GOMEL STATE MEDICAL UNIVERSITY
Normal and Pathological Physiology Department

PHYSIOLOGY OF RESPIRATION

REGULATION OF RESPIRATION

Lecture 3

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Lecture plan:

1. Influence of irritant receptors on the respiratory center. Participation of the proprioreceptors of respiratory muscles in the regulation of respiration.
2. Role of the pneumotaxic center in the regulation of respiration. Role of the upper airway receptors in the activation of the respiratory center.
3. Role of the cerebral cortex in the regulation of respiration. Influence of nonspecific factors on respiration. Coordination of respiration and circulation. Regulation of the tone of the smooth muscles of the bronchi and bronchioles.
4. First inspiration of newborns.
5. Features of respiration in different conditions.

1. Influence of irritant receptors on the respiratory center

In the epithelium and subepithelial layer of the airways, there are receptors that are called ***irritant receptors***. They are especially numerous in the region of the lung roots.

They have the properties of:

a) mechanoreceptors;

b) chemoreceptors.

They are excited in dramatic changes (increase or decrease) of the lung volume. The excitation threshold in them is higher than in all other receptors. Impulses in the afferent fibers of the irritant receptors arise in groups only within a short period of time during the change of the lung volume but some of them are excited also during general inspiration and expiration.

As stimulators of the irritant receptors there can be:

- **dust particles;**
- **mucus;**
- **gases of caustics** (tobacco smoke, ammonia, etc.);
- **biologically active substance** formed in the walls of the airways (histamine);
- they can be strongly excited in a number of **diseases** (pulmonary edema, pneumothorax, bronchial asthma, etc.).

Stimulation of the irritant receptors results in:

- **cough;**
- **unpleasant sensations like burning or scratching;**
- **intensifying of inspiratory activity;**
- **shortening of expiratory phases;**
- **hyperpnoea;**
- **reflex of bronchoconstriction.**

The irritant receptors take part in appearance of an original reflex, the so-called ***«deep sigh»*** reflex. At rest a person makes deep sighs approximately **3 times per hour.** A sigh results from an intermittent inflation of the lungs with a large volume, i.e. this is essentially a deep breath that is incorporated into the ventilation cycle and results in excitation of irritant receptors. The sigh is accumulated on one of the next inspirations, which results in lung expansion and regeneration of their ventilation.

J receptors (juxtacapillary) are located in the alveolar wall near the capillaries. These receptors are stimulated by the increase of the alveolar interstitial fluid volume. Their activation results in ↑ of respiration rate and ↓ of tidal volume (rapid and shallow breathing).

Such effects occur in case of pulmonary edema or pneumonia.

Participation of the proprioreceptors of respiratory muscles in the regulation of respiration

The receptors of respiratory muscles take part in the regulation of respiration (***proprioreceptors***), in particular, stretch receptors — ***muscular spindles.***

Due to heavy breathing (inspiration or expiration) the receptors are excited, which results in increased contractions of respiratory muscles (proprioceptive reflex). Thus, the conformity of the mechanical parameters of respiration to the resistance of the respiratory system is reached.

2. Role of the pneumotaxic center in the regulation of respiration

The pneumotaxic center is located in the pons varolii. If to dissect the brain stem below the *pons varolii*, breathing does not stop, but its rhythm is irregular, which leads to respiration at which long expiration may be interrupted with short inspirations. This respiration type is called ***gasping*.**

If, after the brain dissection on the border between the pneumotaxic center and medulla, to perform vagotomy, apnoea will occur at the inspiratory phase. Sometimes this condition is interrupted with the expiratory movements. Such sustained, gasping inhalation followed by short, inefficient exhalation is called ***apneusis***. In these conditions braking influences on inspiration are eliminated. It means that the pneumotaxic center takes part in the changing the inspiration-expiration phases.

The pneumotaxic center:

- **raises the activity of the inspiration standstill mechanism.**
- **activates the expiration center.**
- **provides smooth transition of the inspiration-expiration phases.**

Thus, in the pons varolii there is a central mechanism promoting the change of the respiration phases, that is the periodic activity of the respiratory center.

Role of the upper airway receptors in the activation of the respiratory center

An inspiratory stream of air stimulates the receptors of the nasal mucous membrane (mainly, cold receptors). Impulses from the receptors of the nasal mucous membrane go to the brain along the fibers of the trigeminal nerve and influence the respiratory center (weak inhibiting).

