**(Slide 1) Lecture 12**

**Respiratory physiology. Part 2**

**(Slide 2)** Lecture plan:

1. General Concepts of Regulatory Mechanisms of Respiration.
2. Structure of Proper Inborn Respiratory Reflexes.
3. Receptors of Proper Respiratory Reflexes.
4. Afferent Part of Respiratory Reflexes.
5. Respiratory Center.
6. Efferent Part of Respiratory Reflexes.
7. Mechanism of the Central Nervous Control of the Respiratory Apparatus.
8. Humoral Mechanisms of Breathing Control.
9. Modifications in Respiratory Functions.

**(Slide 3)** **General Concepts of Regulatory Mechanisms of Respiration.** Regulation is a complex of central and peripheral mechanisms that work in cooperation to provide useful adaptive results vital for an organism. According to the modern classification, these results may be metabolic, homeostatic, behavioral and social. Results achieved by respiratory mechanisms are the optimal level of gases and optimal acid-alkaline balance in the internal environment of the body, in other words, the optimal levels of PCO2, pH and PO2. In adults, the main controllers of breathing are PCO2-sensitive mechanisms. In newborns, breathing is controlled by PO2-sensitive mechanisms.

**(Slide 4)** **Physiological functions are regulated by neuroreflex and humoral mechanisms.**

**(Slide 5)** In breathing both inborn (unconditioned) and acquired (conditioned) reflexes participate. Inborn reflexes are subdivided into proper and conjugated ones. In a proper respiratory reflex, excitation from chemoreceptors controlling pCO2, pO2 and pH goes directly to the nerve center, without involving any intermediate elements. In conjugated reflexes, excitation may arise from any receptors capable of initiating a reflex (temperature receptors, nociceptors, olfactory, taste receptors, etc.), and at first goes to the nerve centers of the reticular formation and only from there to the respective nerve centers. Thus, reticular formation is an intermediate element of a conjugated reflex. For example, stimulation of thermal receptors may cause a change in rhythm and depth of breathing through the initial change in the activity of nerve centers of reticular formation in the brainstem.

**(Slide 6) Video\_Regulation of Respiration.**

**(Slide 7) Structure of Proper Inborn Respiratory Reflexes.** According to the modern concepts, structure of any reflex comprises 6 elements: 1 – receptors, 2 – afferent pathway including an afferent neuron; 3 – nervous center; 4 – efferent pathway; 5 – effector organ; 6 – feedback mechanism

**(Slide 8) Receptors of Proper Respiratory Reflexes.** Receptors of the proper respiratory reflexes are chemoreceptors that control PCO2, pH and PO2 of blood. Chemoreceptors are concentrated in the so called vascular reflexogenic zones. A reflexogenic zone is an area with the highest concentration of receptors of the same type responsible for a particular reflex. The main reflexogenic zones for respiratory reflexes are paired zones in the bifurcation of the common carotid artery (a. Carotis communis), carotid bodies and the aortic arch. Receptors of these reflexogenic zones are peripheral chemoreceptors. Central chemoreceptors are located in the medulla oblongata and in the biological membranes of cells of the respiratory center; they respond to variations in PCO2 and pH.

**(Slide 9)** Irritant receptors are localized in the airways. They combine properties of both chemoreceptors and mechanoreceptors. They are activated by a rapid mechanical deformation of the lung tissue and by aromatic substances (odors). They participate in defense reflexes: sneezing and coughing.

**(Slide 10)** J-receptors (juxta-receptors) are localized in the intercellular space of the alveoli. J-receptors respond to increase in pressure in the pulmonary circulation on physical exertion or in pathological processes. The unpleasant subjective sensations termed “dyspnea” (difficulty in breathing) are considered to be associated with these receptors.

**(Slide 11) Video\_Central and Peripheral Chemoreceptors.**

**(Slide 12) Afferent Part of Respiratory Reflexes.** Paired sinocarotid reflexogenic zone is connected with the CNS through a branch of IX cranial nerve (n. glossopharyngeus) called carotid nerve (n. caroticus), or Hering’s nerve named after the scientist who described it. Aortic reflexogenic zone is connected with the CNS through a branch of X cranial nerve (n. vagus), called Cyon-Ludwig nerve, or depressor nerve (n. depressor). The nerve received its name after the scientists who first described it. Ludwig was German physiologist, and Cyon was Russian physiologist, a teacher of I.P. Pavlov. Pulmonary reflexogenic zone is connected with the CNS through afferent fibers of the vagus nerve.

