Comenius University in Bratislava

Jessenius Faculty of Medicine in Martin

PATHOLOGICAL PHYSIOLOGY

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Chapter 1

INTRODUCTION TO PATHOPHYSIOLOGY

What is pathophysiology?

Physiology (from Greek fysis = nature; logos = science) is science about "logic of bodily functions" of healthy organisms. **Pathophysiology** (from Greek pathos = disease, pain, suffering) is "science of bodily functions" of organisms affected by disease. It deals with causes and mechanisms which change the normal logic of life to the logic of life altered by pathological process.

Definitions of pathophysiology

Pathophysiology is modern integrative biomedical field built on results of basic and clinical research, using them to elucidate the mechanisms responsible for initiation, progression and cessation of pathological processes and thus creating grounds for their understanding and rational influencing.

What does pathophysiology deal with?

Pathophysiology **studies and evaluates changes of functions** of tissues, organs and systems of organism, which occur due to pathological reasons and in unfavourable conditions, using knowledge from biology, anatomy, histology and embryology, biophysics, physiology, biochemistry, pathological anatomy, microbiology and immunology as well as social sciences.

Pathophysiology also focuses on **explanation of mechanisms** which contribute to manifestation of pathological processes in organism – it elucidates induction, development and cessation of **signs and symptoms of diseases.**

Pathophysiology also pays attention to **dynamics of pathological processes,** investigates and evaluates their course in time and space, their intensity and quality. Last but not least, the attention of pathophysiology is devoted to investigation of **protective and defensive mechanisms** of the organism existing at cellular, tissue, organ and system levels.

Importance of pathophysiology for medical students and doctors

Pathophysiology allows health professionals to find answers to important medical

questions, such as:

- **What caused the disease?**
- **Why did the disease develop in individual person?**
- **Which mechanisms contribute to disease occurrence, development, and treatment?**

These answers are important not only for understanding the diseases onset and development but also for finding appropriate diagnostic methods and tools, or rational therapy. Without basic knowledge of pathophysiology, the medical student or doctor cannot understand the pathogenesis of diseases sufficiently deep enough to perform rational prevention, diagnosis or therapy of diseases. Successful study of clinical disciplines is based on **the ability of student to integrate the knowledge received in theoretical studies** (studies of sciences) **with focus on their application in the study of pathological processes.** This integration is provided in pathophysiology.

Placement of pathophysiology in pregradual medical education

Pathophysiology creates a **"virtual bridge"** between theoretical and clinical disciplines. Such a bridge is necessary while medical education is organized as a study of individual subjects with low degree of horizontal and vertical coordination and integration. Pathophysiology is sometimes called **"theory of medicine"**, because it allows focusing on general and special pathomechanisms contributing to occurrence and development of practically every disease. Pregradual medical education can be viewed on metaphorically as construction of **"house of medicine"** (more detailed explanation available in the handout on departmental webpage). The construction requires many "building blocks" from the student which are knowledge from all the theoretical disciplines as well as from philosophy, sociology, ethics and anthropology (the foundations of the house). Student must learn how to apply this knowledge, use it in solving medical problems – health complaints of patients. Without good quality of knowledge from pathophysiology, it is impossible to build "virtual house of medicine" properly.

Structure of pathophysiology

Pathophysiology is divided into parts based on pathomechanisms which are focused into:

1) General pathophysiology, which focuses on general pathomechanisms of occurrence and

development of diseases. Each of these mechanisms contributes to occurrence and development of **more than one pathologic process or disease.**

2) Special pathophysiology focuses on study of pathomechanisms, which are responsible for occurrence and development of one single disease (nosology unit).

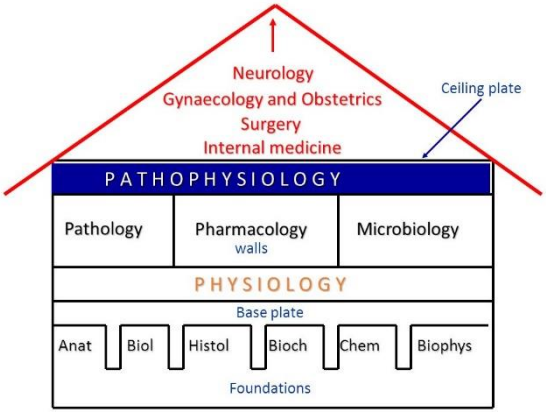


Figure 1.1: Virtual "house of medicine"

General pathophysiology is system of knowledge about general patho- and sanogenetic mechanisms contributing to occurrence, development and cessation of diseases. It focuses on description of causes and conditions which contribute to disease pathogenesis. **Causes of diseases** can be different kinds of noxae – biologic, chemical, physical and social. **Disease conditions** are the states, which promote influence of noxae to the organism and thus the disease. These conditions include e.g. malnutrition, decreased immunity, stress, genetic predisposition and many others. General pathophysiology also focuses on description of general mechanisms contributing to **recovery from previous disease**, as well as mechanisms contributing to health promotion (disease prevention, aetiology of health).

