Chapter 1

Pathophysiology of the respiratory system

1.1 The transport of oxygen to the organism

The transport of substances across the membranes, the synthesis of necessary substances, the maintenance of bioelectric potentials and many other processes in the organism can be kept in action at the required level only by continual supply of energy. One part of the energy is consumed by the mechanical activity of organs and of the organism as a whole. **The generation of ATP, as a form of energy utilization in the cells, depends on oxygen supply**. The atoms of hydrogen are released in mitochondria from molecules of glucose and subsequently bind with oxygen in a series of oxidative reactions, while energy from adenosine diphosphate is utilized for generation of ATP. The lack or insufficient supply of oxygen, and also the inability to utilize oxygen result in a condition called hypoxia. If hypoxia lasts for a certain time, it causes a functional impairment of the cells and finally their death. Hypoxia leads to an important deterioration of energy production in the cells and hence it disturbs their equilibrium. Several disorders of organism may result in hypoxia.

If the cell needs energy, the ATP phosphate radical is hydrolized, energy is released from its bond and ADP remains. The repeated synthesis of ATP depends on series of chemical reactions. Cytoplasmatic enzymes convert glucose to pyruvate, fatty acids and amino acids to acetoacetic acid. Pyruvate and acetoacetic acid are converted to acetyl-CoA which is transported into the mitochodria. Acetyl-CoA is a common intermediate metabolite of carbohydrates, proteins and fats, which initiates the oxidative phosphorylation after its entry into the Krebs cycle. Mitochondria contain enzymes forming a chain for transport of electrones. The external membrane separates the mitochondria from the cellular cytoplasm. It is smooth and contains channels enabling the passage of small molecules. The inner mitochondrial membrane is infolded thus forming the cristae and its permeability is very low. The space between the membranes, i.e. the intermembraneous space, is called matrix. The matrix contains enzymes responsible for several metabolic processes. The inner mitochondrial membrane contains enzymes of the respiratory chain. A part of ATP, as a product of Krebs cycle, is synthetized in mitochondria. Approximately 90 per cent of ATP is generated by the subsequent oxidation of the released hydrogen. Atoms of hydrogen and electrons (H^+ and e^-) are transferred through a chain of oxidation-reduction reactions to oxygen which represents the final recipient for the formation of water. During these reactions ATP is generated. This process of electron transfer from the donor to the recipient, resulting in phosphorylation of ADP to ATP is called oxidative phosphorylation. The molecules of ATP are sythetized in the mitochondrial matrix. Their utilization takes place in the cellular cytoplasm. They are tranferred through the mitochondrial membrane by the enzymatic system called translocase. By this system one molecule of ATP is exchanged for one molecule of ADP.

The oxidative phosphorylation depends on ade-

quate oxygen supply, on demands of the cells, and on their ability to utilize oxygen. The demands of the cells for oxygen depend on their metabolic activity. The higher the metabolic activity, the higher the concentration of hydrogen ions which are the final products. The consequent change in pH of blood acts as a stimulus for the respiratory centre to increase the oxygen supply for the oxidative phosphorylation. The rate and the depth of respiration, the blood saturation with oxygen and carbon dioxide, the total capacity of the oxygen transfer and the degree of perfusion determine the quantity of oxygen, entering the cells per minute. The intact mitochondria, the respiratory chain enzymes and the transport of electrons determine the ability of the cell to utilize the oxygen effectively.

1.1.1 Oxygenation

This term includes the processes of oxygen transport to the tissues and of carbon dioxide and other waste products elimination. The oxygenation is effective when there is equilibrium between the supply and the need of oxygen. **The oxygen supply of the cells depends on pulmonary ventilation, perfusion, on exchange and binding of respiratory gases and on the ability and capacity of blood to transport the oxygen**.

Ventilation, perfusion and exchange of the respiratory gases in the lungs are the primary functions of the cardiopulmonary system. Ventilation includes the mechanics of inspiration and the providing of atmospheric air to the alveoli, and the mechanics of expiration during which the air with decreased oxygen and increased carbon dioxide levels is expired. Ventilation depends on many factors – neurogenic and chemical factors, respiratory muscles, compliance of the lung tissue, and the airway resistance to the airflow. The exchange of respiratory gases in the organism depends on oxygen diffusion from alveoli to the blood and then from the blood to the tissues. In this way, but vice versa carbon dioxide is eliminated from the body. The exchange of respiratory gases depends also on the integrity, thickness and area of the membrane which represents the site of the gas exchange. It further depends on the relative gradient of gases and their solubility on both sides of the membrane, on the affinity of haemoglobin to oxygen, and on the distribution of ventilation and perfusion.

