

1.9.3 Interstitial lung diseases induced by drugs

The effects of drugs can be very different. They can lead in some cases to fatal end. The biopsy shows damage of parenchymal cells and oedema of alveolar walls. Macrophage-lymphocytic alveolitis with neutrophils, but also with eosinophils can be found in alveoli. The chronic form of impairment induced by drugs is very difficult to prove. In the majority of cases there is macrophage-lymphocytic alveolitis with polymorphonuclear leucocytes of the mixed type.

Antineoplastic drugs cause in 2–3 per cent of patients interstitial fibrosis. Similarly antibiotics, salts of gold and other drugs can initiate the arise of interstitial fibrosis. A close correlation between effects of some herbicides and arise of interstitial fibrosis has been found. Radiotherapy can also act as the initiating mechanism.

Infection caused by Mycoplasma, Legionella pneumoniae, and HIV infections associated with parasitic infection caused by Pneumocystis carinii, progress into the form of interstitial lung disease.

It is very important to bear in mind that also the inhalation of oxygen in high concentration for several days causes a damage of the pulmonary parenchyma. The toxicity of oxygen can be very dangerous to patients with respiratory failure. The respiratory failure breaks down as chronic pulmonary fibrosis begins to develop.

1.10 Respiratory failure

1.10.1 Acute and chronic respiratory failure

The respiratory organs procure the necessary *supply* of O_2 and elimination of CO_2 in all physiological situations, in order to maintain the optimal pO_2 and pCO_2 in the arterial blood. **Respiratory failure represents a condition with impaired exchange of gases between the alveolar space and pulmonary capillaries. It is manifested by changes of the pO_2 and pCO_2**

in arterial blood; when pO_2 falls below normal values (excluding the right to left shunt in the heart) and pCO_2 rises above the physiological value (excluding the respiratory compensation of metabolic alkalosis). The definition of the respiratory failure has results from laboratory findings, completed by clinical symptoms. Respiratory failure is not a disease, it is a state, developing during various disorders. Sometimes the lungs can be intact. E.g. after an overdose of sedatives, hypnotics the respiratory failure may develop because of the respiratory centre depression.

pO_2	10,0 – 13,3 kPa (75–100 mm Hg)
pCO_2	4,8 – 6,1 kPa (36–46 mm Hg)

Table 1.1: Normal values of blood gases

pO_2	< 8 kPa (60 mm Hg)
pCO_2	> 7 kPa (55 mm Hg)

Table 1.2: Values of blood gases in respiratory failure

Respiratory failure is traditionally distinguished as being acute or chronic. It is an artificial classification which is more traditional than logical. A rapid deterioration in chronic respiratory failure should be considered as an acute respiratory failure which does not agree with our conception of the acute state being changed to a chronic one. Nevertheless, this classification is important from the etiologic point of view and from that of the possibilities of treatment.

Respiration includes four processes: ventilation, diffusion, perfusion, the governing and control of respiration. Disturbance of any of these four activities can cause the respiratory failure.

During **hypoventilation** the changes in pO_2 and pCO_2 in the arterial blood are parallel. The simple, uncomplicated hypoventilation leads to decrease in pO_2 and to increase in pCO_2 by identical value. However, this is not an universal principle.

Disorder of diffusion during normal activity is usually not manifested by marked changes in pO_2 and

pCO₂. Very severe disorders of diffusion can be manifested by changes in levels of arterial blood gases at rest.

The disturbance of ventilation-perfusion balance can participate in origin of hypoxia and hypercapnia. The uncomplicated disorder of ventilation-perfusion ratio becomes apparent especially by an elevation of the pCO₂ without a marked decrease in pO₂, because the increased pCO₂ stimulates the chemoreceptors and causes hyperventilation. This will procure a better supply of oxygen, however when there is a ventilation-perfusion imbalance, hyperventilation is not sufficiently effective in *elimination of the "over-volume"* of CO₂. Under physiological conditions, during hyperventilation, carbon dioxide is eliminated more intensively (it is more diffusible than oxygen), and thus, there is a tendency to alkalosis.

If right-to-left pulmonary shunts are present, one part of the deoxygenated blood flows into the systemic circulation. It occurs in pulmonary arteriovenous fistulas, pulmonary oedema, pneumonias and intraalveolar haemorrhage. These changes are manifested by increase in pCO₂.

A decrease in O₂ in the inhaled air leads to a decrease in pO₂ in arterial blood. It can occur when barometric pressure falls, however more often during a fire or industrial breakdowns, when in consequence of the presence of unwanted gases in the atmosphere the partial pressure of oxygen is lower in the air. The condition resulting from these changes is not considered to be a respiratory failure.

