
1.6 Chronic diseases of the airways

Chronic airways disease represent a group of diseases attacking the airways, yet their clinical manifestations and states are not strictly defined and specified. This group includes diffuse disorders of the airways:

1. simple and obstructive chronic bronchitis
2. pulmonary emphysema
3. bronchial asthma

1.6.1 The simple and obstructive chronic bronchitis

The simple chronic bronchitis is characterized by a chronic productive cough. It is caused by a pathogenic factor irritating the airways, nevertheless, hyperreactivity of airways is not involved. The clinical symptomatology is represented by:

- excessive production of mucus (expectoration of the mucus)
- cough lasting for three months in course of two or more following years
- the absence of bronchiectasis, tuberculosis or any other cause of mentioned symptoms

The individual symptoms can be of varying intensity. Some patients are almost symptomless. With the exception of *smoker's morning cough* they have no troubles.

The simple chronic bronchitis can be found in about 10–25 per cent of the adult population. The productive cough can be more often observed in men than in women and more often in persons older than 45 years. The criteria of chronic bronchitis are fulfilled by almost every smoker over 45 years of age.

The pathogenic factor present in the inhaled air:

- stimulates the secretion of mucus in the mucous membrane of airways

- impairs the clearing function of the mucociliary system
- reduces the resistance toward infections of respiratory system by damaging the alveolar macrophages

Microscopical analysis of the airways reveals enlargement of mucous folds in large airways. Rather hyperplasia than hypertrophy of the cells of the submucous glands is involved. Inflammatory alterations of various degree can be observed. In the obstruction of small bronchioles participates also the accumulated secrete. Microscopic examination shows centrilobular emphysema although clinical manifestation of emphysema is not present. Symptomless smokers have usually this histological findings although their state can be clinically considered as physiological. The cause of these changes in smokers is not clear.

Three main factors participate in the obstruction of airways. The first is the chronic inflammation. It leads to structural changes in the mucous membrane of airways, inducing increased resistance of airways toward the air flow. The second factor is the bronchoconstriction due to the inflammatory process. The third factor is the gradually developing decrease in lung tissue elasticity.

Clinical manifestation of chronic bronchitis is the cough. Typical is that it occurs in the morning after getting out of bed. Very often the cough appears following the smoking of the first morning cigarette. The cough is productive, the patient expectorates a mucous sputum. At the end of this *expectoration* wheezing can occur. It is caused probably by bronchospasm induced by the cough. If the sputum is purulent, in cultivation are *Haemophilus influenzae* and *Streptococcus pneumoniae* found. In this case is the term *muco-purulent bronchitis* more convenient. It is necessary to exclude a neoplastic process. Cough can be provoked by every respiratory manoeuvres.

Patients with chronic bronchitis often have overweight and are usually cyanotic. The right ventricular hypertrophy is often present. Alveolar hypoventilation and hypoxia cause pulmonary vasoconstriction and increased blood pressure in pulmonary circulation. After a certain time the muscularization of arterioles and fixed high pressure in pulmonary circulation occur. The condition can progress until a right heart failure develops. Hypoxia stimulates erythropoiesis. Polycythaemia intensifies the cyanosis and

increases the pulmonary hypertension by increasing the blood viscosity, which overloads the right ventricle, and thus the circulus vitiosus closes.

1.6.2 Pulmonary emphysema

It is characterized by an abnormal and permanent distention of alveoli. This enlargement is usually associated with destruction of alveolar walls without the development of fibrosis. The destruction of capillaries can be the underlying cause of pulmonary hypertension development. In consequence of these changes the elastic qualities of the lung tissue decrease leading to the collapse of airways during expiration. As a result the obstruction of airways and increase in their resistance develop which is manifested during the expiration by air retention in alveoli. This condition could be termed as chronic obstructive pulmonary disease. From this point of view the described emphysema would be the type A of chronic obstructive pulmonary disease. Obstructive bronchitis without emphysema would be the type B.