General pathologic processes include e.g. stress, hypoxia, hyperoxia, dystrophy, apoptosis, necrosis, oedema, disturbances of regulation (feedback systems), inflammation, fever, damage of DNA and others.

Protective and adaptation mechanisms can and also do contribute to multitude of diseases. These mechanisms include e.g. **renin-angiotensin-aldosterone system,** which in healthy organism plays the role of regulation of volume and composition of body fluids, but its inadequate hyperfunction leads to hyperhydration and vice versa hypofunction leads to hypohydration. Other examples of pathologic processes to which the dysfunction of protective and adaptation mechanisms contribute includes atrophy and hypertrophy of tissues and organs, dysfunction of mechanisms maintaining acid-base balance, disturbances of

quality and quantity of immune mechanisms (local or systemic). **Therefore, the changes of intensity and quality of defensive/adaptation processes of the organism are an important factor contributing to occurrence and development of disease processes.**

Special pathophysiology focuses on pathomechanisms, defence and adaptation mechanisms, as well as sanogenetic mechanisms contributing to occurrence, development and cessation of pathologic processes in individual organs and organ systems and also on mechanisms contributing to occurrence and development of signs and symptoms taking place in individual organs and organ systems. Special pathophysiology consists of pathophysiologies of organs and systems – **cardiovascular, haematopoietic, respiratory, gastrointestinal, endocrine, uropoietic, nervous, locomotor, and cutaneous.**

Pathologic processes situated in one organ/system do manifest not only by dysfunction of given organ/system, but they do influence other organs/systems with variable intensity as well. In severe disturbance of one system the dysfunction of whole organism develops – **"sick" is not only individual organ, but the organism as a whole.**

Methods of research in pathophysiology

Pathophysiology acquires new knowledge about causes and mechanisms of occurrence, development and cessation of diseases by using two types of research methods:

- **Observation** based on doctor's senses or on technological tools.
- **Experimental methods**: development of models of pathological processes in experimental animals and their research – experimental pathophysiology.
- **Modern imaging techniques**: use of non-invasive methods in identification of pathologic processes in real patients, e.g. MRI, PET and others – clinical pathophysiology.

In pathogenesis of diseases, **quantitative changes** of individual functions take place – their **increase** or **decrease** outside of reference interval; e.g. overall increase of function of thyroid gland leads to hyperthyroidism, and significant decrease leads to hypothyroidism.

But also **new qualitative processes** which arise under pathological conditions, are important – these do not exist in healthy organism. One of the most important of these is "vicious circle" (*circulus vitiosus*). Its development and function is based on activation and self-maintenance of positive feedback loops activity, which leads to persistence and/or amplification of pathological process – e.g. in failure of left or right ventricle (heart failure),

in development of systemic inflammatory response syndrome (SIRS) in severe tissue damage.

Wide array of medical terms are used in elucidation and description of pathologic processes, which are needed to be understood in study of pathophysiology. Some of them are explained below.

Nosology – scientific discipline about disease; about individual types of diseases. It defines and describes them; presents individual diseases as nosology units. These are the base for **disease classification.**

Disease aetiology – discipline about causes and conditions of disease development. Nowadays, the term **aetiology of health** is also accentuated as a new philosophy of medicine characterized by **prevention of diseases**. It originates in the idea that if we know the cause(s) and mechanisms of disease onset, and if we know also the defensive and supportive mechanisms of organism which strengthen and improve the health of an individual, and we can promote them, then we can decrease the risk for disease development.

- **Pathogenesis –** discipline about mechanisms of occurrence and development of diseases.
- **Sanogenesis –** discipline about mechanisms which contribute to cessation of disease and recovery from previous illness.
- **Semiology –** discipline about disease manifestation

Diseases manifest by two kinds of signs – **subjective and objective.** Both types of manifestations are important for doctors and cannot be mutually replaced or interchanged. **Subjective feelings,** by which patient describes his/her disease are called **symptoms**. They cannot be clearly quantified, but their intensity and quality can be partly objectified (description, visual scale). **Objective manifestations of disease** are those which can be detected by patient/doctor senses or by using different sensors/equipment. These manifestations can be objectively evaluated – they can be measured and are called **signs.** They show changes of function and structure of cells, tissues, organs and organ systems of organism.

Thanatology is scientific discipline focusing on processes leading to termination of life – about death. To this term **euthanasia** also belongs. It is the term for complex reasoning and methods of deliberate termination of life of human based on his/hers urgent and repeated request. It is illegal in Slovakia (more in handout on the departmental web page).