The perfusion of the lung represents the bloodflow enabling the oxygen transport between alveoli and blood. It depends on the pumping capacity of the heart, the condition of the pulmonary vessels, and on pressure relations.

The utilization of oxygen represents processes by which oxygen is used in ATP formation. It depends on the condition of cells and the mitochondrial mechanisms. The rate of oxygen utilization depends on the metabolic activity.

1.1.2 Hypoxia

Between the requirements of cells and the actual oxygen supply can arise differences due to disturbance of some processes. The result is the lack of oxygen in tissues. It means that oxygenation is not effective. In this situation a condition develops which is called hypoxia. Hypoxia, as a term is used frequently. But it should be used exclusively **in relation to the condition in which the oxygenation at the cellular level is impaired or inadequate**. The partial pressure of oxygen (pO_2) in tissue is usually lower. It can be the consequence of the disturbed oxygenation.

Under the condition of hypoxia in organism the oxidative phosphorylation is disturbed and therefore also the generation of energy in the cell is impaired. During the lack of oxygen lasting one minute, the ATP to ADP ratio falls ten times. Glycolysis, which is a series of chemical reactions, by which glucose is converted to pyruvate and hydrogen, does not need oxygen. Glycolysis can function also during hypoxia, the gain of ATP however, is low. If the supply of oxygen is normal, glycolysis cannot continue, because it is inhibited by the feedback mechanism of pyruvate and hydrogen. Under anaerobic conditions pyruvate and hydrogen are converted to lactate, which inhibits the glycolysis by the feedback mechanism. Anaerobic glycolysis provides energy during the insuficient oxygen supply. This way of energy gaining cannot be useful for a long period of time. After a certain time it leads to the impairment of cells. A higher level of lactic acid during hypoxia shifts the pH in the cell to the acid values. When the lactic acid diffuses from the cells into the environment, metabolic acidosis develops very quickly. In this situation the efficiency of the Na^+K^+ pump decreases, as there is not enough energy for its activity. Finally, the low efficiency of the Na^+K^+ pump results in an accumulation of Na^+ in the cells and the escape of K^+ into the intercellular space. The changes in ion concentra-

tions are the underlying cause of osmotic oedema of mitochodria and cells. These changes affect just the metabolically active cells. The function of mitochondria could recover by an adequate oxygen supply. But if the pH drops without control, the intracellular enzymes can be released damaging thus the intracellular structures including the nucleus. They inhibit the chemical reactions and the homeostatic control of cells. These changes result in cellular death. The effect of hypoxia is identical in all types of cells. First of all, anaerobic metabolic processes take place, subsequently lactic acid is produced, the mitochondrial ATP production decreaeses, the pH shifts to the acid values, an finally acidosis in cells and irreversible changes in cellular structure and their nuclei due to the released intracellular enzymes develop.

1.1.2.1 Causes of hypoxia

Hypoxia can be induced by combined action of various factors concerning the supply of oxygen or actual oxygen demands of cells and tissues.

Stagnant or ischaemic hypoxia results from reduced perfusion of tissues.

Anaemic hypoxia is caused by a decrease in oxygen transport capacity of blood.

Hypoxic hypoxia occurs when the oxygen concentration decreases in arterial blood.

Histotoxic hypoxia arises when the cells are not able to utilize the transferred oxygen.

Hypoxia of tissues can arise also when the oxygen demand of cells is very high owing to the raise of their metabolic activity.

The disorders of ventilation and of exchange of gases cause a decreased saturation of arterial blood with oxygen. That is why hypoxic hypoxia arises. The disorders of perfusion cause that the capacity of blood for the oxygen transfer is poorly utilized. Some toxic substances inhibit the transport of electrons in the respiratory chain. That is why the oxidative phosporylation is decreased or even stopped. This kind of hypoxia (histotoxic hypoxia) is caused by cyanide and arsenic compounds

In some diseases the oxygen supply is normal, yet it fails to satisfy the enormously increased demands. It occurs usually when the metabolic processes increase markedly. Increased demands for oxygen supply occur during physical effort, fever, anxiety and stress. In severe injury, burns and sepsis, the organism is permanently on the border of tissue hypoxia. Increased oxygen supply demands can be caused by hyperthyroidism. Thyroxine enhances metabolic processes and the oxygen consumption. If the demands further increase, hypoxia can develop rapidly.