**(Slide 13) Respiratory Center.** Respiratory center is a complex of nerve cells in the CNS that are interrelated to provide the optimal frequency and depth of breathing. In the narrow sense the respiratory center is an aggregation of nerve cells in the medulla oblongata (bulbar center). Among neurons of the bulbar center there are neurons that are active either on inspiration, or on expiration. The first group of neurons makes the inspiratory part of the respiratory center, and the second group forms the expiratory part. Inspiratory neurons are characterized by higher excitability than expiratory ones. These groups of neurons of the respiratory center are in reciprocal interrelations that means that activation of one group is accompanied by inhibition of the other.

**(Slide 14)** The pons contains nerve cells forming the pneumotaxic nerve center that controls activity of the expiratory part of the bulbar nerve center.

**(Slide 15)** In the hypothalamic region of the diencephalon there are nerve cells that control activity of the sympathetic and parasympathetic divisions of the autonomic nervous system. It is known that activation of the sympathetic autonomic nervous system causes dilation of bronchi, and activation of the parasympathetic autonomic nervous system causes their constriction. This evidences that the hypothalamic region also participates in control of breathing.

**(Slide 16)** Cortical nerve centers provide voluntary control of breathing – we may voluntarily change the frequency and depth of respiratory movements, hold our breath on inspiration or on expiration.

In summary, it can be said that the respiratory center is represented by neurons on different levels of the CNS that make up a single hierarchic system providing control of breathing.

**(Slide 17) Efferent Part of Respiratory Reflexes**. Efferent neurons of respiratory reflexes are α1 motoneurons that supply respiratory muscles. The ventral horns of the 3d-4th cervical segments of the spinal cord contain motor neurons which form the phrenic nerve (n. phrenicus), and the ventral horns of the 1st-12th thoracic segments contain motor neurons that make up intercostal nerves (nn. intercostalis) supplying external oblique intercostal muscles.

**(Slide 18) Feedback.** Feedback serves to provide the respiratory nerve center with information about the condition of effector organs (respiratory muscles and lungs). Therefore, feedback arises from receptors in the effector organs. These are proprioceptors of respiratory muscles (intrafusal fibers) and stretch receptors of the airways. There exist two groups of stretch receptors. The first group consists of high-excitability receptors capable of generating low-frequency bioelectrical impulses. The second group includes low-excitability receptors that generate high-frequency impulses. The first group receptors are activated at the beginning of inspiration, the second group ones – at the end of inspiration.

**(Slide 19)** Proprioceptors are connected with the CNS through afferent fibers traveling in somatic nerves, for example, in segmental somatic nerves (nn. intercostalis). Stretch receptors are connected with the СNS through the afferent branches of the vagus nerve.

**(Slide 20) Video\_Brain Respiratory Centers**

**(Slide 21) Central Nervous Control of the Respiratory Apparatus.** Aggregates of neurons that discharge periodically during inspiration, post-inspiration or expiration are distributed bilaterally in the bulbar brainstem, from the rostral pons (Pontine control of respiration) to the caudal border of the medulla. Synaptic interactions among the neurons establish the network respiratory rhythm, and their connections with cranial and spinal motoneurons and interneurons set up the timing and patterns of contraction in the muscles of respiration.

**(Slide 22)** Three regions of the medulla in particular have been studied for their roles in respiratory rhythmogenesis:

1. the PreBötzinger Complex (PreBötzinger Complex Inspiratory Neurons and Rhythm Generation);
2. the para-facial regions;
3. retrotrapezoid regions (Respiratory network analysis and isolated respiratory centre functions).

Their functional integrity is essential for a normal respiratory rhythm, and in the PreBötzinger and para-facial areas neurons with autorhythmic pacemaker properties have been identified (Respiratory network analysis, isolated respiratory centre functions; Pacemaker neurons and respiratory control).

