

Министерство здравоохранения республики Беларусь  
Учреждение образования  
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
Обсуждено на заседании кафедры  
Протокол №7 от 30.08.2017

**МЕТОДИЧЕСКАЯ РАЗРАБОТКА**  
Для проведения занятия со студентами  
3 курса ФПСЗС, обучающихся на английском языке  
по патологической физиологии

Тема: **Патофизиология внешнего дыхания**

Theme: **Pathophysiology of external respiration**

Время 3 ак. часа

**Actuality of the theme.** The disorder of external breath arise for action of the various factors of the external and internal environment, however all of them for the mechanism of development are united in three groups - ventilating, diffusing and perfusing. The most seriously by manifestation of disorder of external breath is respiratory insufficiency is, as a result of which the gas structure of blood is changed and arises dispnea. On character of dispnea it is possible to make submission about the reason of a pathology. In particular, the deep and often breath arises for cardiac-vascular was insufficiency and anemias, deep and rare - for stenosis of respiratory paths, often and surface – for inflammation or edema lungs.

**Learning goals of the lesson:** to study etiology and pathogenesis of disorders of external respiration.

**Educational goals of the lesson:** formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

**Objectives of the lesson:**

1. To be able to explain causes and mechanisms of violations of alveolar ventilation, diffusion of gases and blood circulation in lungs.
2. To know mechanisms of disturbance of regulation of external respiration.
3. To know mechanisms of compensatory and actually pathological changes in respiratory and cardiovascular systems with various types of respiratory failure.

**To repeat the following questions from related disciplines to ensure absolute mastery of the material:**

1. Structure of alveoli (histology, cytology, embryology disciplines).
2. Anatomic structure of respiratory system (anatomy discipline).
3. Structure and principles of functioning of respiratory center. Mechanisms of inhalation and exhalation. (normal physiology discipline).

**Control questions of the lesson:**

1. Disorders of alveolar ventilation: types, causes, mechanisms, consequences.
2. Reflex respiratory disorders, respiratory center lesions.
3. Pathological forms of respiration: characteristics, mechanisms.
4. Disturbances of pulmonary blood flow. Local unevenness of ventilation-perfusion relations.
5. Disturbance of alveolo-capillary diffusion: causes and consequences.
6. Compensatory-adaptive processes in system of external respiration with damage to its certain links.
7. Changes in ventilation parameters, gas composition of blood and ABS in disturbance of external respiration.
8. Respiratory failure: definition, stage, manifestation. Shortness of breath: types, mechanisms of development.

**Calculation of study time**

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

## Additional materials:

The respiratory system has a vital charge: to provide for the exchange of oxygen and carbon dioxide between the air and the blood. Oxygen is required by all cells so that the life-sustaining energy source, adenosine triphosphate (ATP), can be produced. Carbon dioxide is produced by metabolically active cells and forms an acid that must be removed from the body. For gas exchange to be performed, the cardiovascular and respiratory systems must work together. The cardiovascular system is responsible for perfusion of blood through the lungs. The respiratory system performs two separate functions: ventilation and respiration.

## Physiologic Concepts

### Alveolus

The functional unit of the lungs is the alveolus (plural, alveoli). There are more than a million alveoli in each lung. Alveoli are small, air-filled sacs across which oxygen and carbon dioxide and other gases diffuse. The large number of small alveoli ensures that the total area available for the diffusion of gas in each lung is enormous. If the airflow into an alveolus is blocked, it collapses and is unavailable for gas exchange. If airflow into several alveoli is blocked, exchange of gases may be impaired to the extent that the person becomes hypoxic or unconscious or dies.

### Ventilation

The movement of air from the atmosphere into and out of the lungs is called ventilation. Ventilation occurs by bulk flow. Bulk flow is the movement of a gas or a fluid from high to low pressure.

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Ventilation is determined by the  $F=P/R$

F – the bulk flow air

P – the difference in pressure between the atmosphere and alveoli, and

R – the resistance offered by the conducting airways

### Pressure

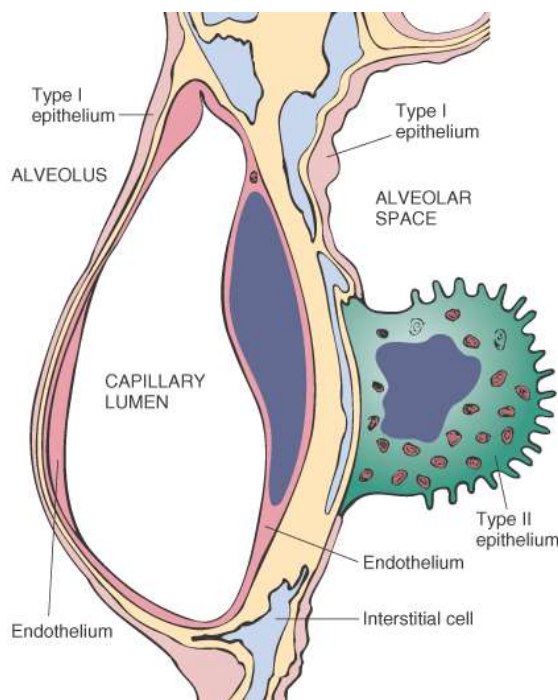
Alveolar pressure varies with each inspiration and drives the flow of air. With the onset of inspiration, the thoracic cavity expands. As the thoracic cavity expands, the lungs also expand. According to Boyle's law, if the volume of an air-filled chamber increases, the pressure of the air in the chamber decreases.

Therefore, as the lungs expand, pressure in the alveoli decreases to below atmospheric pressure, and air rushes into the lungs from the atmosphere (from high pressure to low pressure). At the end of inspiration, the thoracic cavity relaxes, causing pressures in the alveoli, which are filled with the air of inspiration, to be higher than in the atmosphere. Air then flows out of the lungs and down the pressure gradient.

### Bronchial Resistance

Resistance of the airways is usually low. Resistance is increased when the smooth muscle of the bronchiolar tubes constricts. Constriction of the bronchi results in a decrease in airflow into the lungs. Resistance is inversely proportional to the radius of a vessel to the fourth power. This means that if the radius of a bronchiolar tube decreases by one-half, the resistance to airflow in that tube increases by 16 (i.e.,  $2^4$ ). Therefore, when the air passages constrict even slightly, resistance to airflow goes up significantly.