The prevalence of pulmonary emphysema in the industrially developed countries is very high. In necroptic findings evident signs of emphysema can be found in 65 per cent of deceased men and in 15 per cent of deceased women. The relation between smoking and destruction of alveolar septa is proved. Several factors however participate in the process of destruction. Smoking increases the number of polymorphonuclear leucocytes and pulmonary alveolar macrophages in the lungs. The underlying cause can be the fact that the cigarette smoke stimulates the pulmonary alveolar macrophages. These cells produce chemotactic factors which attract polymorphonuclear neutrophils. Several components of the cigarette smoke induce the release of elastase from polymorphonuclear neutrophils. Also the macrophages, stimulated by the cigarette smoke, enhance their own secretion of enzymes similar to elastases. The elastases of polymorphonuclear leukocytes and pulmonary alveolar macrophages can cause destruction of cells and the alveolar elastic net. This situation is in fact a load for the lungs with excess of elastases (proteases) which have to be counterbalanced by the antiprotease system of the lungs. So on the one hand the proteases are released, and on the other hand the antiprotease system is present. The conception of the protease and antiprotease theory gained a support especially based on the find-

ing, that patients with inherited deficit of alpha-1-antitrypsin have a very marked and progressive panacinar emphysema. In the airways and in serum of these patients is either a very low level of alpha-1-antitrypsin or it is absent completely. The deficiency of this antiprotease factor enables the elastase from neutrophil leukocytes to act. In smokers are also the levels of other inhibitors of elastase decreased. The cigarette smoke inactivates the inhibitor of alpha-1-proteinase. In addition, smoking influences unfavourably the reparative processes in the lungs (Fig. 1.1).

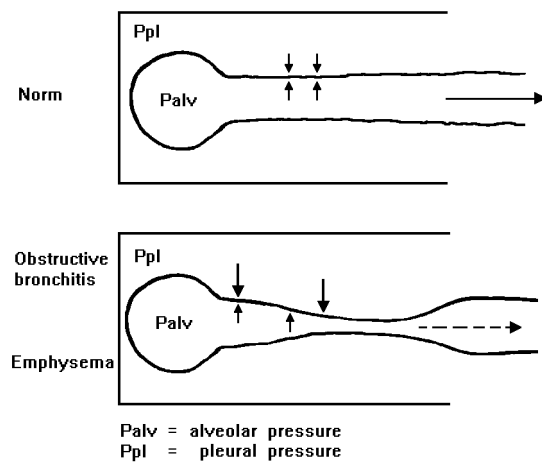


Figure 1.1: Pressure changes in lungs in obstructive bronchitis and in emphysema

The genetically conditioned **deficiency of alpha-1-antitrypsin** occurs in 2 per cent of patients with chronic obstructive pulmonary disease. Family aggregation of this disorder has been demonstrated. This deficiency is transmitted as an autosomal recessive trait. In heterozygotes a moderately reduced autoproteolytic activity in serum is found.

The destructive processes result in the alveolar septa destruction, hence leading to reduction of the respiratory surface. The involvement is usually not homogenous. In centrilobular emphysema the destruction is localized mainly in the central parts of the lobules. In panacinar form the lesion is almost diffuse. In the large airways inflammatory changes are present. The airways are narrowed, there are

signs of obliteration and the bronchioles are filled with mucus closely adherent to the lumen.

The clinical symptomatology is dominated by dyspnoea. At the onset of disease the dyspnoea occurs during physical exertion, later it appears already at rest. The patients are asthenic. Cyanosis is present only in the terminal stages. The examination of the lungs reveals hyperinflation.

Chronic bronchitis and emphysema develop as two distinct processes usually simultaneously. The whole development of disease can be temporarily or permanently dominated by one of these processes. The inflammatory processes of the airways, increased secretion of mucus and bronchospasm can reach different intensities. Similar to chronic bronchitis, also the emphysema causes obstruction of airways and decrease in the lung tissue elasticity. The narrowing of the airways is associated with an increase in the resistance and decrease in velocity of the air flow during expiration, which can be detected by functional examination of the lungs (Fig. 1.1 and Fig. 1.2).

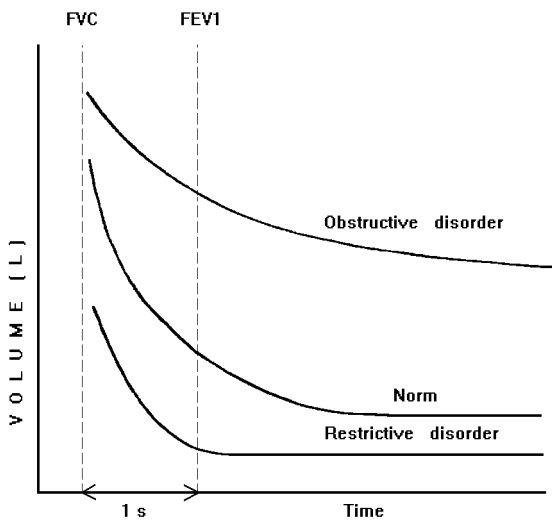


Figure 1.2: Forced expirium curve in functional examination of lungs

1.6.3 Bronchial asthma

Bronchial asthma is a disease of airways characterized by increased responsiveness of trachea and