**(Slide 23)** Respiratory neurons of the brainstem receive modulatory synaptic input from non-respiratory regions such as the motor cortex, pontine and medullary reticular formation, cerebellum, hypothalamus, other limbic and cardiovascular regions of the brainstem as well as from extrapyramidal motor areas (Anatomy and function in the respiratory network). These nonrespiratory modulatory inputs adapt breathing rhythm and pattern to accommodate activities such as phonation, swallowing, coughing, physical exertion, defecation and postural change.

**(Slide 24) Rhythm Formation in Bulbar Respiratory Neurons.** The membrane potential of medullary respiratory neurons normally oscillates between cycles of depolarization and hyperpolarization. The pattern of depolarization or hyperpolarization may be augmenting (increasing in intensity from onset to termination), decrementing (declining in intensity) or plateau (constant from onset to termination). In association with the patterns of depolarization, periodic discharges can be augmenting, decrementing or of constant intensity. The rhythm and pattern of discharge in bulbar respiratory neurons result from a combination of intrinsic membrane ion conductances, synaptic interactions among the neurons, and input from other CNS neurons and peripheral sensory afferents. Intrinsic membrane ion conductances initiate membrane depolarization that triggers action potential discharge, control the rate of depolarization and hyperpolarization, and terminate action potential discharge (PreBötzinger Complex Inspiratory Neurons and Rhythm Generation).

**(Slide 25)** Tonic excitatory drive comes from at least two sources. One is from CO2-sensitive neurons in the medulla (Central nervous chemoreceptors and respiratory drive; Medullary raphe nuclei and respiratory control). A second is from non-respiratory reticular activating neurons. These excitatory inputs can be suppressed or reinforced by feedback synaptic input from medullary and pontine respiratory neurons. Chemoreceptor and mechanoreceptor afferents from the carotid bodies (Carotid body chemoreceptors and respiratory drive), heart, lungs, chest wall and upper airways also influence discharge properties of bulbar respiratory neurons. All afferent inputs and synaptic interactions among the respiratory and non-respiratory neurons are regulated chemically by neurotransmitters and neuromodulators, including excitatory and inhibitory amino acids, acetylcholine, peptides, monoamines and adenosine.

**(Slide 26) Involuntary control.** Involuntary respiration is under subconscious control. The diaphragm and intercostal muscles, the primary respiratory muscles, are stimulated by groups of neurons located in the pons and medulla. These neurons form the respiratory control centre. They send impulses to the primary respiratory muscles, via the phrenic and intercostal nerves, which stimulates their contraction. There are three main groups of neurons involved in respiration:

1. The ventral respiratory group controls expiration.
2. The dorsal respiratory group controls inspiration.
3. The pontine respiratory group controls the rate and pattern of breathing.

Once the neurons stop firing, the inspiratory muscles relax and expiration occurs.

**(Slide 27) Voluntary Control.** Voluntary respiration is under conscious control. It is controlled via the motor cortex in the cerebrum, which receives inputs from the limbic system and hypothalamus. The mechanisms involved aren’t completely understood, but signals are thought to be sent to the spinal cord from the motor cortex, which are then passed onto the respiratory muscles.

**(Slide 28) Humoral Mechanisms of Breathing Control.** Humoral control of physiological functions is provided by various chemical substances present in the internal environment of the body. The great variety of chemical substances participating in the humoral control of breathing fall into three groups:

1) biologically active substances including hormones;

2) soluble salts (electrolytes);

3) substances released into the internal environment in result of metabolism.

**(Slide 29)** The first group includes such hormones as epinephrine that directly influences neurons of the respiratory center. Some hormones can influence breathing indirectly through changing metabolism in tissues (for example, thyroid hormones and hormones of the endocrine part of pancreas).

**(Slide 30)** The second group includes electrolytes containing Ca++, Na+, K+, etc. Calcium ions are known to influence release of transmitters from the presynaptosome of chemical synapse, and act as a factor of electromechanical coupling in muscle fibers. Na+ and K+ ions participate in initiation and conduction of excitation. Therefore, variation in the concentration of these ions in the internal environment influences the condition of all elements of the system of breathing control.

The third group includes CO2, organic acids (carbonic, lactic, pyruvic acids), products of ATP metabolism. The main factor controlled by all regulatory mechanisms is concentration of CO2 and of its derivatives in the internal environment.