Bronchiolar resistance is determined by parasympathetic and sympathetic nervous system innervation of the smooth muscle of the bronchi and local chemical mediators.

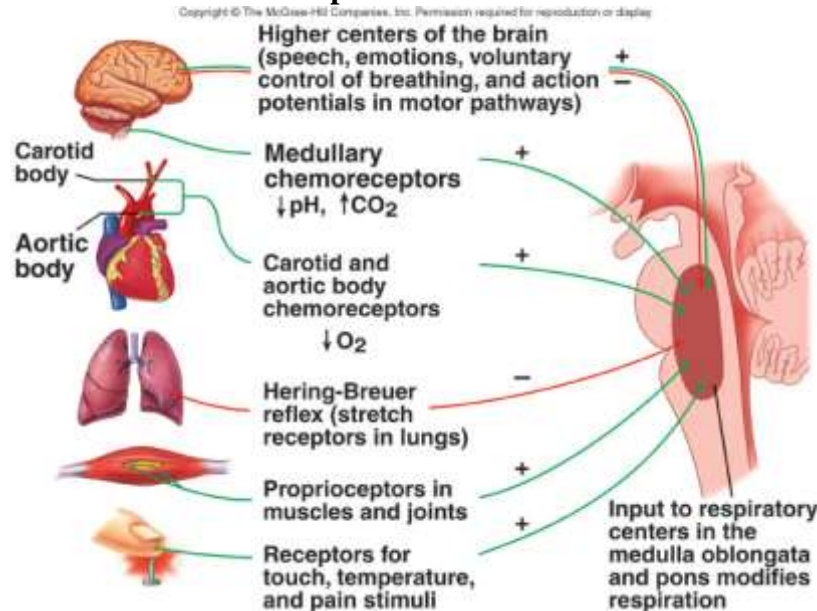


Parasympathetic nerves are carried to the bronchial smooth muscle by way of the vagus nerve and cause contraction or narrowing of the airways, increasing resistance and reducing airflow. Parasympathetic nerves release the neurotransmitter acetylcholine (ACh). ACh acts by binding to cholinergic receptors on the smooth muscle of the bronchi.

Sympathetic innervation of the bronchial smooth muscle occurs by way of nerve fibers from the upper thoracic and cervical ganglia and causes relaxation of the bronchi.

This reduces and increases airflow. Sympathetic nerves release the neurotransmitter norepinephrine. Norepinephrine acts by binding to  $\alpha_2$  adrenergic receptors on the smooth muscle of the bronchi.

## Nervous Control of Respiration



Ventilation is controlled by the respiratory center in the lower brainstem areas of the medulla and pons. In the medulla, there are inspiratory and expiratory neurons that fire at opposite times in a preset pattern of rate and rhythm. Respiratory neurons drive ventilation by exciting motor neurons that innervate the main muscle of inspiration (the diaphragm) and the accessory muscles (the intercostal muscles).

### Central Chemoreceptors

Central chemoreceptors in the brain respond to changes in the hydrogen ion concentration of the cerebral spinal

fluid. Increased hydrogen ion concentration increases the firing rate of the chemoreceptors, while decreased hydrogen ion concentration decreases the firing rate of the chemoreceptors. Information from the central chemoreceptors is delivered to the respiratory center in the brain, which in response increases or decreases the breathing pattern. Hydrogen ion concentration usually reflects carbon dioxide concentration. Therefore, when carbon dioxide levels rise, hydrogen ion levels rise, and the firing rate of inspiratory neurons is increased, causing an increase in respiratory rate. This is an example of negative feedback, because with an increase in the rate of breathing, the excess carbon dioxide and hydrogen ion will be blown off. With low carbon dioxide and low hydrogen ion levels, the firing rate of the inspiratory neurons returns toward baseline, and respiration slows.

### Peripheral Chemoreceptors

Peripheral chemoreceptors exist in the carotid and the aortic arteries, and monitor oxygen concentration in arterial blood. These receptors, called the carotid and the aortic bodies, send their impulses to the respiratory center of the medulla and pons primarily to increase the rate of ventilation when oxygen is low. They are less sensitive than the central chemoreceptors. The peripheral chemoreceptors also respond with an increase in firing rate to increased hydrogen ion dissolved in the blood. This is important because under certain circumstances free hydrogen ion increases without causing a change in carbon dioxide concentration (e.g., during conditions of metabolic acidosis caused by prolonged diarrhea or diabetes mellitus). Free hydrogen ion is relatively impermeable across the blood-brain barrier, so it is unable to activate the central chemoreceptors directly.

### Motor Neurons Driving Respiration

The major motor neuron controlling respiration is the phrenic nerve. When activated by the central inspiratory neurons, the phrenic nerve causes the diaphragm muscle to contract and the chest to expand. As the chest expands, air begins to flow from the atmosphere into the lungs. Airflow into the lungs is called inspiration. As inspiration continues, firing of the central inspiratory neurons slows and firing of the expiratory neurons increases, causing cessation of motor neuron activity and relaxation of the diaphragm. Chest expansion reverses and air flows out of the lungs. Airflow out of the lungs is called expiration.

## Respiration

Respiration refers to the diffusion of gases between an alveolus and the capillary that perfuses it. Respiration occurs by diffusion, which involves the movement of a gas down its concentration gradient. The rate of diffusion of a gas (e.g. oxygen and carbon dioxide) is determined by

$$D = \frac{[(X_a - X_c)] \times SA \times T}{d \times k}$$

where [D with dot above] is the rate of diffusion,  $X_a$  is the concentration of gas in the alveolus,  $X_c$  is the concentration of gas in the capillary,  $SA$  is the surface area available for diffusion,  $T$  is the temperature of the solution,  $d$  is the distance across which diffusion must occur, and  $k$  is a physical constant that takes into account non-variable characteristics of the gas such as its molecular weight and its specific solubility coefficient.

Causes of diffusion impairments: thickening of alveolus wall, thickening of capillary wall, in-alveolar edema, interstitial edema, dilation of capillaries.