1.1.2.2 The influence of hypoxia on organs and systems

The blood flow through the tissues is principally determined by local oxygen requirement. **The myogenic theory** supposes that the concentration of oxygen regulates the contractility of precapillary sphincters. When the concetration of oxygen in the tissues increases, the precapillary sphincter contracts. It remains contracted until the concentration of oxygen returns to normal. When the concetration of oxygen regains its physiological value, the sphincter opens. **The metabolic or vasodilatory theory** assumes that substances causing vasodilatation affect the precapillary sphincter directly. Decreased oxygen concentration induces the production of vasodilatatory substances. Under the condition of the oxygen deficiency they cause vasodilatation of the precapillary sphincters. The essential vasodilating substance is lactic acid, the product of the anaerobic processes.

The blood flow through the tissues depends on the degree of their activity. It means, according to the myogenic and also to the metabolic theory, that the metabolically active tissues have a better oxygen supply, resp. they involve mechanisms preventing the development of tissue hypoxia. The problems begin if the organism is not able to keep the oxygen supply at the required level. The reasons reside in global or often in local disorders concerning the tissue blood supply.

The degree of hypoxia can vary. It is also important whether the hypoxia lasts for a short time, or whether it is of chronic character. **During chronic hypoxia** compensatory mechanisms develop, which can be useful until a certain stage. Hypoxia stimulates the kidneys to produce erythropoietin which causes the release of erythrocytes from the bone marrow, thus stimulating erythropoiesis. If **global hypoxia** is involved, the highest increase of erythropoietin is observed after 5 days. These events can result in useful polycythaemia. It occurs regularly in patients with chronic obstructive bronchitis and in patients with congenital heart defects.

During **local hypoxia**, a collateral circulation develops as a compensatory mechanism. Besides, the sensitivity of the cells to hypoxia varies. Some cells (the nervous tissue) survive merely a few minutes, others a relatively long time (fibroblasts) without oxygen supply. The cells of the central nervous system are extraordinarily sensitive to hypoxia. During hypoxia the permeability of capillaries in the brain increases very quickly. Hypoxia can result in cerebral oedema. Hypoxia of the brain causes a variety of clinical symptoms: disorders in behaviour, syncopes, disorders in concetration, lethargy, confusion and perceptive disorders. None of these symptoms is specific for hypoxia, however in their evaluation, the hypoxia must be considered as the underlying cause.

In the pulmonary circulation hypoxia causes vasoconstriction of precapillary vessels increasing thus the resistance in the pulmonary circulation. If hypoxia lasts for a long time, its consequences include a change in the right ventricular function and as a matter of course a permanent pressure increase in the pulmonary circulation.

Myocardium in comparison with other tissues has a very small capacity to gain energy under anaerobic conditions. It is sufficient merely for a few minutes. Anaerobic glycolysis cannot cover the required production of ATP. The stores of glycogen decrease very rapidly and markedly during oxygen deficiency. In the myocardium are only few anaerobic glycolytic enzymes present. That is why irreversible damage of myocardium and death of cardiomyocytes arise very soon during insufficient oxygen supply. The conducting system of heart is also very sensitive to the insufficient oxygen supply. Usually at the onset of hypoxia tachycardia occurs. If hypoxia lasts for a longer period of time, bradycardia supersedes the tachycardia. In hypoxia also the resting membrane potential changes in consequence of a disturbance in sodium, potassium and water equilibrium in the cell membrane, leading to subsequent action potential alteration and changes in the electrocardiogram.

The renal functions depend on the oxygen supply. During hypoxia they can be seriously impaired. A marked renal hypoxia may cause a clinically manifested acute renal failure.

The blood is flowing to **the liver** from the arterial system and from the portal vein. The portal vein blood contains low concentration of oxygen. The admixture of arterial and portal blood increases the oxygen concentration available for the liver cells, but in spite of that, they get only the essential quantity of oxygen. Arterial hypoxia has an immediate influence on hepatocytes, which are very sensitive to the oxygen insufficiency.

Hypoxia is often manifested as pain. Reduced perfusion of tissue decreases not only the oxygen supply but also the *removal* of waste products of metabolism from tissues. During hypoxia lactic acid cumulates in tissues. This directly stimulates the nerve endings thus causig the pain during hypoxia.

Fatigue, weakness and intolerance to effort are very often due to insufficient production of energy in mitochondria during hypoxia. In fact, fatigue represents physical and psychical exhaustion. The term weakness refers to the lack of strength for common daily human activities. The intolerance to effort is, in fact, an inadequate reaction of the organism even to small physical effort.