The right ventricle of the heart, having a relatively thin wall, *is not a good generator of pressure*. It is not able to keep an increased pressure in the pulmonary circulation for a longer period. A rapid increase in the pulmonary circulation resistance can lead to the *cor pulmonale acutum*. Besides in massive pulmonary embolism, it can occur also during acute asthmatic attack or acute obstruction of airways. *Cor pulmonale acutum* can develop also in patients with chronic lung diseases if an acute respiratory failure arises. It occurs usually in patients which already developed hypertrophy of the right ventricle. In the deterioration of right ventricle function participate:

1. alveolar hypoxia and acidaemia, causing arterial vasoconstriction in the pulmonary circulation
2. reduced perfusion in a certain region of lungs

3. hyperinflation of the lungs, that increases resistance in the pulmonary circulation
4. reduced contractility of the myocardium, induced by arterial hypoxia

It is very important to distinguish these factors not just because of their reversibility, but also because of a complex approach to the respiratory failure treatment.

The respiratory failure is defined, as mentioned above, by arterial hypoxia with or without hypercapnia. According to this if hypoxia with hypercapnia are found, the condition can be considered as global respiratory failure, and if only hypoxia without hypercapnia is observed, the state has to be regarded as a partial respiratory failure.

1.10.2 The causes of origin and deterioration of the respiratory failure

Diseases causing acute or chronic obstructions of airways very often result in respiratory failure (about 80 per cent). Whether the respiratory failure will develop or not, depends on the extent of obstruction and the velocity of its development. The obstruction of the upper airways is accelerated by inflammatory process, oedema of the mucous membrane, or by chemical or mechanical damage. Acute obstruction of the lower airways deteriorates not only by oedema of the mucous membrane, but also by increased secretion of mucus, and bronchospasm.

Besides the airways also the alterations of parenchyma participate in the origin of respiratory failure. **An acute infiltration of the pulmonary parenchyma** in pneumonia can lead to respiratory failure. Besides pneumonia, the acute infiltration can occur also after inhalation of various toxins. In the development of the chronic diffuse infiltration of lungs many causes may be involved. After reaching a certain degree, it is manifested as a respiratory failure. The condition is accelerated and deteriorated by infections of the airways.

The pulmonary oedema, chronic or acute, is an important factor in the origin of respiratory failure. The increase in hydrostatic pressure in pulmonary capillaries is unfavourable not only from the haemodynamic point of view, but also concerning the exchange of respiratory gases.

Respiratory failure appears or deteriorates if pulmonary oedema is combined with heart disorders.

Increased permeability of the endothelial layer of the capillaries and alveolar-epithelial layer is observed. In this situation a generalized pulmonary oedema with hypoxaemia may develop. Hypoxaemia is caused by the right-to-left functional shunt due to the present oedema. A state arises (not a disease) termed adult respiratory distress syndrome (ARDS), which is associated with diffuse damage of the lung parenchyma. It can occur in several conditions being not explicitly of pulmonary origin. It occurs in generalized infections, acute hypotension and in metabolic disturbances. Histological examination reveals in particular the damage of alveolar epithelial cells of type I. Usually the capillary endothelium is partially damaged; oedema and intraalveolar haemorrhage are present. Later also changes in epithelial cells of the type II can be observed, as well as infiltration of tissue and depositions of collagen. The mortality reaches up to 70 per cent.

Embolism in the pulmonary circulation can severely deteriorate the respiratory failure. It occurs commonly during disseminated intravascular coagulation when thrombocyte-fibrin aggregates are formed. The state deteriorates severely if pulmonary vasculitis is present. Respiratory failure can develop also due to injury of thorax caused by trauma (fractures of sternum or ribs deteriorate the ventilation very markedly), or during the spontaneous pneumothorax.

Disorders of neuromuscular system are manifested by decrease in pulmonary ventilation. Polyneuritis as well as the myopathies and muscular dystrophies, accelerate the progression of the respiratory failure. Reduced ventilation appears in disorders of the CNS (trauma, vascular disorders, infections) and following administration of substances depressing the respiration centre: e.g. anaesthetics, sedatives, opiates, barbiturates alcohol etc.

A special situation arises in obese patients. Pauses of apnoea are observed during the sleep accompanied with decreased respiratory amplitudes due to patients obesity. Apnoeic pauses may occur also during the day (daytime somnolence), the condition progresses and chronic respiratory failure develops (the Pickwickian syndrome).

Hypoxia due to respiratory failure results in changes in CNS and cardiovascular system func-

tions. One of the first signs may be ataxia reminding the effect of alcohol. A more expressive hypoxia with its depressive effect on the respiratory centre can start the *circulus vitiosus*. The respiratory centre depression leads to the deterioration of ventilation which intensifies the hypoxia. In the initial phase of hypoxia the cardiovascular symptoms i.e. tachycardia and increased blood pressure appear. If hypoxia becomes profound bradycardia and depression of the myocardium occur. The blood pressure falls in consequence of decreased cardiac output. An increased level of reduced haemoglobin is manifested by cyanosis. The hypoxia compensation includes enhanced amplitude and frequency of breathing. The sympathetic nervous system becomes activated, hence the heart rate and the cardiac output per minute increase. If the compensation is insufficient, the amount of 2,3 DPG in the erythrocytes increases due to anaerobic metabolism. The erythrocytes count, the amount of haemoglobin, and the haematocrit are elevated owing to the hypoxia of kidneys. The change in the blood viscosity impairs further the oxygen supply of tissues. The blood flow in the capillaries slows down and cyanosis occurs.