## Pulmonary Circulation

The pulmonary circulation consists of deoxygenated blood traveling in the pulmonary artery from the right side of the heart. This blood perfuses the respiratory portions of the lungs and participates in the exchange of oxygen and carbon dioxide across the capillaries and alveoli. After picking up oxygen and releasing carbon dioxide, the blood returns to the heart by way of the pulmonary vein. Pressure and resistance to flow in the pulmonary circulation are usually low, with a mean pulmonary pressure of approximately 12 mmHg compared with a mean systemic pressure of approximately 90 mmHg. The pulmonary circulation is compliant and can accommodate large variations in blood volume. Therefore, the pulmonary circulation can act as a reservoir for blood that can be called upon in times of decreased systemic blood volume or pressure.

## Ventilation: Perfusion Ratio

Ventilation refers to air moving into and out of the lungs. Perfusion is the blood passing through the pulmonary circulation to be oxygenated. The ventilation: perfusion ratio,  $V/Q$ , is the ratio of airflow into the lungs divided by the pulmonary blood flow. In this expression,  $V$  is the volume of air moved with each breath, expressed as milliliters per minute (mL/min), and  $Q$  is the rate of blood flow in the pulmonary circulation, also expressed as mL/min. Normally, perfusion is slightly greater than ventilation and the  $V/Q$  ratio is approximately 0.8. Therefore, the alveoli receiving oxygen are well perfused by blood, allowing optimal conditions for gas exchange.

## Elasticity

Elasticity of the respiratory system refers to the degree to which the lungs resist inflation or stretching. The alveoli and other lung tissue normally resist stretching and recoil after the force causing the stretch or expansion is removed. This situation is partially caused by the surface tension of each alveolus and partially by the presence of elastic fibers throughout the lungs, which tend to recoil after stretch. Conditions such as emphysema reduce the elastic recoil of the lungs, resulting in chronic overinflation. The reciprocal of elasticity of the lungs is termed lung compliance. Compliance refers to the ease of inflation or stretching of the lungs. Lung compliance is reduced by fibrosis, infection, or adult respiratory distress syndrome (ARDS).

## Pleural Pressure

The lungs are surrounded by a thin membrane called the pleura. The outer layer of the pleural membrane is attached to the wall of the thoracic cavity. The inner layer of the pleura is attached to the lungs. With expansion of the thoracic cavity during inspiration, the outer layer is pulled out; this force is transmitted to the inner layer, which expands the lungs. In between the inner and outer layers of the pleura is the pleural space. This space is filled with a few milliliters of fluid that surround and lubricate the lungs. The pleural fluid is at negative pressure and opposes the elastic recoil (collapse) of the lungs. This helps keep the lungs expanded.

## Surface Tension

Surface tension refers to the tendency of water molecules to pull toward each other and to collapse a sphere. Because each alveolus is lined with a thin water layer, the surface tension within each alveolus

could be high, making it extremely difficult to expand an alveolus. With each breath, a certain pressure must be exerted to overcome the surface tension of the water layer. The amount of pressure needed to expand the alveolus is described by Laplace's law.

### **Surfactant**

Certain cells inside the alveolus, called type II alveolar cells, produce an important substance called surfactant that helps reduce the surface tension of the alveolus, making it easier to inflate. Surfactant is a phospholipid that acts like a detergent to intersperse between water molecules in the alveolus, thereby weakening the bonds between them. This reduces surface tension and the tendency of the sphere to collapse.

When surfactant is present, a small alveolus actually requires less pressure to inflate than a large one because the surfactant is packed tightly together, greatly reducing the surface tension of the alveolus. This serves to compensate for the effect of small radius in Laplace's law.

### **Typical pulmonary gas exchange dysfunction**

1. Violation of alveolar ventilation
2. Violation of lung perfusion
3. Violation of ventilation-perfusion relationships
4. Violation of lung diffusion capacity
5. Mixed forms

### **Impairments of alveolar ventilation**

Impairments of alveolar ventilation, alveolar hyper- and hypoventilation

Alveolar hyperventilation exists when  $\text{PaCO}_2$  is below 37 mm Hg. Hypoxemia controls ventilation by stimulating the peripheral chemoreceptors. In pulmonary disorders and congestive heart failure, hyperventilation results from stimulation of afferent vagal receptors in the lungs and airways. Low cardiac output and hypotension stimulate the peripheral chemoreceptors and inhibit the baroreceptors, both of which increase ventilation. Metabolic acidosis that occurs in many conditions activates both the peripheral and central chemoreceptors. Psychogenic states and severe cerebrovascular insufficiency may interfere with the inhibitory influence normally exerted by cortical structures of the brainstem respiratory neurons. Fever and sepsis also cause hyperventilation through the effects on midbrain and hypothalamus. The alkalemia associated with hypocapnia may produce dizziness, visual impairment, syncope and seizure which are secondary to cerebral vasoconstriction. Tetany is secondary to decreased free serum calcium and muscle weakness is secondary to hypophosphatemia. Patients with a primary respiratory alkalosis are also prone to periodic breathing and central sleep apnea.

Alveolar hypoventilation is clinically important when  $\text{PaCO}_2$  is generally in the range of 50 to 80 mm Hg.

### **Mechanisms of alveolar hypoventilation:**

- I. Disturbances of respiratory mechanics: a) obstructive disorders and b) restrictive disorders (parenchymal and extraparenchymal)
- II. Dysfunction of respiratory control: a) abnormalities in peripheral and central chemoreceptors and b) impaired function of brainstem respiratory neurons

Obstructive hypoventilation is characterized by an increase in resistance to airflow owing to partial or complete obstruction at any level, from trachea to respiratory bronchioles. The major obstructive disorders are emphysema, chronic bronchitis, bronchiectasis and asthma as well as a compression or obturation of airways. Any process that narrows the airway lumen leads to early airway closure. Patients must increase their resistance work in order to overcome increased airways resistance forces. In this condition, the interpleural pressure may become positive leading to airway compression and further increasing airway resistance. Excess mucus production and contraction of bronchial smooth muscle, as occurs in asthma and chronic bronchitis, or loss of radial traction on the airways due to destruction of alveolar septa, as occurs in emphysema, are most common causes of early airway closure.