Learning objectives in pathophysiology

The goal of teachers involved in teaching pathophysiology is to help students to acquire knowledge about basic mechanisms which contribute to occurrence, development and cessation of diseases. To achieve this goal, students have to:

a) Know, understand and properly use **pathophysiological terms,**

b) Know, understand and properly use the **separate pathomechanisms** in elucidation of pathogenesis of diseases,

c) **Connect separate pathomechanisms** into **rational pathogenetic network** typical for pathologic processes and individual diseases,

d) Understand pathological process occurring in one organ as **action which has response in the whole organism**,

e) Understand **pathological process as dynamic action**.

Chapter 2

HEALTH AND DISEASE

Health and disease are two main categories of medicine. Medicine as an art and science cannot function without their definition, because based upon these definitions the whole healthcare policies of countries revolve.

Definition of health according to WHO

Health is state of complete physical, mental and social well-being while maintaining the functions of all organs, important social functions and ability of organism to adapt to ever-changing conditions of the environment.

In medical practice the term "health" is understood in more pragmatic manner – it is **a sum of abilities of organism to cope with changes of outer environment without occurrence of severe and long-lasting disturbances of homeostasis of inner environment.**

Health has two aspects:

1) subjective – consists of person's **feelings**

2) objective – is determined from objective parameters of structure and functions of organism.

Subjective aspect derives **humane point of view** towards health and is the base of holistic medicine. It is also base for osteopathic medicine in some western countries.

Objective aspect derives **scientific point of view** towards health and is the base of allopathic medicine. It expresses quantitative dimension of life existence. Subjective and objective aspects do not necessarily be equal, there can be differences identified. Nowadays, more and more **complex point of view** towards health is taken into account, which accepts positive sides of both concepts.

Sometimes the terms **health** and **normality** are mixed up without no reason. Therefore, the opinion if the parameters (structural, physiologic, laboratory) are normal then the organism is healthy is accepted. However, these terms are not equivalent, because **health is term determining quality and normality determines quantity.** Therefore, normality or normal value of some parameter is such a value, which occurs in healthy population most

often. Based on empiric findings it was shown that if average value of some parameter is determined, standard deviation is calculated and double of this deviation is added or subtracted from average value we obtain normal (reference) interval for given parameter. If the value of determined parameter is within normal reference interval we consider it to be normal. But a person whose all measured values are normal does not have to feel healthy and vice versa – even person whose measured values are outside the reference interval can feel healthy. Therefore, normality does not always equal to health and abnormal value does not always equal to disease.

Interindividual variability

Each individual has characteristic profile of functions, organ and system structure and almost every individual is extreme in some of his/hers signs and these differ. Interindividual variability within populations develop based on wide range of factors (intrinsic – mostly genetic and extrinsic – physical, chemical, biologic, social) which modulate development of an individual and his signs. It is very likely that this interindividual variability of signs in population is responsible for existence of different vulnerability to disease development or extreme endurance in one of individual's signs. Understanding the importance of interindividual variability in health and disease is the base for **concept of personalized therapy.**

Definition of disease

Disease is biosocial phenomenon representing new quality of life. It is the result of interaction between pathologic and compensatory processes, which lead to disturbance cells, tissues, organs and organ systems, which manifests by limit of ability to adapt to environmental change and development of disturbances of vital signs.

As well as health, the term disease also contains two aspects – **objective and subjective. Objective aspect** means that disease manifests by signs detectable by our senses and/or measurable manifestations. **Subjective aspect** lies within the fact that patient may feel ill, but in his/hers examination we do not have to detect objective signs of disease. But in majority of diseases we will observe subjective and objective manifestations simultaneously.

To disease manifestation contribute the following:

a) pathologic reactions and defensive/adaptation reactions,

b) pathologic processes,

c) pathologic states.

Pathologic reaction is most simple, usually short-lasting, inadequate (quantitatively or qualitatively) reactions: syncope, short-lasting significant increase of blood pressure, tachycardia, vomiting, diarrhoea, hyperaemia, increased endothelial permeability, leucocytosis and others.

Pathologic process is complex of pathologic and defensive/adaptation reactions evoked by action of noxae towards organism. It is a chain of reactions, result of which is deflection of one or more physiologic functions outside the reference interval. Examples of pathologic processes – inflammation, hypoxia, tumour growth, fever, hyperthermia, hypothermia, oedema, acidosis, alkalosis, atrophy, dystrophy and others.

Pathologic state is pathologic change of cell, tissue, organ or organ system, which is stable over time or changes are only minimal during longer period of time. Examples include arthrosis, congenital heart defects, blindness and other.