bronchi to various stimuli and by a reversible bronchoconstriction occurring in attacks, with expiratory dyspnoea, cough and a noisy breathing associated with wheezing during the attack. Wheezing is caused by turbulent airflow through the narrowed airways which contain abundance of viscous secretion. During the attack the resistance of airways increases 5–6 times in comparison with physiological conditions. The vital capacity is usually reduced below 50 per cent. During the attack simultaneously both, hyperinflation and atelectasis can be observed on chest radiogram. The patient is usually restless and anxious, he may be confused in consequence of hypoxia. Especially in the beginning of disease, besides the attack, the patient is usually symptomless. Gradually a state of a moderate, yet permanent obstruction of airways may develop. Also in this state attacks occur, during which bronchoconstriction is intensified.

The reversible disorder of small airways is a combination of bronchiolar smooth muscle contraction, and of bronchial mucous membrane oedema due to increased permeability of capillaries and cellular infiltration. The hypersecretion of viscous mucus contributes to this state.

Bronchoconstriction dominates the clinical manifestation of asthma. Bronchoconstriction can be caused by several different factors. That is why asthma is a heterogenous disease with various etiologies. In spite of considerable differences more types of asthma can be distinguished according to the dominating factor:

- Bronchial asthma is often in a close relation to allergic disease as allergic rhinitis, urticaria and eczema. There is a positive reaction to allergens and increased level of IgE in the serum of patients.
- In other cases neither relation to allergy nor increased level of IgE in serum can be found. Exactly defined immunologic mechanisms are not considered to play a role in pathogenesis of this type of asthma bronchiale.
- In many patients the allergic components are present just at the onset of the disease. These patients belong later to the non-allergic group, or to the group with mixed etiology.

The common sign of various types of bronchial asthma is the non-specific hyperirritability of trachea

and bronchi. Generally the reactivity of the respiratory system in persons with, or without asthma is increased after viral infections, after exposure to different oxidative substances e.g. ozone, and after the application of the exogenous platelet activating factor. Allergens are capable to increase the reactivity of the airways within minutes. It can persist for several weeks.

After being inhaled, the allergens get in contact with the molecules of IgE, which are bound to the surface of mast cells, dispersed in epithelial luminal surface of airways. Degranulation of mast cells arises, thus the mediators for the antigen-antibody reaction are released. Mast cells contain preformed mediators or precursor molecules of these mediators: histamine, kinins, kininogens, thromboxanes, leukotrienes C₄, D₄ and E₄, eosinophil chemotactic factors of anaphylaxis (ECF-A), heparin, superoxide dismutase, prostaglandins PgG₂, PgF₂ alpha, PgD₂, platelet activating factor, neutrophil chemotactic factor of anaphylaxis (NCF-A), inflammatory factors of anaphylaxis, chymotrypsin, trypsin and many other enzymes. These enzymes can cause or contribute to the destruction of tissue closely surrounding the mast cells. An intense inflammatory reaction with bronchoconstriction and increased permeability of the capillaries, with congestion of the vessels and development of oedema can occur after the release of several mediators. Simultaneously the enzymes evoke a long lasting contraction of airways smooth muscles and oedema of the mucous membrane. The released leukotrienes increase the production of mucus and impair the mucociliary transport. Chemotactic (eosinophil and neutrophil) factors of anaphylaxis and leukotriene B₄ attract eosinophils, thrombocytes and polymorphonuclear leucocytes to the site of mast cells stimulation. Eosinophils are very important. After being activated they can produce leukotriene C₄ and the platelet activating factor, thereby they contribute directly to the narrowing of airways and development of mucous membrane oedema. Vice versa, the eosinophils activate the mast cells to release histamine and chemotactic factors. As a result, additional *accumulation* of eosinophils takes place and a *circulus vitiosus* arises. Eosinophils are the source of electrically charged proteins, which inhibit the motility of cilia and impair the integrity of the mucous membrane, and cause exfoliation of epithelial cells into the bronchial lumen.

In asthma the constriction of bronchial smooth muscles, thickening of the mucous membrane and presence of mucus in the airways are always taken into consideration. Until now, most attention was devoted to the constriction of the smooth muscles elicited very probably by the release of bioactive mediators or neurotransmitters. Explanation of the release mechanism of these molecules remains merely speculative.

1.6.3.1 The participation of mediators in asthma development

Histamine (beta-imidazolyl-ethylamine). It is the oldest substance known to have the bronchoconstrictive effect. The greatest amount of histamine is produced by mast cells which are abundant in mucous membrane of airways. Histamine evokes bronchoconstriction also indirectly by affecting the endings of nervus vagus.