In obstructive diseases, the total lung capacity is normal or increased. The hallmark of an obstructive disorder is a decrease in the forced expiratory volume in one second (FEV1) and a reduction of the ratio of FEV1 to forced vital capacity.

Restrictive hypoventilation is characterized by reduced expansion of lung parenchyma with decreased total lung capacity. Most common parenchymal restrictive disorders are sarcoidosis, idiopathic pulmonary fibrosis, pneumoconiosis and drug- or radiation-induced interstitial lung diseases. Adult respiratory distress syndrome illustrates an example of acute restrictive disease. Extraparenchymal restrictive disorders include neuromuscular disorders and chest wall disorders. Most common neuromuscular disorders are poliomyelitis, peripheral neuropathy, myasthenia gravis, muscular dystrophies and high cervical trauma whereas chest wall disorders include obesity, pleural diseases, kyphoscoliosis and ankylosing spondylitis.

The hallmark of a restrictive pattern, found in either parenchymal and extraparenchymal restrictive disorders, is a decrease in lung volumes, primary total lung capacity and vital capacity.

Dysfunction of respiratory control may result from abnormalities in peripheral and central chemoreceptors as well as brainstem respiratory neurons. Defect of peripheral and central chemoreceptors may be observed in carotid body dysfunction, prolonged hypoxia and metabolic acidosis. Impaired function of brainstem respiratory neurons occurs in bulbar poliomyelitis, encephalitis, brainstem infarction and primary alveolar hypoventilation syndrome.

### **Disorders of pulmonary circulation**

All diseases of the respiratory system causing hypoxemia are potentially capable of increasing pulmonary vascular resistance, since alveolar hypoxia is a very potent stimulus for pulmonary vasoconstriction. Pulmonary vascular resistance increases if intraluminal thrombi or proliferation of smooth muscle in vessel walls diminishes the luminal cross-sectional area. Disturbances in the pulmonary vasculature may result from primary cardiac disease or conditions that elevate left atrial pressure, such as mitral stenosis.

### **Impairments of ventilation perfusion ratio**

Gas exchange depends critically on the proper matching of ventilation and perfusion at the acinar level. Increased ventilation raises the arterial blood oxygen tension toward the inspired oxygen pressure whereas increased blood flow causes the arterial oxygen tension to decline toward the mixed venous oxygen tension. The most efficient gas exchange occurs when the ventilation-perfusion ratio (VPR) is approximately equal to 1. In the presence of pulmonary disease, the VPR can vary from zero to infinity.

A low VPR occurs in physiologic and anatomic shunts, when blood from areas with low ventilated mixes with blood from well-ventilated areas, the resultant mixture has an oxygen content dependent on the oxygen tension in the two areas as well as the relative amounts of blood flow from each. An anatomic shunt may be intra- or extrapulmonary. Extrapulmonary anatomic shunts may result from congenital cardiac malformation. Shunting of blood through the pulmonary parenchyma occurs if the alveoli are atelectatic or if they are filled with fluid.

A high VPR is caused either by excessive ventilation or inadequate blood flow to an area of the lung. A high VPR does not cause arterial hypoxia per se. However, if the overall ventilation is normal, excessive ventilation in one section of the lung means there is inadequate ventilation in others. In areas of the lung where the VPR exceeds 1, the alveolar and capillary oxygen tensions are high but the oxygen uptake is poor. Because of the plateau of the oxygen-hemoglobin dissociation curve, oxygen exchange is inefficient because very little extra oxygen is added to the blood by excess ventilation.

### **Tests of Pulmonary Function: Lung Volumes and capacities**

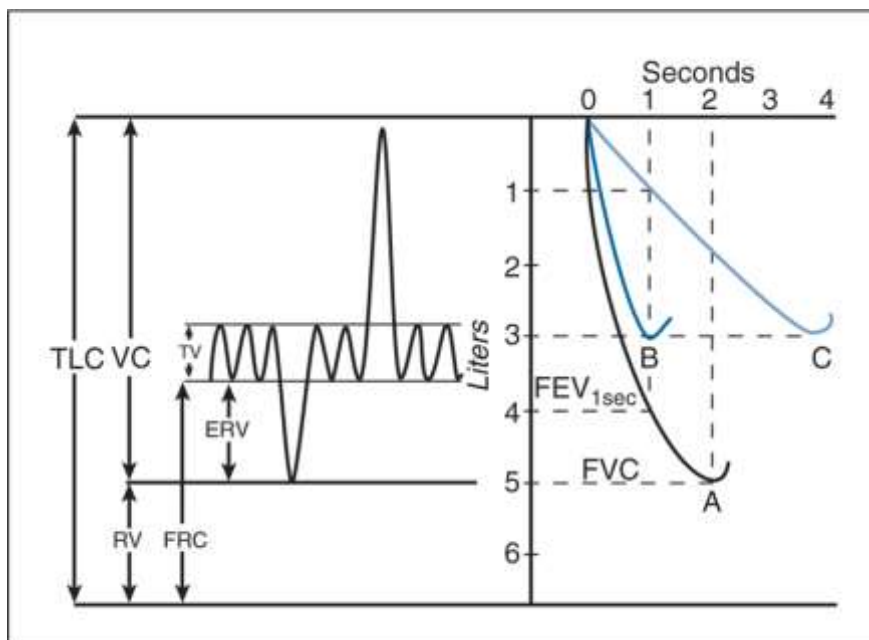
Spirometry is the measurement of the volume of air moving into and out of the lungs and is measured as an individual inhales and exhales into a closed chamber. It is used to determine lung volumes, including tidal, inspiratory reserve, expiratory reserve, and residual volumes, and, calculated from these, vital capacity. The average values presented in the figure for each of these volumes are for an adult male. Values for adult females are approximately 20 to 25% less.

#### **Tidal Volume (TV)**

The amount of air entering or leaving the lungs during a single breath is the tidal volume. The amount of air inspired at rest (inspiratory volume) usually equals the amount expired (expiratory volume). Tidal volume averages approximately 500 mL at rest.

#### **Inspiratory Reserve Volume**





The amount of air above the normal inspiration that can be maximally inspired with each breath is the inspiratory reserve volume. It averages approximately 1500-3000 ml.

### **Expiratory Reserve Volume**

The maximum amount of air that can be exhaled beyond normal exhalation is the expiratory reserve volume. This value averages approximately 1100-1500 ml.