Dynamics of disease

Every disease has its beginning, progress and end, therefore some kind of dynamics. This dynamic is characterized by **disease stages:**

1. stage: latent (hidden – in non-infectious diseases)**, incubation** (in infectious diseases). It is limited by time, which elapses form beginning of action of noxa to organism and occurrence of first (non-specific) manifestations. In this stage there are neither objective nor subjective manifestations present. Duration of this stage depends on the noxa and defensive mechanisms of organism.

2. stage: prodromal. Noxa(e) caused such a damage (extent) to cells (tissues, organs), which will manifest by development of non-specific signs and symptoms of the disease (malaise, somnolence, insomnia, headache, …). It lasts from development of first non-specific signs and symptoms to occurrence of specific signs and symptoms of disease.

3. stage: manifest (damage is localized predominantly in some tissues or some organ(s)) The signs and symptoms specific for some certain disease are present.

4. stage: disease cessation.

a) healing and convalescence

b) death

Disease cessation can occur suddenly, in short period of time – so-called **critical** development of convalescence. It can and also often does occur slowly and gradually – **lytic**

development of convalescence. In both cases, the defensive and reparative processes will prevail over destructive processes.

Forms of healing and convalescence

1) restitutio (sanatio ad integrum) – means the return of structure and function of cells affected by disease back to normality

2) sanatio per compensationem – although the disease did cause loss of cells, parts of tissues or organs, but the remaining parts which were not affected by the disease and repaired pats are able to compensate this loss in a way that their overall function is normal.

Dynamics of a disease is also characterized by the speed of its onset and duration. Based on these criteria, diseases can be divided into groups with:

a) Peracute progress –occurrence and development of disease is very rapid (minutes, hours – e.g. anaphylactic shock, sudden cardiac death, CO poisoning, …)

b) Acute progress – disease occurs and develops for few days to few weeks (usually ends within three weeks – acute myocardial infarction, focal cerebral ischemia, simple bronchitis, rhinitis, …)

c) Subacute progress – disease/pathologic process develops gradually and lasts longer than 3 weeks and usually not longer than 6-8 weeks e.g. bronchopneumonia, some forms of inflammatory processes and others.

d) Chronic progress – disease develops for many weeks, months or even years; lasts longer than 6 weeks, very often throughout the rest of life – e.g. gout, diabetes mellitus, atherosclerosis, venous insufficiency, chronic obstructive pulmonary disease, ischemic heart disease and others.

Course of disease is also characterized by other signs. They are:

- **Exacerbation of disease** – it is sudden amplification of manifestation of chronic disease; e.g. acute exacerbation of chronic obstructive pulmonary disease (COPD).
- **Disease remission** – it is decrease of intensity of manifestation of chronic disease (either spontaneously or due to treatment).
- **Disease recurrence** – it is occurrence of same disease which manifestation subsided due to previous therapy (or spontaneously).

Chapter 3

PATHOPHYSIOLOGY OF IMMUNE SYSTEM

The main function of the immune system is to maintain homeostasis, provide protection and defence against exogenous and endogenous antigens if necessary. Exogenous antigens are e.g. signal molecules of viruses, bacteria, parasites or fungi. Examples of endogenous antigens are cells with modified surface antigens due to viral infection or neoplastic (oncogenic) process. Immune system recognizes them as "strangers" or simply foreign antigens different from the antigens typical for the particular subject. The recognition of "mine" and "not mine" antigens is the key function of immune system.

Identification of foreign antigens (viral, bacterial) associated with pathogens (**pathogen-associated molecular patterns - PAMPs)** is provided by immune cells located directly in the tissues – dendritic cells or tissue macrophages. These cells are equipped with the receptors which are activated by the presence of foreign protein (amino acid sequences) and these receptors are a part of innate immunity. Activation of Toll-like receptors is one of the most important steps in the foreign pattern recognition. The **lipopolysaccharides, peptidoglycans, bacterial RNA, flagellin** or some other components of the bacteria have the ability to activate pattern recognition receptors. Sometimes it is difficult to explain why and how the immune system recognizes the body structures and initiates the immune response towards them. All damaged cells, no matter the cause of damage (burn, virus, trauma, hypoxia etc.), express signals (amino acid sequences) on their surface which label them as "damaged". These **DAMPs** – **damage-associated molecular patterns,** also called alarmins, are present on the cell surface of damaged cells prior to their necrosis and they are recognized as "not mine" by the immune system, which may initiate immune responses.

Individuals with physiological function of immune system have effective protection and defence against infections, properly regulated course and magnitude of immune processes and tolerance towards "own" antigens.

In general, there are two main disturbances of immune system performance – and they can be characterized as either **increased or decreased** performance of the immune system.