Stimulation of the receptors of the upper airways causes a number of protective reflexes:

Sneezing — strong expiration through the nose (stimulation of the receptors of the nasal mucous membrane).

Cough. It develops under the stimulation of the receptors of the larynx, trachea. A cough begins with a deep breath in, at which point the opening between the vocal cords at the upper part of the larynx shuts, allowing additional air to pass through into the lungs. As the diaphragm and expiratory muscles press against the lungs, the pressure in the airways increase, and the larynx and the vocal cords open, producing an explosive outflow of air and a rushing sound as the air moves very quickly past the vocal cords at a speed greater than 160 km per hour.

Plunger reflex. The action of water on the receptors of the inferior nasal ways causes apnea, preventing water into the airways.

Respiration is inhibited during swallowing, ingress of caustics (gases of ammonium) into the nasal cavity.

3. Role of the cerebral cortex in the regulation of respiration

Considering the mechanisms of the regulation of respiration, it is necessary to outline two groups of processes:

- ***Maintenance of constant gas*** pressures of arterial blood. It is provided basically by the respiratory center (***homeostatic reaction***).
- ***Processes of adjusting respiration to changing conditions of the environment and vital activity of the organism*** (***behavioral* regulation**).

Changes of respiration under different conditions: ***speech, singing, attention, emotions, during sleep, influence of the environment, etc*****.**

In the processes of respiratory adaptation to the demands of organism`s physical exertion a special role is played by the **cerebral cortex**.

The changes of respiration differ during excitation of the cortex regions. The removal of the cerebral cortex results in increased lung ventilation.

The participation of the cerebral cortex in the regulation of breathing is proved by the method of **conditioned reflexes** (***pre-start state of sportsmen***), **opportunity of voluntary breath-holding and intensified respiration.**

Influence of nonspecific factors on respiration

These are factors which directly do not participate in the regulation of respiration but influence lung ventilation.

Cold and **warmth** influence the skin, which results in excitation of the respiratory center (in a newborn breathing may be stimulated by contrast baths). Body temperature changes: fever and moderate hypothermia increase lung ventilation. Deep hypothermia, on the contrary, suppresses the activity of the respiratory center.

Pain. Lung ventilation at the first moment of a pain effect can lead to apnoea (in inspiration). Then respiration becomes deeper and more frequent.

Hormones. During physical exercise *adrenaline* increases lung ventilation.

Coordination of respiration and blood circulation

Normal gas exchange in the lungs and tissues and its adaptation to the demands of an organism are provided by the changes of not only lung ventilation but also blood circulation.

1. The reflex influences proceeding from the reflexogenic regions (aortal and carotid) affect the functioning of the cardiovascular and respiratory systems.

2. Respiratory arrhythmia of cardiac activity and blood pressure (the change of heart rate according to the phases of respiration).

3. During physical work and under emotional stress — cardiac output and lung ventilation increase raising the respiratory minute volume.

4. A hemorrhage is accompanied by reduced blood pressure and increased lung ventilation, etc.

This coordination is provided by a close interaction of the neurohumoral mechanisms of the regulation of the cardiovascular and respiratory systems and is carried out mainly by the cerebral cortex and underlying structures among which the most important role is played by the hypothalamus.

Regulation of the tone of the smooth muscles of the bronchi and bronchioles

The tone of the bronchial smooth muscles is regulated by nervous and humoral factors.

The influence of the **parasympathetic nervous system** on the tone of the smooth muscles of the bronchi is exerted by the nerve fibers of the vagus nerve. **The increased tone of the parasympathetic nervous system increases the tone of the bronchial smooth muscles and leads to the narrowing of the bronchi.** The mediator of the vagus nerve fibers innervating the smooth muscles of the bronchi is acetylcholine. It causes contractions of these muscles through the activation of muscarinic **cholinoreceptors.**

The narrowing of the bronchi can be caused also by activating local reflexes in the vegetative ganglions of the airways.

The sympathetic nervous system causes **bronchodilation**. The bronchial tree is very much exposed to adrenaline and noradrenalin released into the blood by the sympathetic stimulation of the adrenal gland medulla. Both these hormones, especially adrenaline because of its greater stimulation of **beta-adrenergic receptors**, cause dilation of the bronchial tree.

Several substances can cause bronchoconstriction. The most important are **histamine and leukotrienes**. They are released in the lung tissues by leukocytes and mast cells and can cause airway obstruction (for example, in allergic reactions).