### **Residual Volume (RV)**

The air remaining in the lungs after maximum exhalation is the residual volume. The normal value is approximately 1,000-1200 ml.

### **Vital Capacity**

The maximum amount of air that an individual can inspire and expire during a single breath is the vital capacity. It is the sum of the normal tidal volume and the inspiratory reserve volume and the expiratory reserve volume ( $VC = IRV + ERV + TV$ ) is the range in lung volume from maximum inspiration to maximum expiration (4600 ml). It is measured by having an individual take a maximum breath and then exhale as much as possible into the measurement chamber. In restrictive pulmonary disorders (e.g., resulting from neuromuscular disease, fibrosis, or loss of surfactant-producing cells), vital capacity is reduced.

**Inspiratory capacity** ( $IC = TV + IRV$ ) is the maximum volume of air a person can inspire beginning from the end of a normal expiration (3500 ml).

**Functional residual capacity (FRC)** is the volume of air in the lungs after a normal expiration (2300 ml) ( $FRC = ERV + RV$ ).

**Total lung capacity (TLC)** is the maximum volume of air that the lungs can hold after the greatest possible inspiration (5800 ml) ( $TLC = IRV + V_T + ERV + RV$ ). It cannot be measured by spirometry because it includes the residual volume.

**Forced vital capacity (FVC)** is the total amount of air expelled after a maximal inspiration. Normal FVC is 5L.

**Forced expiratory volume in 1 second ( $FEV_1$ )**. Amount of air expelled from the lungs in 1 second after a maximal inspiration. Normal  $FEV_1$  is 4L.

Ratio of  $FEV_1/FVC$  is normally 80%.

**Minute ventilation** is the sum of all the air breathed during 1 minute.

$MV = \text{tidal volume} \times \text{respiratory rate}$

normal respiratory rate (12 breaths per minute) and the normal tidal volume (500 ml) = 6000 ml/min:

**Alveolar ventilation** = (tidal volume - dead space volume)  $\times$  respiratory rate (4200 ml/min)

A common test of pulmonary function is to plot the volume of air an individual can expire in the first second of expiration, called the forced expiratory volume in one second ( $FEV_1$ ). A healthy individual can expire approximately 80% of vital capacity as fast as possible in the first second ( $FEV_1/\text{vital capacity}$ ). In obstructive pulmonary diseases such as asthma and emphysema, expiration is particularly affected, and the amount of air an individual can forcefully expire in the first second is reduced. In patients who have restrictive airway disease, expiration is usually normal. Therefore, whereas overall vital capacity is reduced in those who have restrictive airway disease,  $FEV_1$  is normal.

### **Anatomic Dead Space**

The amount of air in each breath that is measured as part of the tidal volume but that does not actually participate in gas exchange is the anatomic dead space. This air fills the conducting passages of the nose, mouth, pharynx, larynx, trachea, bronchi, and the bronchioles. With rapid, shallow respirations, a greater percentage of each breath is wasted simply moving air in and out of the anatomic dead space compared with that seen with slow, deeper breathing.



**Table. Comparison of pulmonary function tests in restrictive and obstructive lung disease**

Parameter	Restrictive Disease	Obstructive Disease
Total lung capacity	Decreased	Increased
Residual volume	Decreased	Increased
FEV <sub>1sec</sub>	Decreased	Decreased
FVC	Decreased	Decreased
FEV <sub>1sec</sub> /FVC	Normal to increased	Decreased
PaO <sub>2</sub>	Decreased	Decreased
A-a gradient	Increased	Increased

## RESPIRATORY FAILURE

Classification of respiratory failure

### By localization of pathological process

- with a predominance of pulmonary disorders
- dominated extrapulmonary disorders

### By etiology:

- acquired
- hereditary (congenital)
  
- infectious
- noninfectious
  
- centrogenic
- neuromuscular
- thorax-diaphragmal
- bronchopulmonary
- Classification of RF

### By type of violation of respiratory mechanics:

- obstructive
- restrictive
- mixed

### By pathogenesis:

- hypoxemic (parenchymal)
- hypercapnic (ventilation)
- mixed

### By time of development

- Acute (minutes / hour - an attack of asthma)
- Subacute (day/week.- hydrothorax)
- Chronic (months / years, emphysema)
- Classification of RF

### By seriousness of the ARF\*:

- First (moderate) - PaO<sub>2</sub> > 70 mm Hg
- Second (middle), PaO<sub>2</sub> 70 - 50 mmHg
- Third (heavy) - PaO<sub>2</sub> < 50 mm Hg

### The pathophysiological mechanisms of ARF

1. Violation of the diffusion of O<sub>2</sub> and CO<sub>2</sub>
2. Shunting of venous blood in the arterial tree
3. Alveolar hypoventilation

4. Violation of the relevant between ventilation and perfusion

#### **Clinical manifestations of RF**

- dyspnea, cyanosis of the skin
- ↑ sputum
- coughing, sneezing
- rales (asphyxia)
- pain in the chest
- disorders of CNS functions (emotional lability, rapid tiring, sleep disorders)

#### **Dyspnea (breathlessness)**

**Breathlessness** — feeling of lack of air and the associated need to strengthen the breathing

#### **Classification of breathlessness**

- «normal» — with heavy physical work
- psychogenic — a hypochondriac patients that suspect pathology in his heart or lung
- somatic — during anemia, neuromuscular disorders, HF, pulmonary pathology

#### **By duration:**

- Constant
  - Habitual physical exercise
  - Slight physical exercise
  - In rest
- Paroxysmal
- Classification of breathlessness

#### **Depending on the breathing phase:**

- inspiratory
- expiratory
- mixed

#### **Inspiratory dyspnea**

- the first stage of asphyxia
- CNS excitation
- exercise in patients with CI
- pneumothorax
- restrictive disorders: cardiac asthma, pulmonary edema

#### **Expiratory dyspnea**

- BA
- Emphysema
- predominance of excitatory influences on breath than depressing
- or ↑ sensitivity of RC to them