1. Decreased function of immunity leads to **immunodeficiency**
2. Increased function and dysregulation of the immune system leads to hypersensitivity – or hyperreactivity

a) increased response against environmental antigens – allergy

b) increased response against "own" antigens – autoimmunity

c) increased response against cells of the other individual used for therapeutic purposes (transplantation, transfusion, mother vs. foetus incompatibility) – isoimmunity

1) Immunodeficiency

Reduced performance of immune system leads to clinical manifestation of immunodeficiency. Problem within the immune system can be related to the isolated problems of immunoglobulins, B cells, T cells or it can be complex disturbance caused by impaired function of cellular and humoral immunity. Immunodeficiency can have inherited or acquired form.

Inherited immunodeficiency is usually caused by genetic disturbances or problems during intrauterine development. The manifestation of immunodeficiency is delayed to the approximate age of 6 months, when the breastfeeding rate decreases and the level of maternal antibodies decreases as well. This is usually the first time when babies are having cold/cough episodes, even healthy babies. Clinical manifestation of immunodeficiency is variable and it depends on the type of immunodeficiency, age of the child and of course severity of immune disturbances. Nearly 50% of inherited immunodeficiencies are related to the abnormal (mainly reduced) **production of antibodies**. Agammaglobinaemia or hypogammaglobinaemia can affect individual classes of immunoglobulins **(IgA, IgM, IgE)** selectively, or all classes of immunoglobulins are affected equally. The problem can be production of heavy and light chains of immunoglobulin molecules as well. Disturbances of B cells combined with reduced production of antibodies lead to the increased rate of infections caused by extracellular pathogens. As an example, we can set Burton's agammaglobinaemia caused by mutations located on the X chromosome, or selective IgA hypogammaglobinaemia, which leads to the defects of mucosal immunity.

Disturbances of T cells manifest by frequent infections caused by viruses or other intracellular pathogens. The example here is aplasia or hypoplasia of the thymus gland which leads to the defect in the maturation of T cells. This disturbance is called **Di George's syndrome**. **Wiskott-Aldrich's** syndrome is another example, where the T cell line defects are associated with the defects of the platelets. Example of combined B and T cell line disturbance is **SCID – severe combined immunodeficiency syndrome**. It is serious condition and a child will die without a bone marrow transplant. Although the disturbance starts at the level of T cells, it combines quickly with the B cell line disturbances. The child

lacks immunity against intra and extracellular pathogens. Other inherited problems are related to the disturbances of phagocytosis, disturbances of the complement cascade, helper cells and many others. They are the scope of paediatrics where they are discussed in detail. More doctors (out of the paediatric field) may get in touch with patients with acquired immunodeficiency.

Acquired immunodeficiency, also called secondary immunodeficiency, typically develops during the lifespan of an individual and they are caused by some other primary diseases. It is important to note that many pathological processes, including the nutrition status may considerably influence the immune performance of the organism and it is not only the HIV/AIDS, as students usually understand.

The most known syndrome of acquired immunodeficiency is AIDS, which is caused by the primoinfection by the HIV virus. HIV is a retrovirus which affects the T cell line, specifically population of T helper cells – line CD4+. Infection of T cells leads to their reduced function and since they are responsible for many processes including the regulation of immune response, their lack leads to the reduced defence against opportunistic bacteria, dysregulation of immune processes, which may in turn lead to the generalized enlargement of the lymphatic nodes. Initial stages of the HIV infection are clinically silent and the immunodeficiency is present in fully developed AIDS – it manifests by **virus infections** (herpes simplex, CMV), **bacterial infection** (tuberculosis), **protozoal infection** (toxoplasmosis, pneumonia caused by *Pneumocystis carinii*), **fungal infections** (candidiasis of skin and mucosa). Reduced performance of anti-cancer immunity may lead to the onset of the oncologic disturbances in the lymphatic tissue (lymphoma, Kaposi sarcoma etc.). Paradoxically, in the everyday clinical practice we are frequently facing diseases, which are not AIDS, yet they lead to severe immune defects. Typical example of such disease is diabetes mellitus. It is serious metabolic disturbance of metabolism of carbohydrates, lipids and proteins, but long-lasting diabetes and its complications lead to immunodeficiency. Skin defects (which are very common in diabetic patients) represent the defect of important body barriers, which are part of innate immunity. Furthermore, hyperglycaemia in the not properly compensated diabetes leads to disturbed chemotaxis, opsonisation and phagocytosis, while the hyperglycaemic fluid is perfect medium for bacterial growth. Considerable effect here is played by the damaged vessels - their role is crucial in inflammation – and if the vascular tissue does not respond appropriately in the inflammation, this process (non-specific defensive process) would not be effective enough.