**(Slide 31) Origin of Breathing Rhythm**. Breathing rhythm is of reflex nature. Increase in the partial tension of CO2 stimulates chemoreceptors of the main reflexogenic zones. Afferent neurons of these receptors start generating low-frequency impulses that reach the neurons of the respiratory center and excite higher excitability neurons – inspiratory neurons which begin to generate impulses that go to the motor neurons of the spinal cord supplying respiratory muscles. This process called “the central inspiratory activity” stimulates the motor neurons which initiate contraction of respiratory muscles, and inspiration starts.

**(Slide 32)** Expansion of the chest on inspiration causes increase of lungs in volume. At the beginning of inspiration high-excitability stretch receptors of the lung tissue are activated and start generating low-frequency impulses that increase excitation of inspiratory neurons. Inspiration deepens, the chest and lungs further expand. This stimulates low-excitability stretch receptors which begin to generate high-frequency impulses that stimulate low-excitability expiratory neurons. Excitation of expiratory neurons causes inhibition of inspiratory neurons, since they are in reciprocal interrelations. Thus, central inspiratory activity terminates. Excitation of motor neurons supplying respiratory muscles stops. The muscles relax, and expiration starts. This is the sequence of events responsible for alternation of inspiration and expiration.

**(Slide 33)** At rest, the respiratory system performs its functions at a constant, rhythmic pace, as regulated by the respiratory centers of the brain. At this pace, ventilation provides sufficient oxygen to all the tissues of the body. However, there are times that the respiratory system must alter the pace of its functions in order to accommodate the oxygen demands of the body.

**(Slide 34)** Hyperpnea. Hyperpnea is an increased depth and rate of ventilation to meet an increase in oxygen demand as might be seen in exercise or disease, particularly diseases that target the respiratory or digestive tracts. This does not significantly alter blood oxygen or carbon dioxide levels, but merely increases the depth and rate of ventilation to meet the demand of the cells. In contrast, hyperventilation is an increased ventilation rate that is independent of the cellular oxygen needs and leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH.

**(Slide 35)** Interestingly, exercise does not cause hyperpnea as one might think. Muscles that perform work during exercise do increase their demand for oxygen, stimulating an increase in ventilation. However, hyperpnea during exercise appears to occur before a drop in oxygen levels within the muscles can occur. Therefore, hyperpnea must be driven by other mechanisms, either instead of or in addition to a drop in oxygen levels. The exact mechanisms behind exercise hyperpnea are not well understood, and some hypotheses are somewhat controversial. However, in addition to low oxygen, high carbon dioxide, and low pH levels, there appears to be a complex interplay of factors related to the nervous system and the respiratory centers of the brain.

**(Slide 36)** First, a conscious decision to partake in exercise, or another form of physical exertion, results in a psychological stimulus that may trigger the respiratory centers of the brain to increase ventilation. In addition, the respiratory centers of the brain may be stimulated through the activation of motor neurons that innervate muscle groups that are involved in the physical activity. Finally, physical exertion stimulates proprioceptors, which are receptors located within the muscles, joints, and tendons, which sense movement and stretching; proprioceptors thus create a stimulus that may also trigger the respiratory centers of the brain. These neural factors are consistent with the sudden increase in ventilation that is observed immediately as exercise begins. Because the respiratory centers are stimulated by psychological, motor neuron, and proprioceptor inputs throughout exercise, the fact that there is also a sudden decrease in ventilation immediately after the exercise ends when these neural stimuli cease, further supports the idea that they are involved in triggering the changes of ventilation.

**(Slide 37)** High Altitude Effects. An increase in altitude results in a decrease in atmospheric pressure. Although the proportion of oxygen relative to gases in the atmosphere remains at 21 percent, its partial pressure decreases. As a result, it is more difficult for a body to achieve the same level of oxygen saturation at high altitude than at low altitude, due to lower atmospheric pressure. In fact, hemoglobin saturation is lower at high altitudes compared to hemoglobin saturation at sea level. For example, hemoglobin saturation is about 67 percent at 19,000 feet above sea level, whereas it reaches about 98 percent at sea level.