#### **Mechanism of dyspnea development**

- Hering-Breuer reflex (inhibits or stimulates the breath in tension or decay of the alveoli)
- Excitation of interstitial lung tissue receptors (J-receptors (juxtacapillar) - respond to elevated levels of fluid in the interstitial perialveolar space, at increasing hydrostatic pressure in the capillaries)
- Reflexes from chemoreceptors of aorta and carotid sinus (in acidosis, respiratory failure, anemia: ↓pO<sub>2</sub>, ↑ pCO<sub>2</sub> or ↑ [H<sup>+</sup>] - i ↑ excitation of inspiratory center
- Reflexes from baroreceptors of aorta and carotid sinus (in blood loss, shock, collapse when BP < 70 mmHg by activating the center of expiration)
- Reflexes in RT: presence of irritating particles - bronchitis, asthma.
- Reflexes of the respiratory muscles (by excessive stretching of intercostal muscles and strong excitation of stretch receptors in the ↓-elasticity of the lungs, narrowing of the upper RT)

- Direct stimulation of neurons RC (excessive excitation of chemoreceptors medulla)
- RC stimulation by metabolic products

Pathological types of breathing

- periodic
- terminal
- dissociated

**Periodic breathing.** They are characterized by alternating breaths and pauses apnea. The basis are the disorders of automatic control system of breathing.

- **Cheyne-Stokes:** pauses interspersed with respiratory movements, which first increases with depth, and then decreases.

Pathogenesis: instabilities in the feedback system regulating ventilation.

- **Biota:** pauses alternated with respiratory movements normal by rate and depth.

Pathogenesis: the damage of the brainstem - pneumotaxic system (the middle part of pons) that is a source of its own slow rhythm. In normally it suppressed by inhibitory influence of the cortex.

**Terminal breathing.** They are accompanied by serious violations of rhythmogenesis

- **Kussmaul** (big breath). A deep breath and forced long exhale. It's noisy, deep breath

In patients with impaired consciousness in diabetic, uremic, hepatic comas.

Pathogenesis: disorders of excitability of the respiratory center in brain hypoxia, metabolic acidosis, toxic effects

- **apneustic** enhanced long convulsive breath, occasionally choking by exhalation

Pathogenesis: the defeat pneumotaxic center

- **gaspig:** single, deep, rare, decreasing in strength sighs.

Occurs in the terminal phase of asphyxia, at bulbar paralysis of the respiratory center.

Pathogenesis: impulse source - cells of caudal medulla oblongata. Respiratory neurons are resistant to external influences.

**Dissociated breathing:**

- paradoxical movement of the diaphragm: with bilateral paralysis of the diaphragm (diaphragm lifted on inspiration, on the exhale - descend).
- asymmetry of movement in the left and right chest part. In damage of respiratory muscles may occur discoordination tors of the upper and lower parts of the thorax.
- "Ataxic" ugly breath Grokko-Frugoni characterized by dissociation of the respiratory movement of the diaphragm and intercostal muscles. Etiology: stroke, brain tumors, severe disorders of the nervous regulation of respiration.

## Asphyxia

Asphyxia (from Greek. a - denial, sphysis - heart rate) - a life-threatening pathological condition caused by acute or severe emerging deficiency of oxygen in the blood and the accumulation of carbon dioxide in the body.

**Etiology:**

- the mechanical difficulties of the air passage on large airway (larynx, trachea)
- disorders of breathing regulation and respiratory muscles

**Phases of mechanical asphyxia:**

**Phase 1:**

- activation of RC: increased and prolonged breath (inspiratory dyspnea)
- general excitement
- increased sympathetic tone (eyes widen, tachycardia, increased BP)
- convulsions
- refractory strengthening respiration
- lowering PaO<sub>2</sub> increase P CO<sub>2</sub> irritate both inspiratory and expiratory respiratory centers

**Phase 2:**

- decrease in breathing and increased movement on the exhale (expiratory dyspnea)
- begins to dominate the parasympathetic tone (narrowed eyes, decreased BP, bradycardia)

- hard change in arterial blood gas inhibit RC and the center of circulatory regulation

### **Phase 3 (preterminal):**

- cessation of the respiratory movements
- loss of consciousness
- drop in BP
- stop respiration due to inhibition of the RC

### **Phase 4 (terminal)**

- deep sighs, like gasping breath
- death occurs from paralysis of the bulbar respiratory center
- heart continues to contract 5-15 minutes after the cessation of breathing

## **Pulmonary hypertension**

Pulmonary hypertension — is an increase in pressure in the vessels of the pulmonary circulation.

### **Causes:**

- Euler-Liljestrand reflex. ↓oxygen tension in the alveolar air → ↑ tone of the pulmonary arteries. If in certain area of lung alveolar ventilation is reduced accordingly should decrease blood flow. Obstructive pathology → ↑ resistance and pressure in pulmonary circulation
- Reduction of vascular (reserve) channel.

↑ blood flow meets ↑ resistance (exercise)

- ↑ blood viscosity.
- ↑ cardiac output.
- BAS. Serotonin develops microcirculation disorder. During hypoxia ↓lung destruction of norepinephrine, that narrowing arteriolas.
- Left ventricular HF

### **Types and causes of pulmonary hypertension**

1. Precapillary pulmonary hypertension observed in:
  - arteriolar spasm
  - compression / obturation of capillary of pulmonary vessels
  - irritation of receptors of pulmonary vessels by embolus
  - ↑ pressure in pulmonary artery may be in compression of pulmonary capillary due to ↑ pressure in respiratory tract and alveoli, which is observed when coughing
2. Post-capillary pulmonary hypertension (manifested in form of lungs stagnation) develops at:
  - compression of pulmonary veins
  - mitral stenosis
  - cardiosclerosis
  - hypertension
  - left ventricular failure
  - shunting of pulmonary blood flow
  - in heart defects (with shunt right - left): tetralogy of Fallot, transposition of great vessels, atrophy of valves in pulmonary artery
  - lung hypotension in collapse, shock
3. Disorders of ventilation-perfusion relationships

## **Adult Respiratory Distress Syndrome (ARDS)**

ARDS is a disease characterized by widespread breakdown of the alveolar and/or pulmonary capillary membranes. ARDS occurs after a major pulmonary, cardiovascular, or system-wide insult.