Another example is a patient with **chronic renal failure** (end-stage kidney). Retention of nitrogen containing molecules (creatinine, methyl guanidine etc.) is potentially toxic for bone marrow, which leads to the reduced production and maturation of immune cells. In general, these "uremic" toxins severely inhibit the function of immune cells. The dialysis units are pathogen-free units, and every single patient must increase his/hers awareness of infections, because they typically run without fever, without proper "immune response" and may lead to serious complication (sepsis). **Liver diseases,** for example, lead to the reduced production of proteins, including acute phase proteins, which help to initiate and regulate the immune response and inflammation. Patients with **nutrition problems, adrenal gland dysfunction, patients with cancer and many more chronically ill patients** exposed to long-lasting stress develop immunodeficiency. The reason is that **cortisol** produced during the stress response has inhibitory effect and chronic stress (distress) frequently leads to the immune problems.

2) Increased reactivity of the immune system

Increased reactivity of the immune system in general is called **hypersensitive state.** Exact mechanisms leading to hypersensitive states are not clear, but contribution of genetic factors, repeated infections and environmental pollutants in the air, water and food has been discussed lately. Based on the mechanisms leading to hypersensitivity, it is possible to distinguish several categories of these reactions.

1st type of hypersensitive reaction – IgE-mediated immune reaction

It is immediate reaction of the immune system which appears in case of the second (repeated) exposure to the antigen, which is in this case also called allergen. Mechanisms leading to this type of the response are genetically determined in a way of atopy - genetic predisposition to increased production of IgE and increased density of receptors for Fc fragments on the mast cell surface, which can specifically bind with the IgE. Important role is played by the first exposure of the individual to the allergen, because this is the initiation of so-called "sensitisation" (fig. 1). During the first exposure, allergen is recognized by immune cells in the tissue and the main role of these cells is to recognize and present the antigen to the other immune cells. APCs (antigen presenting cells) are phagocytes and after the reaction with the antigen, they present it to the Th lymphocytes. Th cells activate other lineages of the T cells and also B cells, which transform into the plasmatic cells capable to produce antibodies. Antibodies of the IgE class will bind to the Fc fragments of their receptors on the

surface of the mast cells. This is the first contact with the antigen, which somehow prepares the individual to possible future exposures to this allergen. The allergen can be foreign protein (e.g. cow milk protein), polysaccharide, different venoms, toxins or even medications.

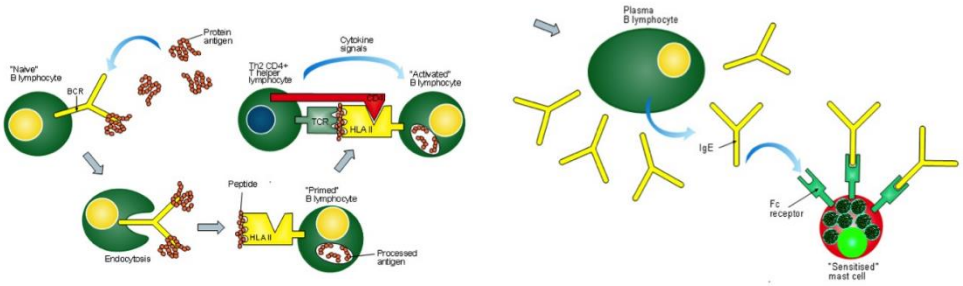


Figure 3.1: First exposure leading to the sensitization of an individual

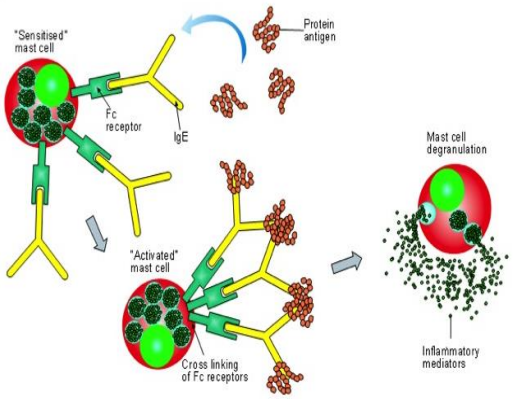


Figure 3.2: Repeated exposure leads to the immediate degranulation of the mast cells.

Repeated exposure of previously sensitized individual to the allergen leads to the allergic reaction which consists of two phases. **Early phase** starts immediately after the exposure, lasts for couple of hours and it is mediated by degranulation of mast cells and basophils with the release of histamine, bradykinin, prostaglandins and other signalling molecules. **Late phase** starts after 3-8 hours and it is characterized by the activation of cell lineages and by infiltration of exposed sites of the body (skin, mucosa). Allergic reaction plays an important role in the pathogenesis of diseases such as **bronchial asthma, allergic rhinitis, conjunctivitis, anaphylaxis, angioedema, atopic dermatitis, urticaria and so on.**