Acetylcholine. Acetylcholine is released from the intrapulmonary endings of vagus nerve branches. Acetylcholine causes directly constriction of smooth muscles by stimulation of the muscarinic receptors. The effect of atropine derivatives in the therapy of asthma confirms the importance of acetylcholine in the pathogenesis of asthma.

Kinins. Bradykinin and other molecules with similar effect are released from plasmatic precursors by proteolytic effect of kallikrein. One type of kallikrein is released from mast cells during their activation. Besides inducing the bronchospasm, it increases also the permeability of capillaries and accelerates the development of oedema. In the clinical practice no substances are used which would influence the production and the effect of kinins.

Adenosine. Adenosine is formed from ATP during the metabolism acceleration. Above all, the bronchodilatory effect of theophylline - an adenosine antagonist - indicates that adenosine participates in the pathogenesis of asthma bronchiale. Theophylline is an inhibitor of phosphodiesterase. That is why the concentration of cAMP is increased. The increased ratio cAMP/cGMP has a bronchodilatory effect. (The majority of bronchoconstrictive substances act by increase of cGMP).

Leukotrienes. The leukotriene LTC₄, LTD₄, LTE₄ (formerly called the slow reacting substance of anaphylaxis - SRS - A), and LTB₄ are formed from the arachidonic acid after its release from cellular

membranes. Mast cells, eosinophils and alveolar macrophages can produce them. The molecules of LTC_4 and LTD_4 are three thousand times more effective in bronchoconstriction than histamine.

PAF-platelet activating factor. It is a phospholipid produced by several cells, which take part in the development of inflammation. It is produced by mast cells and eosinophils. It acts as a bronchoconstrictive agonist by activation off specific receptors.

Tachykinins are small peptides (substance P, neurokinin A, neurokinin B), released from specific nerve endings. Activation of specific receptors can cause constriction of smooth muscles and secretion of mucus. These peptides are very rapidly degraded by action of specific peptidases.

There are several ways to induce the constriction of bronchial smooth muscles. Bronchoconstriction dominates the clinical picture, however its underlying causes can be considerably diverse.

Many drugs can induce asthmatic episodes. The most known is the effect of acetylosalicylic acid, very probably by interference in the metabolism of arachidonic acid with leukotriene formation. Yet also other non-steroid anti-inflammatory drugs, beta adrenergic antagonists (blocking the "dilating" beta-receptors), dyes and other substances can induce asthmatic attacks. The mechanism how they evoke the episodes is not precisely known.

In large urban agglomerations with a high concentration of noxious substances in the atmosphere the manifestation of respiratory disorders arise also in healthy population, and patients suffering from bronchial asthma can develop attacks.

There are numerous substances with bronchoconstrictive effect in our surroundings: the salts of heavy metals, wooden dust, pollen, components of plastic materials, animal hairs and secretions. In some cases specific IgE is produced. The noxious substances from the surroundings can also directly release bronchoconstrictive substances.

Infections of the respiratory system may evoke asthma. The triggering mechanism can include **physical exercise**. During physical exercise the pulmonary ventilation increases. The inspired air is colder and less saturated with water vapours. That is why the winter sports are more provocative than e.g. swimming.

An emotional stress can, in some patients, represent an important factor of bronchial constriction.

It can act as a triggering factor, or a factor supporting the persistence of bronchial asthma. Emotional hyperventilation plays a certain role as well.

1.6.3.2 The histological findings in asthma

Necroptic examination shows **hypertrophy of smooth muscles in bronchioles, hyperplasia of the mucosal and submucosal vessels, oedema of mucous membrane of bronchi and bronchioles, denuded epithelial surface, pronounced thickening of the basement membrane and eosinophilic infiltration in the bronchial wall. Sometimes also mucous cylinders can be found in bronchioles.** Typical emphysematous tissue destruction is not observed.

From the pathophysiological standpoint, the main cause, responsible for typical alterations in asthma is **the reduced lumen of airways** caused by contraction of bronchial and bronchiolar smooth muscles. In addition, the wall of bronchioles is oedematous, the mucous membrane is covered with a closely adherent secretion. The deterioration of pulmonary functions is considerably diverse. Certain changes usually dominate in patients leading to almost the same consequences: increased resistance of airways, decreased volume of air in forced expiration, hyperinflation of the lungs, an increased work of breathing, changes in elasticity of the lungs, abnormal distribution of the pulmonary ventilation and perfusion, and a change in saturation of blood with oxygen and CO_2 . Asthma is characterized by a primary disorder of the airways. The changes result in a series of alterations ending with hypertrophy of the right ventricle and pulmonary hypertension. During the attack the vital capacity decreases to, or below 50 per cent of normal. The forced expiratory volume per second is about 30 per cent and the airflow rate reaches just 20 per cent of the normal values. The residual volume of the lungs is enormously increased. It can reach 400 per cent in comparison with the norm.