### **Causes of Adult Respiratory Distress Syndrome**

ARDS can occur as a result of direct injury to the capillaries of the lungs or to the alveoli. However, because the capillary and the alveolus are so intimately connected, extensive destruction of one typically leads to destruction of the other. This destruction occurs because of the release of lytic enzymes when cells die; it also occurs with activation of the inflammatory reaction subsequent to cell injury and death.

### **Risk factors for ARDS:**

- Gram-negative sepsis (40% of cases)
- Gastric aspiration (30% of cases)

- Severe trauma with shock (10% of cases)
- Diffuse pulmonary infections, heroin, smoke inhalation

### **Capillary Destruction**

If breakdown is initially of the capillary membrane, movement of plasma and red blood cells into the interstitial space occurs. This increases the distance across which oxygen and carbon dioxide must diffuse, decreasing the rate of gas exchange. Fluid accumulating in the interstitial space moves into the alveoli, diluting surfactant and increasing surface tension. The exertion of pressure needed to inflate the alveoli is vastly increased. Increased surface tension coupled with edema and swelling of the interstitial space leads to widespread compression atelectasis, resulting in a loss of lung compliance, significantly decreased ventilation, and hypoxia. Causes of pulmonary capillary breakdown include septicemia, pancreatitis, venoms, and uremia. Pneumonia, smoke inhalation, trauma, and near drowning can also destroy the capillary membrane and initiate ARDS.

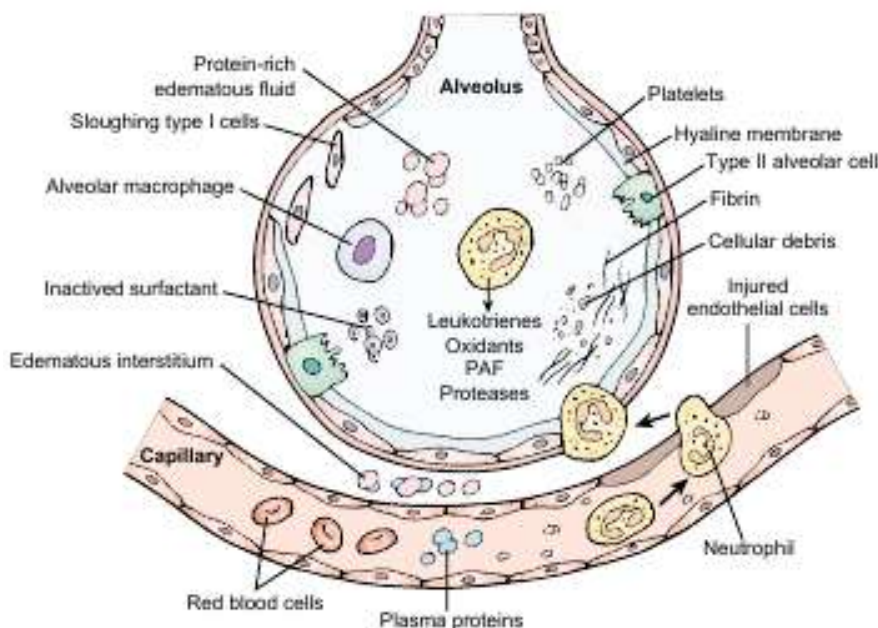
### **Alveolar Destruction**

When the alveoli are the initial damage site, the surface area available for gas exchange is reduced, and, again, the rate of gas exchange is decreased. Causes of alveolar damage include pneumonia, aspiration, and smoke inhalation. Oxygen toxicity, which occurs after 24 to 36 hours of high-oxygen treatment, can also be a cause of alveolar membrane damage through the production of oxygen free radicals and by damaging the surfactant-producing cells.

Without oxygen, vascular and pulmonary tissues become hypoxic, leading to further cell injury and death. Once the alveoli and capillaries are damaged, inflammatory reactions, including macrophage and neutrophil infiltration and the release of various cytokines, are initiated that lead to swelling and edema of the interstitial space and damage to the neighboring capillaries and alveoli. Within 24 hours of ARDS onset, hyaline membranes form within the alveoli. These are white fibrin deposits that progressively accumulate and further decrease gas exchange. Eventually, fibrosis obliterates the alveoli. Ventilation, respiration, and perfusion are all compromised. Mortality associated with ARDS is approximately 50%.

### **Pathogenesis**

Acute damage to alveolar capillary walls and epithelial cells → alveolar macrophages release cytokines → cytokines are chemotactic to neutrophils → neutrophils transmigrate into the alveoli through pulmonary capillaries → capillary damage causes leakage of a protein-rich exudate producing hyaline membranes. → neutrophils damage type I and II pneumocytes → decrease in surfactant causes atelectasis with intrapulmonary shunting → repair by type II pneumocytes → progressive interstitial fibrosis (restrictive lung disease)



**FIGURE The mechanism of lung changes in ARDS.** Injury and increased permeability of the alveolar capillary membrane allow fluid, protein, cellular debris, platelets, and blood cells to move out of the vascular compartment and enter the interstitium and alveoli. Activated neutrophils release a variety of products that damage the alveolar cells and lead to edema, surfactant inactivation, and formation of a hyaline membrane.

### **Clinical Manifestations**

- Significant dyspnea.
- Decreased lung compliance.

- Rapid shallow breathing initially, resulting in respiratory alkalosis as carbon dioxide is blown off. Later, as the person fatigues, breathing may become slow and infrequent.

### **Diagnostic Tools**

Arterial blood-gas analysis demonstrates reduced arterial oxygen concentration despite oxygen therapy. Oxygen therapy is ineffective in ARDS, regardless of the amount of oxygen supplied, because diffusion of the gas is limited owing to fibrin accumulation, edema, and capillary and alveolar breakdown.

### **Complications**

Respiratory failure may develop as the disease progresses and the individual has to work harder to overcome decreased compliance of the lungs. Eventually, exhaustion sets in and ventilation slows. This results in respiratory acidosis as carbon dioxide accumulates in the blood. Respiratory slowing and a fall in arterial pH are indications of impending respiratory failure and possible death.

Pneumonia may develop after ARDS because of fluid accumulation in the lungs and poor lung expansion. Renal failure and gastrointestinal stress ulcer can occur as a result of hypoxia.