Extreme hypoxaemia can be manifested by cyanosis. Cyanosis is a clinical sign of a violet-blue colouring of the skin and visible mucous membranes. It appears when the amount of reduced haemoglobin exceeds a certain limit. Cyanosis does not reflect the oxygenation degree, because it is caused by the amount of the reduced haemoglobin. Cyanosis appears when there are more than 5 grammes of reduced haemoglobin per 100 ml of capillary blood. In this case the saturation with oxygen (in the capillary blood) is lower than 75 per cent. It is evident, that if the haemoglobin level is low, 5 grammes of reduced haemoglobin per 100 ml of capillary blood is impossible to be found. People with a low level of haemoglobin are hypoxic without signs of cyanosis. On the contrary, in polycythaemia (increased number of erythrocytes) and if the amount of haemoglobin is increased, cyanosis can be observed even when oxygen supply is sufficient. The presence or absence of cyanosis does not represent an indicator of oxygenation. Cyanosis has to be considered in relation with other findings.

1.1.3 Dyspnoea

Dyspnoea is another symptom of disturbed oxygenation. It is, in fact, a subjective feeling perceived as difficulty or distress in breathing, so called shortness of breath. This feeling can appear in healthy persons too, if the demands on the breathing exceed their possibilities, e.g. during extreme physical effort

or excitement. In ill persons it can occur already during moderate physical effort or even at rest. Dyspnoea is always a subjective feeling of breathlessness or of dificulty in breathing. A variable clinical pattern of this condition is described. Some patients describe dyspnoea as lack of air or impossibility to get a breath.. Higher effort and breathing with a greater participation of respiratory muscles can be observed. **Dyspnoea does not reflect directly the condition of oxygenation. It is rather a symptom expressing the disproportion between the requirement of respiration and the ability of respiratory organs and the organism as a whole to maintain the required respiration**. Dyspnoea can be a permanent condition, or it can occur in episodes. The afferent information plays a certain role in the dyspnoea development. An episode of dyspnoea can arise during the night. The nocturnal, paroxysmal dyspnoea can be very dramatic as it can be accompanied by cough and a subjective feeling of breathlessness. In other cases dyspnoea can be associated with a certain enforced position – orthopnoea. Orthopnoea is a severe degree of breathlessness, during which the patient is not able to stay in a recumbent position, just in sitting position, or is for a short time not able to stay in standing position. In patients with cardiopulmonary diseases can often be the so called panic dyspnoea observed. There are probably more mechanisms which are responsible for the arise of dyspnoea. But almost regularly during dyspnoea a congestive pulmonary circulation can be observed. The changes of the pulmonary circulation have greater participation in arise of dyspnoea than the single.

It is not possible to measure directly the condition of oxygenation in the tissues. There are however several possibilities of indirect estimation of the cellular oxygenation degree. Firstly, the determination of blood saturation with gases of respiration is performed, furthermore the condition of ventilation, perfusion and the lung volumes are determined, and in addition, the cardiovascular system functions are measured. The transport of oxygen to the tissues depends on the efficiency of circulation and thus on the heart performance. The capacity of blood to transport oxygen has an important role. Together with the patientd's subjective sensations these methods represent a better possibility to approach to the conception of the supply of tissues with oxygen.

1.2 Pathophysiology of respiration and respiratory organs

Respiratory organs from pathophysiological point of view can be considered as two parts of one system. The first part is represented by organs in which gas exchange takes place, i.e. airways and lungs. The other part is represented by all structures and their functions responsible for the air transport from the external environment into the gas exchange units. This "pumping" is performed by the chest, respiratory muscles, nerves, nervous centers, and neurohumoral control.

1.2.1 Pulmonary ventilation and its disorders

Ventilation of the lungs is a complex of processes ensuring the transport of air into the lungs and the expiration of air enriched in carbon dioxide with low oxygen content. The complex of these processes which are the basis of ventilation depends on the intact chest, perfectly working airways, neurochemical regulative control of breathing, and lung tissue itself.

During inspiration the thoracic cavity enlarges due to the contraction of the respiratory muscles. When the diaphragm contracts, it moves downward into the abdominal cavity. The elevation of sternum and of ribs causes enlargement of the thoracal cavity in the back to front diameter. The inspiration is an active process which depends on several factors. **The expiration** is a passive process, depending on relaxation of inspiratory muscles. The elastic properties of chest and lungs are important factors. The chest and the lungs have generally a permanent tendency to restriction. The intrapleural pressure is negative and keeps the lungs distended. During inspiration the intrapleural pressure becomes more negative thus distending the lungs. The distension of the lungs during more negative intrapleural pressure depends on elastic fibres and the total elastic properties of the lungs. Alveoli have a tendency to collapse. It is caused by the moist surface of alveoli tending to