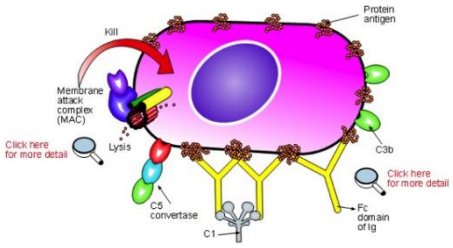
Serious, life-threatening consequences of IgE mediated hypersensitive reaction is anaphylaxis. Anaphylaxis is caused by massive degranulation of mast cells with the release of histamine and other vasoactive mediators. Clinical presentation of anaphylaxis is caused by

the bond of histamine on its receptors in the tissues. The results are generalized itching, vasodilatation of the peripheral circulation, increased capillary permeability, decrease of peripheral vascular resistance; therefore, decrease of blood pressure. As a response to it, baroreflex initiates the sympathetic response, mainly tachycardia. Increased perfusion of skin leads to erythema (the colour of the skin is red). Furthermore, histamine causes bronchoconstriction, which leads to the dyspnoea sensation and if untreated, it may eventually lead to respiratory failure. If anaphylactic response becomes strong, and if left without therapeutic intervention, the patient may easily develop mismatch between the circulation volume and volume of the vascular network, which may lead to the circulatory anaphylactic shock.

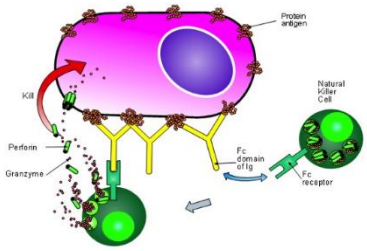
2nd type of hypersensitive reaction – cytotoxic reaction

The main mechanisms leading to this type of hypersensitive reaction is production of antibodies against antigens located on the cell surface of the "own" structures, tissues or cells. The result of this reaction is lysis – death of the targeted cells and this reaction is tissue specific. Destruction of cells can be caused by several mechanisms.

a) antibodies produced by activated B cells bind to the TSA (tissue-specific antigen) of the targeted cells and this leads to development of the complex antigen – antibody which activates the complement system. Cytolytic enzymes – the products of the complement activation are able to cause the lysis of the cells carrying the antigen-antibody complex on their surface. Example of such a reaction is for example autoimmune haemolytic anaemia or post-transfusion haemolytic reaction.



b) antibodies which bind to the TSA of the targeted cells "label" the cells in a process called opsonisation; therefore, these cells can be recognized by macrophages as strangers. Macrophages or natural killer cells identify and destroy the opsonized cells by regular phagocytosis. Since this process requires antibody to label the cells and finally macrophages to destruct them, this is called ADCC – antibody-dependent cell cytotoxicity. Example of such a process can be **Hashimoto's thyroiditis**.



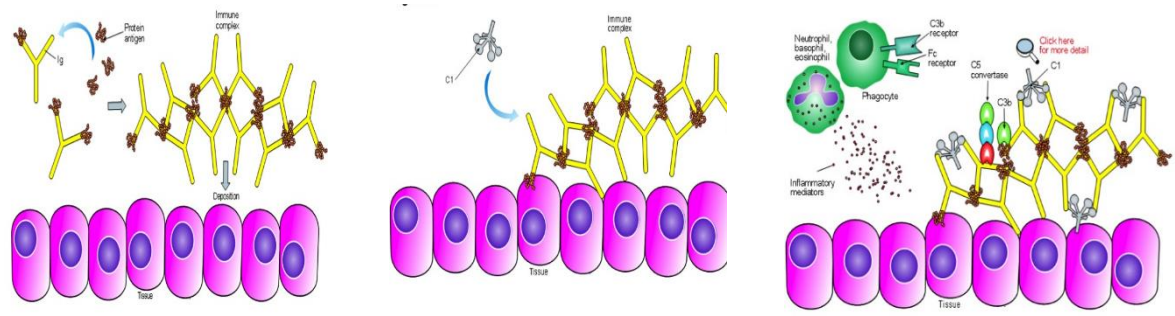
c) TSA of the targeted cells is recognized directly by the cytotoxic T lymphocytes and after their interaction, T cells cause the lysis of the targeted cells by action of cytolytic enzymes they produce.

There are also situations in which the lysis of the cells is not the end stage step, but the antibodies rather influence the function of targeted cells. An example can be **Graves' disease,** where the antibodies bind directly to the TSH receptor expressed on the cellular surface of thyroid cells. The result is a hyperfunction of the thyroid gland leading to thyrotoxicosis. Another example can be **myasthenia gravis** – a disease characterized by production of antibodies against the receptors for acetylcholine located at the neuromuscular synapse of striated muscles.