4. First inspiration of newborns

Umbilical ligation and development of hypoxia are followed by inhibition of the intra-uterine respiratory movements, and then within 1–1.5 minute the first respiratory movements appear.

During the first inspiration the thorax expands, ribs rise, their heads are fixed in the intervertebral fossae and they do not return to their initial position.

During the first respiratory movement negative pressure develops in the thoracic cavity which is 10–15 times higher than during a subsequent quiet breath.

Such a significant increase of negative pressure provides overcoming of the elastic recoil of pulmonary tissue and lung expansion. Active inspiration is followed by active expiration.

During subsequent respiratory movements lung distension is increased, their elastic recoil is reduced, the work of the respiratory movements is reduced.

After three respiratory movements pulmonary tissue becomes regularly pellucid, therefore, stretched. That is why the first inspiration is the heaviest, the most difficult.

Factors causing the first inspiration:

1. Umbilical ligation — ***anoxia***. Decreased O_2 level in the blood increases the excitability of the respiratory center and its sensitivity to CO_2.

2. Accumulation of CO_2 — irritant capable to activate the respiratory center.

3. Metabolic acidosis developing after the removal of the placenta when extraction of acidic products is stopped and the alkaline reserves are reduced (decrease of pH).

4. Along with it, the stimuli for the appearance of respiration are **various thermal, mechanical, thermal, and sensory irritants** influencing the newborn who upon birth gets into a completely different environment.

5. Besides, there is an opinion that after the transit of a fetus through the **birth canal, the constrained thorax** due to its elasticity sharply extends, and significant negative pressure is accumulated in the thoracic cavity promoting the entry of air into the airways.

5. Features of respiration in different conditions

1. Respiration in muscle work. A person at **rest** consumes 250–300 mL of oxygen per 1 min, in fast walking — up to 2.5 L per minute, in hard **physical work** — up **to 4 L per minute.** Simultaneously, the formation of CO_2 and acidic products increases.

Lung ventilation increases proportionally to energy expenses (can reach up to 120–150 L per minute).

As muscle work starts, pCO_2 rises and blood pH goes down. Lung ventilation increases when the gas composition of blood is not changed yet. It means that at the beginning of muscle work***, hyperpnea*** is induced by nervous factors. The cerebral cortex, producing voluntary movements, activates the respiratory center directly and through the hypothalamus. Besides, the essential role in the given process is played by impulses from the proprioreceptors (mechanoreceptors) of contracting muscles.

Then during muscle work there is a slow increase of lung ventilation up to a steady state.

Lactic acid formed during muscle work cannot be oxidized completely to H_2O and CO_2. It is accumulated in muscles and comes into the blood. This is an oxygen debt. Respiration strengthens and there comes a state when respiration and blood circulation achieve a certain level when short-breathing stops (dead point in sportsmen). Then hyperpnoea leads to the removal of CO_2 excess and rising of pH. The balance between the arrival and consumption of O_2 (a second wind phenomenon in sportsmen) is established.

At this phase the chemoreceptors are stimulated. Increased CO_2 formation in increased lung ventilation provides constant CO_2 volume in the blood.

Stimulation of the chemoreceptors is strengthened by the action of the lactic acid lowering the pH level of blood. A rise of the body temperature is also significant since it increases the respiration rate through the hypothalamus.

After the end of the work, lung ventilation is reduced but not to the initial level. It remains increased for some minutes under the influence of lactic acid and other suboxides.

There is gradual «repayment» of the ***oxygen debt***.

Along with increased lung ventilation in physical work there are increased values of:

- heart rate (from 70 up to 150–200 beats per minute);
- stroke volume (from 70 mL up to 200 mL);
- cardiac output (from 4–5 L to 20–30 L);
- blood flow in working muscles;
- dissociation of HbO_2 (decrease of pH, rising of pCO_2, temperature);
- oxygen utilization coefficient increases from 30–40 % to 50–60 %.
- oxygen capacity of blood due to the release of depot blood. Besides, water loss occurring during the work due to sweating results in increased erythrocyte and Hb concentrations.

