implicated in sudden unexplained deaths in infancy during sleep.[80] These may be mediated by a decrease in serotonergic

receptor binding in the raphe medullary nuclei that modulate respiration, central chemoreception, upper airway integrity, and cardiovascular control Ongoing research will likely elucidate the exact mechanisms and a cure for SIDS.[81]

High-Altitude Periodic Breathing

High-altitude exposure is characterized by the appearance of periodic breathing during sleep. The alveolar and, concomitantly, the arterial P_{CO_2} vary with altitude. For people traveling to a high altitude, hypoxia at a higher altitude increased carotid peripheral chemosensitivity with resultant increased ventilation, hypocapnia, and periodic breathing. In fact, periodic breathing increased during acclimatization over 2 weeks at altitudes > 3,730 m, despite improved oxygen saturation, due to an increase in loop gain of the respiratory control system. Interventions (eg, oxygen and acetazolamide) to reduce loop gain have been used as potential therapies

Sleep-Disordered Breathing

Patients with CSA due to CHF demonstrate pulmonary vascular congestion leading to hyperventilation and hypocapnia; hence, they experience no rise in end-tidal carbon dioxide (P_{ETCO_2}) from wakefulness to sleep.[84] The AT in patients with CHF is close to the eupneic P_{CO_2} owing to increased controller gain. Consequently, small decrements in P_{CO_2} cause central apnea despite the stabilizing effect of a low plant gain secondary to hyperventilation and reduced steady state P_{ETCO_2}.

Opioid-Induced Sleep Apnea

Multiple endogenous opioids in the medullary and pontine respiratory regions are tonically active and depressant to the

respiratory network, suggested by the fact that the opioid-receptor blocker naloxone stimulates respiratory output in anesthetized normoxic normocapnic