Hypercapnia during the respiratory failure affects very markedly the functions of CNS. The communication with the patient worsens; the raising level of CO₂ induces somnolence, confusion, finally coma and death. The effects of hypercapnia on the circulation are complicated. In general, the activation of the sympathetic nervous system prevails, it is locally influenced by accumulation of CO₂ and that is why in some areas vasoconstriction and in others vasodilatation preponderate. Tachycardia is usually present. The blood pressure can be increased, decreased, or normal.

The gradually raising hypercapnia is not very dramatic. In chronic respiratory failure with hypercapnia the patients complain of headaches and somnolence. These symptoms are probably caused by vasodilatation of cerebral vessels due to increased CO₂.

The acute respiratory failure can lead to death very quickly. Death results from hypoxia in the CNS. The administration of oxygen in high concentration to the patient is a possible solution of hypoxia. In chronic respiratory failure, the administration of O₂ does not improve the condition; retention of CO₂ increases and the relations between ventilation and perfusion change. A certain solution is a prolonged administra-

tion of O₂ in low concentrations (to 15 hours daily). In typical cases the arterial pO₂ can be 30 mmHg, pCO₂ 70 mmHg and pH 7.30. These three values signalize a fatal hypoxia. Inhalation of oxygen in high concentration improves the hypoxia, but simultaneously it causes a depression of respiration leading to increased hypercapnia. The stimulants of the respiratory centre are considered to be obsolete, because although improving the hypoxia at the beginning, later they intensify the hypercapnia. Hypercapnia causes dilatation of the cerebral vessels and hence increases the intracranial pressure, resulting in papilloedema. Hypercapnia associated with hypoxia have catastrophic consequences on the CNS functions. The gradually increasing hypercapnia has a narcotic effect. Disturbances of the heart rhythm occur. In this situation the mechanical lung ventilation represents the only possible treatment.

1.10.3 Adult respiratory distress syndrome – ARDS

This term is applied to acute states of diverse etiologies, characterized by diffuse infiltrative lung lesions with very severe arterial hypoxia in adults. The neonatal form is distinguished mainly by the fact, that primarily the *immaturity* in alveolar surfactant production is involved. In ARDS the changes concerning surfactant are secondary.

In the ARDS of any etiology is **always an increased volume of fluids in lungs present.** However, no cardiopulmonary oedema is present. The pressure in the pulmonary capillaries in ARDS is not elevated, but the permeability of the alveolar-capillary membranes is increased. The increase in permeability results from the direct chemical damage caused by inhalation of toxic gases. More often an indirect damage occurs, caused by activation and aggregation of blood elements inside the pulmonary capillaries. It occurs e.g. in septicaemia or endotoxaemia. Aggregation of thrombocytes appears. Monocytes and polymorphonuclear leucocytes adhere to endothelial surface. They induce an inflammatory reaction and release the inflammatory mediators e.g. leukotrienes, tromboxanes, and prostaglandins. Alveolar macrophages as well as monocytes release oxidants, mediators, and a series of degrading enzymes and peptides, which damage directly the endothelial and alveolar surfaces. In

addition, the polymorphonuclear leucocytes release their lysosomal enzymes. The lesions of alveolar membranes lead to the leak of fluid, macromolecules and cellular particles from capillaries into the interstitium and due to further deterioration also into the alveoli. Increased permeability of capillaries to proteins facilitates the development of pulmonary oedema. The damage of pneumocytes in the alveoli impairs the production of surfactant. These changes accompanied with the presence of fluid and fibrinogen in the alveoli lead to their collapse. The ventilation – perfusion relation in the lungs is changed owing to the collapsed alveoli. In addition, the accumulated fluid in the lungs decreases the compliance of lung tissue. And that is why the respiratory work increases. Yet it cannot eliminate the progressing hypoxia.

Clinical manifestation of ARDS includes increased frequency of breathing, arterial hypoxaemia and dyspnoea.

A similar condition arises rather frequently during a haemorrhagic shock (or after an overdose of certain drugs). It is called the *shock lung*. In the haemorrhagic shock the capillary endothelium is damaged (hypoperfusion, hypotension, the complex of adaptation and compensatory mechanisms and factors, and humoral substances). Capillaries are obliterated by microaggregation of leucocytes and thrombocytes. The released hydrolytic enzymes destroy the endothelial cells. As a result the increase in capillary permeability and interstitial oedema supervene. Because of the decreased pulmonary blood flow (probably) the production of surfactant decreases. Decreased production of surfactant facilitates the development of oedema. Pulmonary vasoconstriction induced by hypoxia of tissues deteriorates further the state of the capillaries. Finally alveolar haemorrhages occur.

The mortality in patients with ARDS or with conditions called *shock lungs* is very high. In the past it reached almost 100 per cent. Now it is about 50–60 per cent. In favourable cases, after overcoming ARDS, the recovery lasts 4–6 months. Fibrotic changes can persist, these are irreversible.