**(Slide 38)** As you recall, partial pressure is extremely important in determining how much gas can cross the respiratory membrane and enter the blood of the pulmonary capillaries. A lower partial pressure of oxygen means that there is a smaller difference in partial pressures between the alveoli and the blood, so less oxygen crosses the respiratory membrane. As a result, fewer oxygen molecules are bound by hemoglobin. Despite this, the tissues of the body still receive a sufficient amount of oxygen during rest at high altitudes. This is due to two major mechanisms. First, the number of oxygen molecules that enter the tissue from the blood is nearly equal between sea level and high altitudes. At sea level, hemoglobin saturation is higher, but only a quarter of the oxygen molecules are actually released into the tissue. At high altitudes, a greater proportion of molecules of oxygen are released into the tissues. Secondly, at high altitudes, a greater amount of BPG is produced by erythrocytes, which enhances the dissociation of oxygen from hemoglobin. Physical exertion, such as skiing or hiking, can lead to altitude sickness due to the low amount of oxygen reserves in the blood at high altitudes. At sea level, there is a large amount of oxygen reserve in venous blood (even though venous blood is thought of as “deoxygenated”) from which the muscles can draw during physical exertion. Because the oxygen saturation is much lower at higher altitudes, this venous reserve is small, resulting in pathological symptoms of low blood oxygen levels. You may have heard that it is important to drink more water when traveling at higher altitudes than you are accustomed to. This is because your body will increase micturition (urination) at high altitudes to counteract the effects of lower oxygen levels. By removing fluids, blood plasma levels drop but not the total number of erythrocytes. In this way, the overall concentration of erythrocytes in the blood increases, which helps tissues obtain the oxygen they need.

**(Slide 39)** Acute mountain sickness (AMS), or altitude sickness, is a condition that results from acute exposure to high altitudes due to a low partial pressure of oxygen at high altitudes. AMS typically can occur at 2400 meters (8000 feet) above sea level. AMS is a result of low blood oxygen levels, as the body has acute difficulty adjusting to the low partial pressure of oxygen. In serious cases, AMS can cause pulmonary or cerebral edema. Symptoms of AMS include nausea, vomiting, fatigue, lightheadedness, drowsiness, feeling disoriented, increased pulse, and nosebleeds. The only treatment for AMS is descending to a lower altitude; however, pharmacologic treatments and supplemental oxygen can improve symptoms. AMS can be prevented by slowly ascending to the desired altitude, allowing the body to acclimate, as well as maintaining proper hydration.

**(Slide 40) Acclimatization.** Especially in situations where the ascent occurs too quickly, traveling to areas of high altitude can cause AMS. Acclimatization is the process of adjustment that the respiratory system makes due to chronic exposure to a high altitude. Over a period of time, the body adjusts to accommodate the lower partial pressure of oxygen. The low partial pressure of oxygen at high altitudes results in a lower oxygen saturation level of hemoglobin in the blood. In turn, the tissue levels of oxygen are also lower. As a result, the kidneys are stimulated to produce the hormone erythropoietin (EPO), which stimulates the production of erythrocytes, resulting in a greater number of circulating erythrocytes in an individual at a high altitude over a long period. With more red blood cells, there is more hemoglobin to help transport the available oxygen. Even though there is low saturation of each hemoglobin molecule, there will be more hemoglobin present, and therefore more oxygen in the blood. Over time, this allows the person to partake in physical exertion without developing AMS.

**(Slide 41)** Lesson assignment:

Kaplan Medical USMLE Step 1 Physiology: On the website of the department. Pages: 135 – 190.

Questions that we will analyze for a lesson on this topic:

1. General Concepts of Regulatory Mechanisms of Respiration.
2. Structure of Proper Inborn Respiratory Reflexes.
3. Receptors of Proper Respiratory Reflexes.
4. Afferent Part of Respiratory Reflexes.
5. Respiratory Center.
6. Efferent Part of Respiratory Reflexes.
7. Mechanism of the Central Nervous Control of the Respiratory Apparatus.
8. Humoral Mechanisms of Breathing Control.
9. Modifications in Respiratory Functions.

Finish for today

The full lecture is at the indicated website.

**Thank you for attention**