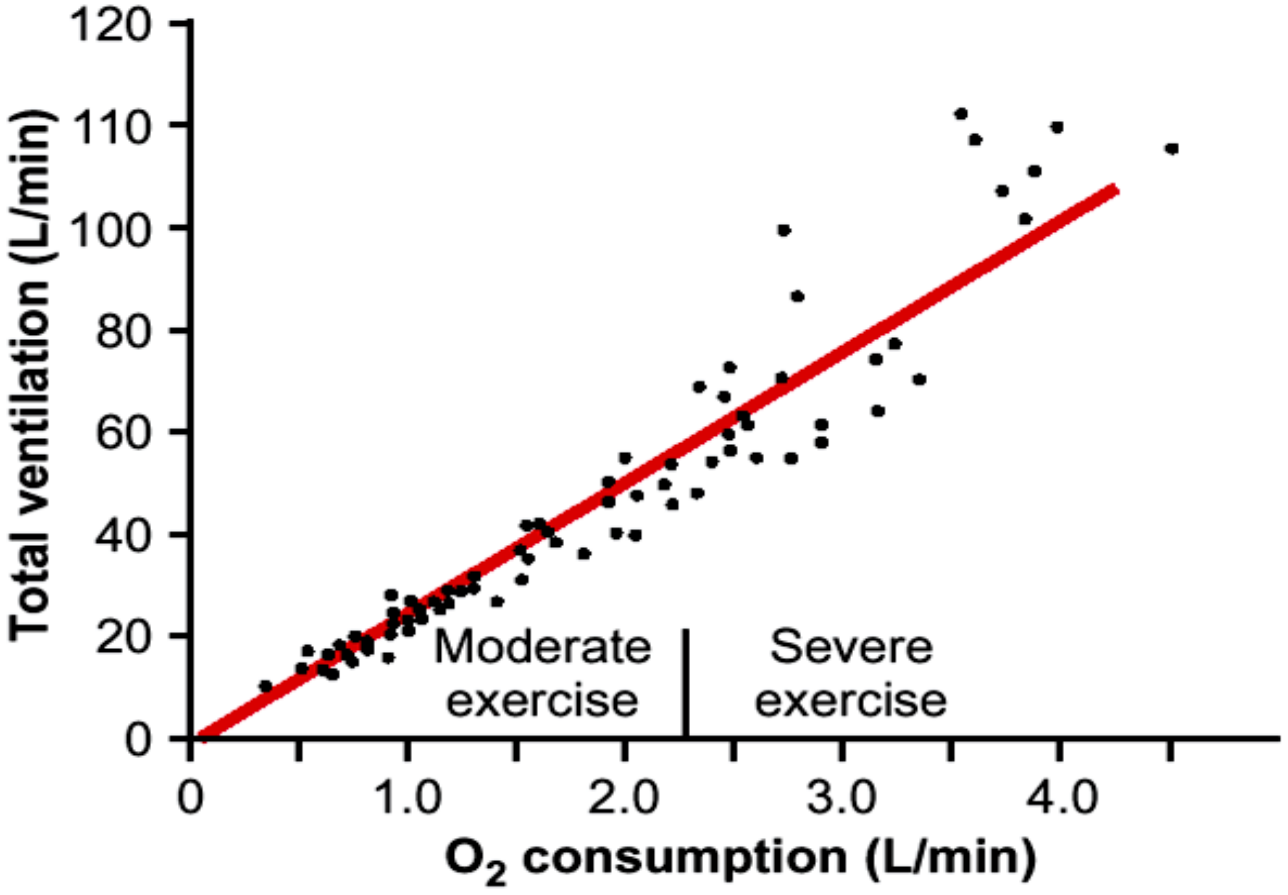

Figure — Increase of ventilation under exercise

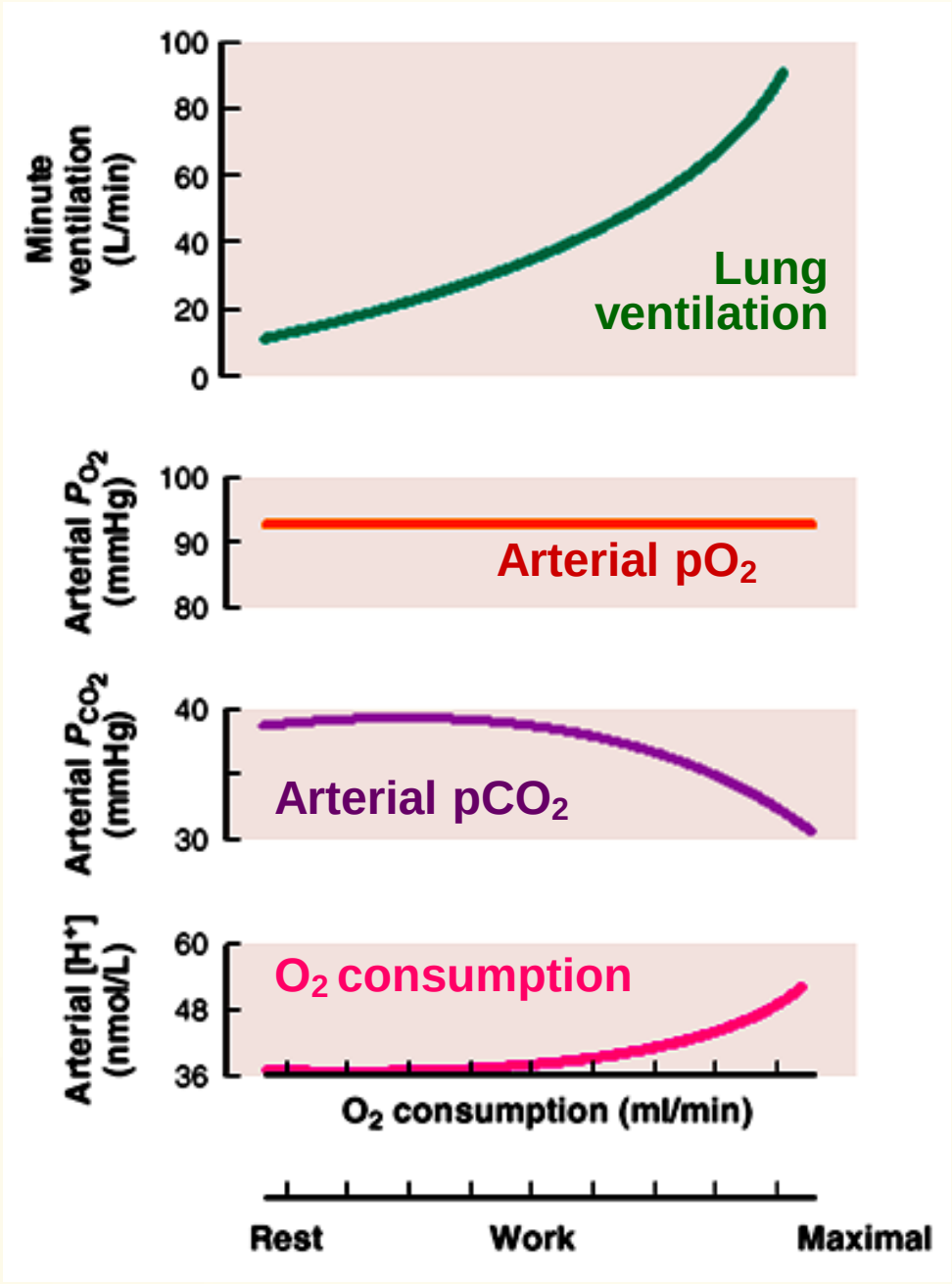

Figure — Effects of exercise

(Arterial pO_2 does not change even under heavy exercise)

2. Respiration in the conditions of low atmospheric pressure (*climbers, depressurization cabins of pilots, parachutists, artificial pressure chamber*). The consequence is ***hypoxia as a result of decreased pO_2***.

At high altitudes (higher than **2 km)** lung ventilation increases due to the stimulation of the carotid and aortal chemoreceptors.

Elevated blood pressure and heart rate are directed to intensify the supply of tissues with O_2.

But increased lung ventilation causes a decreased pCO_2 level (*hypocapnia*). Hypocapnia inhibits the respiratory center thus limiting lung ventilation.

At an altitude of **4–5 km** mountain illness develops. The ***signs of mountain or altitude illness are*** drowsiness, decrease of appetite, apathy or euphoria, short-breathing, tachycardia, giddiness, vomiting, headache. Slowly developing hypoxia is especially dangerous because a person can lose consciousness before realizing the signs serving as signals of danger.

At an altitude of **7 km** loss of consciousness, breathlessness and blood circulation disorders hazardous for life can occur. As a result of hypoxia there are no unpleasant sensations, there is no feeling of anxiety or awareness of danger, and loss of consciousness can occur suddenly.

At high altitudes life is possible only if oxygen devices are used or in pressurized cabins, space suits in which high atmospheric pressure is maintained.