During the attack hypoxia, hypocapnia and respiratory alkalosis are observed. Absence of hypocapnia signals a very severe obstruction of airways. Similarly, the metabolic acidosis appearing during an asthmatic attack is a sign of marked obstruction of the airways. The volume of respiratory gases in blood per se does not correlate with the clinical picture.

Cyanosis occurs in patients very late. Other important symptoms, like retention of CO_2 , tachycar-

dia, tachypnoea have a high predictive value. It is very hazardous to judge the state of the patient just according to the clinical symptomatology alone. It is inevitable to measure the tension of respiratory gases in blood.

Clinical symptomatology is always represented by a triad of symptoms, which are constantly observed: dyspnoea, cough and wheezing. They are always present during the attack in advanced phases of the disease. Attacks often occur at night. The cause is not quite clear. It may reflect the circadian variations in catecholamine and histamine levels or the increased tone of parasympathetic nervous system at night. During the attack the expiration is prolonged, tachypnoea, tachycardia and increased systolic pressure are present. Sometimes also an unproductive cough occurs. The lungs are *overfilled* with air, the back to front diameter of the thorax increases. The retained air in lungs increases the pressure in the thoracic cavity. That is why the breathing becomes more difficult, the patient is restless, cyanosis, tachycardia and increased filling of jugular veins may occur. The episode of attack usually ends with coughing out some viscous sputum, containing cylinders of mucus formed in distal parts of bronchioles (Curschmann's spirals – i.e. cylinders from the bronchioles, consisting of mucus and cells), eosinophils and Charcot-Leyden crystals (crystallized proteins of eosinophils).

Sometimes the cough during the attack may be ineffective. The mucus can obturate some bronchioles and as result atelectasis in some areas of the lungs occurs. Pneumothorax is a very rare complication.

An attack of bronchial asthma has to be distinguished from other diseases associated with dyspnoea. Wheezing occurs also in other endobronchial diseases (neoplasms, aspiration of foreign bodies), or in bronchial stenosis. An attack of bronchial asthma can resemble the acute failure of the left ventricle. During the left ventricle failure gallop rhythm occurs and the sputum is sanguinolent.

The therapy of asthma is aimed, above all, at the elimination of bronchoconstriction. The relaxation of bronchial smooth muscles can be induced by stimulation of beta 2-adrenergic receptors. Several substances having these effects are used in therapy of asthma (fenoterol, salbutamol, terbutaline).

Theophylline is also used as an moderately effec-

tive bronchodilator. It prevents the adenosine formation and inhibits its receptors.

Antihistamines act as antagonists of H₁ receptors. They block the effect of histamine on smooth muscles of airways.

Anticholinergic drugs inhibit the release of acetylcholine from nervus vagus endings in the airways. The effect of atropine is known for more than a hundred years.

Substances acting as antagonists of LTD₄ and PAF receptors are tested nowadays. The glucocorticoids are widely used in the therapy of asthma. These drugs reduce the allergic and inflammatory reactions, decrease the number of cells participating in the development of inflammation. They can be applied also by inhalation. The bronchoconstriction is influenced indirectly, mediated by mitigation of the mucous membrane inflammation.

1.7 Bronchiectasis

Bronchiectasis is an irreversible dilatation of one, or several bronchi. Dilatation is caused by destruction of the bronchial elastic-muscular wall. It occurs usually as result of a chronic inflammatory process. The surroundings of the bronchus are affected by inflammatory alterations leading either to destruction of the bronchial wall, or they develop secondarily due to the stagnation of the secretion. Before the era of antibiotics bronchiectasis was an incurable disease, which participated not only in morbidity, but also in mortality of patients suffering from infections of the respiratory system.

In addition to the infections associated with the destruction of bronchial wall there are other alterations and disturbances (long lasting obstinate cough) which participate in the development of bronchiectasis. Several disorders of mucociliary function form **favourable conditions for bronchiectasis development**. Dyskinesia of cilia or the complete absence of their motility may be transmitted as an autosomal recessive trait (primary ciliary dyskinesia, immotile cilia syndrome). In men with this disorder sterility occurs because of absence of the sperm cell motility. Also in women decreased fertility ap-