Disseminated intravascular coagulation may develop because of the large amount of tissue that can be destroyed during ARDS.

### **Infant respiratory distress syndrome (IRDS) = respiratory distress syndrome of newborn (RDSN)**

IRDS is a result of surfactant deficiency, which causes increased surface tension in the air-liquid interface of the terminal respiratory units leading to atelectasis, increased ventilation perfusion mismatch, and potential lung injury due to a marked pulmonary inflammatory response. IRDS formerly known as hyaline membrane disease, is the major cause of neonatal respiratory distress.

The incidence of IRDS increases with decreasing gestational age, and infants born below 30 weeks gestation are at the greatest risk for IRDS.

### **Causes:**

- Hyaline membrane disease (HMD) — deficiency of surfactant as a consequence of either insufficient production by the immature lungs or a genetic mutation in one of the surfactant proteins, SP-B.
- Infection
- Retained fetal lung fluid (transient tachypnoea of the newborn (TTN))
- Aspiration (meconium, blood or liquor)
- Pneumothorax
- Congenital abnormalities including: pulmonary hypoplasia, diaphragmatic hernia, airway obstruction, congenital cardiac disease

### **Pathogenesis:**

The primary cause of RDS is inadequate pulmonary surfactant. The structurally immature and surfactant-deficient lung has ↓compliance and a tendency to atelectasis; other factors in preterm infants that ↑ the risk of atelectasis are decreased alveolar radius and weak chest wall. With atelectasis, well perfused but poorly ventilated areas of lung lead to V/Q mismatch (with intra-pulmonary shunting) and alveolar hypoventilation with resultant hypoxemia and hypercarbia. Severe hypoxemia and systemic hypoperfusion result in decreased O<sub>2</sub> delivery, anaerobic metabolism and subsequent lactic acidosis. Hypoxemia and acidosis may further impair oxygenation by causing pulmonary vasoconstriction, resulting in right-to-left shunting at the levels of the foramen ovale and ductus arteriosus. Other factors, such as baro/volutrauma and high PaO<sub>2</sub>, may initiate release of inflammatory cytokines and chemokines causing more endothelial and epithelial cell injury. The injury results in reduced surfactant synthesis and function as well as increased endothelial permeability leading to pulmonary edema. Leakage of proteins into the alveolar space further exacerbates surfactant deficiency by causing surfactant inactivation. Macroscopically, the lungs appear congested, atelectatic and solid. Microscopically, diffuse alveolar atelectasis and pulmonary edema are seen. An eosinophilic membrane composed of a fibrinous matrix of materials from the blood and cellular debris (the hyaline membrane) lines the visible airspaces that usually constitute dilated terminal bronchioles and alveolar ducts.

### **Clinical features:**

Signs of RDS appear immediately after birth or within 4 h. RDS is characterized by tachypnea (>60 breaths/min), intercostal and subcostal retractions, nasal flaring, grunting, and cyanosis in room air.

Tachypnea is due to an attempt to increase minute ventilation to compensate for a decreased tidal volume and increased dead space. Retractions occur as the infant is forced to generate a high intrathoracic pressure to expand the poorly compliant lungs. Grunting results from the partial closure of the glottis during forced expiration in an effort to maintain FRC. After an initial improvement with resuscitation and stabilization, an uncomplicated course is often characterized by a progressive worsening for 48 to 72 h. Recovery usually coincides with a diuresis after an initial period of oliguria. Other clinical features may include hypotension, acidosis and hyperkalemia. The typical chest radiograph shows low lung volumes and a bilateral, reticular granular pattern (ground glass appearance) with superimposed air bronchograms. In more severe cases, there is complete "white out" of the lung fields. Application of positive airway pressure may minimize or even eliminate these radiographic findings. Acute complications include air leaks and intracranial hemorrhage. Long-term, RDS has been associated with an increased incidence of chronic lung disease, ROP, and neurologic impairment.

### **Questions for self-control of knowledge:**

1. Give definition of "respiratory failure".
2. What are mechanisms of extrapulmonary disorders of alveolar ventilation?
3. Describe type of obstructive ventilation disorders in upper and lower airway
4. What are mechanisms of early expiratory airway closure?
5. Describe type of restrictive disorders of alveolar ventilation.
6. What is pulmonary surfactant system?
7. What are causes and mechanisms of ARDS?
8. Describe pre-and postcapillary forms of pulmonary hypertension.
9. Name pathological types of breath?
10. What are functional tests to assessment external respiratory disorders?
11. Describe compensatory-adaptive processes in external respiratory system in damaging single its parts?
12. What are causes of metabolic disturbances in lungs? How these disturbances are effect on hemodynamics and hemostasis system?

### **Tasks for self-managed student work:**

1. Etiology and pathogenesis of acute respiratory failure in respiratory distress syndrome.
2. Metabolic changes in lung function and effect of these changes on hemostatic system.
3. Principles of prevention and therapy of external respiration pathology.

## **Literature**

### **Basis literature:**

1. Литвицкий, П. Ф. Патофизиология = Pathophysiology: лекции, тесты, задачи : учеб. Пособие / П. Ф. Литвицкий, С. В. Пирожков, Е. Б. Тезиков. – М. : ГЭОТАР-Медиа, 2016.– 432 с.

### **Additional literature:**

2. Kumar, V. Robbins and Cotran Pathologic basis of disease, 7th Edition / V.Kumar, A.K. Abbas, N. Fausto. — Philadelphia: Elsevier Inc., 2005. – 1629 p. Режим доступа: <http://www.rkmyat.in/up1/34/1629.pdf>. – Дата доступа: 30.08.2016.
3. Кидун, К. А. Тестовые задания по патологической физиологии = Test tasks on pathological physiology : в 3-х ч. Ч. 3, Частная патофизиология : учеб.-метод. пособие для студ. 3 курса фак. по подг. спец. для зарубеж. стран, обуч. на англ. яз. по спец. «Лечебное дело», мед. вузов / А. К. Кидун. – Гомель : ГомГМУ, 2015. – 113 с.
4. Научная электронная библиотека eLIBRARY.RU [Электронный ресурс] / Научная электронная библиотека. – М., 2005. – Режим доступа: <http://www.elibrary.ru>. – Дата доступа: 26.08.2017.

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