A long stay in the conditions of low atmospheric pressure is accompanied with ***acclimatization***, such as:

1. The erythrocyte count in the blood (erythrogenesis strengthens) is increased.

2. The amount of Hb is increased, which results in augmentation of the oxygen capacity of blood.

3. Lung ventilation increases.

4. Dissociation of HbO_2 increases (due to augmentation in erythrocytes of 2,3-glycerophosphate).

5. The length and density of capillaries increase.

6. Cell resistance (especially nervous ones) to hypoxia increases.

All effects of hypoxia can be divided into **4 zones** separated from each other by effective thresholds

1. *Neutral zone* (*up to 2,000 m*) — physiological functions practically do not suffer.

2. *Zone of complete compensation* (2,000–4,000 m). Even in a person at rest heart rate, stroke volume, CO and MLV increase. Physical and mental working capacity is a little reduced.

3. *Zone of incomplete compensation* or zone of danger (*4,000–7,000 m*). The threshold of safety (4,000 m) is reached. Muscular twitching appears, blood pressure decreases, consciousness is dimmed (foggy brain). Work capacity is reduced, the ability to decision-making and reactions is affected.

4. *Critical zone (>7,000 m)* pO_2 in alveolar air becomes lower than the critical threshold (30–35 mm Hg). Loss of consciousness, cramps occur. This process is reversible if the duration of the stay is not long. If a person stays at this altitude for a long time, the CNS is damaged, which may lead to death.

7–8 km — life-hazardous for most people.

8.5–9 km — the limit above which a human cannot ascend without O_2.

9–12 km — a human must apply an oxygen device.

12 km — a human must wear a space suit in which high pressure is maintained.

A person can hold breath for 1–2 minutes. After prior hyperventilation a trained person can hold breath for 3–4 minutes. This is the limit of human stay under water. But the danger is that a rapid decrease of blood oxygenation can result in loss of consciousness, and under the influence of the increased pCO_2 level of blood breath will occur, and the diver will be breathless having water in the lungs.

Table — Critical zones of hypoxia (in respiration at the lowered atmospheric pressure)

Name of a zone	Altitude	Changes in the functioning of the organism
Neutral zone	up to 2,000 m	Physiological functions practically do not suffer
Zone of complete compensation	2,000–4,000 m	• Lung ventilation increases (due to the stimulation of carotid and aortal chemoreceptors). • Heart rate increases. • Systolic and minute volume of blood increase. • Blood pressure increases. • Physical and mental work capacity is a little reduced
Zone of incomplete compensation (zone of danger)	4,000–7,000 m	• Signs of mountain illness develop: apathy or euphoria, shortbreathing, tachycardia, giddiness, vomiting, headache. • Muscular twitching appears. • Blood pressure decreases. • Working capacity is reduced, the ability to decision-making and reactions is affected. • Consciousness is dimmed
Critical zone	>7000 m	• pO_2 in alveolar air becomes lower than the critical threshold (30–35 mm Hg). • Cramps, loss of consciousness, breathlessness, and blood circulation disorders dangerous for life can occur. If such a state lasts for a long period of time, the central nervous system is damaged, which may cause death

3. Respiration in the conditions of high atmospheric pressure (*work under water, diving*). The pressure in water increases by about 1 atm for each 10 m increase in depth. At a depth of 100 m a person should inhale a gas mixture under a pressure exceeding atmospheric pressure by 10 times. Therefore, oxygen in the gas mixture is added at an amount so that its pO_2 at the depth was close to that in usual conditions.

At depths under the influence of pressure gases are dissolved in the blood. Due to fast decompression gases pass from the dissolved state into gas state, and air vesicles are formed, which results in gas embolism (***Caisson disease***). If a diver does not fully exhale upon ascent, the air in the lungs expands as the pressure decreases, overinflating the lungs and forcing air vesicles (emboli) into the bloodstream.

When the gas emboli reach the arteries to the brain, the blood blockage causes unconsciousness. **Other symptoms are: muscle pain, giddiness, vomiting, shortbreathing.** In this case it is necessary to place the person into a compression chamber, to create the pressure in it conforming the pressure at the depth from which the person has been lifted; which again will lead to dissolution of the air vesicles in the blood, and then gradually to decreased pressure (decompression). Gas transition from its dissolved state into gas will happen slowly and the vesicles will be removed from the organism without causing gas embolism.