3rd type of hypersensitive reaction – immune-complexes mediated hypersensitivity

This type of hypersensitivity is characterized by production of immune complexes in the circulation without selective tissue specificity. Circulating immune complexes (CIC) have tendency to be deposited into vascular wall, also to the extravascular location (A), and their distribution is not tissue or organ specific. Production of immune complexes is a regular part of the immune response; however, normally, they are quickly cleaved from the circulation by the monocyte-macrophages system. In case of hypersensitivity, this cleavage is not fast enough, thus leading to deposition of CIC into the vessels etc. Deposition of immune complexes leads to the activation of the immune effector mechanisms with the primary objective to destroy the immune complexes. This may happen via complement (B) or via cells providing phagocytosis. One way or another, activation of complement system and activation of macrophages lead to the presence of factors which are potentially aggressive not only to the immune complexes, but also to the surrounding structures which are destroyed due to this process (C).

A **B** **C**

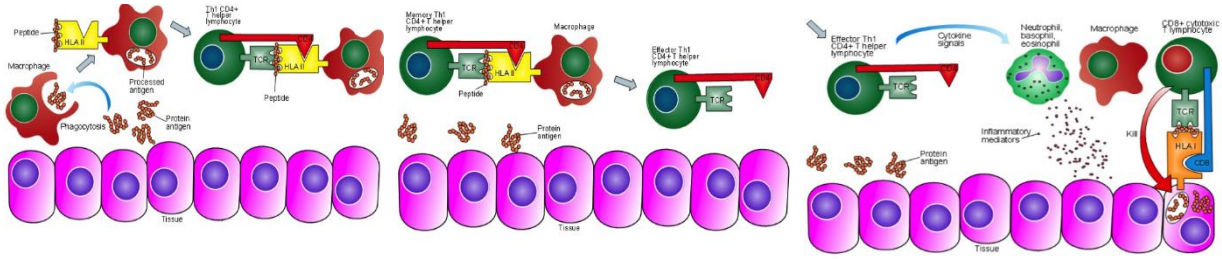


Examples of diseases caused by this type of hypersensitivity are e.g. serum disease which appears after the i.v. administration of heterogeneous serum. Immune complexes are deposited to the vascular walls, joints and kidneys. Disease manifests by redness of the skin above the inflamed joints, fever, pain and lymphadenopathy. Other examples can be specific type of glomerulonephritis caused by deposition of the CIC to the glomerular basement membrane, rheumatoid arthritis or systemic lupus.

Example of the local production of immune complexes is the Arthus' phenomenon. It is characterized by local administration of the antigen to the skin of experimental animals which had high levels of IgG against the inoculated antigen. What happened was a local inflammatory reaction so intense, that it led to the necrosis at the site of inoculation. Arthus' reaction participates in the pathogenesis of diseases such as farmer's lungs disease or lung aspergillosis.

4th type of hypersensitivity – delayed hypersensitivity response

Last type of hypersensitive reaction is characterized by the reaction of macrophages which ingested the foreign antigen (e.g. *Mycobacterium tuberculosis*), but they are not able to destroy it. This leads to the activation of T lymphocytes to start production of lymphokines and these signal molecules, together with the T lymphocytes regulate the course of the immune response. These reactions are very likely important in the defence of the body against intracellular parasites (some bacteria and viruses). The example of the delayed hypersensitivity is graft rejection, rejection of tumours, contact skin allergies or granulomatous reactions.



Allergies

Allergies are hypersensitive reactions of the immune system to the environmental antigens and this type of reactions may lead to the diseases such as bronchial asthma, allergic rhinitis, conjunctivitis, atopic dermatitis, skin contact allergies and food allergies. The prevalence of allergic diseases in population increases and the causes are complex. Very important is the presence of genetic predisposition to produce increased amounts of IgE – atopy, then increased concentration of different pollutants in the air, water, food etc. Considerable attention is given to the so-called hygiene theory. This theory claims that overprotection of children against naturally present microorganisms (extensive disinfection, cleaning of surroundings) does not let the immune system of the child to mature properly and slowly as it would if there are some natural antigens around the new-born or a toddler. Restriction of the antigens leads to the lower stimulation of the immune system and it does not develop the proper way of responses. When the child begins to be exposed to the antigens (kindergarten, day care) the immune system has two ways to choose. Either not to react (and the child will manifest with immunodeficiency) or overreact and the child may develop an allergy. Another debatable factor is nutrition. Immune system in the gastrointestinal system plays an important role in the modulation of overall immune performance. However, it is important to understand that the intestinal barrier of new-borns and toddlers is not well developed and the exotic or inappropriate food may stimulate the GIT immune system, leading to the development of hypersensitivity.

Allergy versus histamine intolerance

Allergic process is a massive source of histamine – the mediator with multiple functions and effects in the body. It is important to distinguish allergy, where the source of histamine are mast cells and basophils, and the release of it is mediated by the immune process. There is one specific condition, which is frequently overlooked, and many health care professionals do not know about it, yet it has its significance in clinical settings. It is **histamine intolerance**. In this case, the histamine that enters the body via food is not

metabolized in the intestinal mucosa, which contains two important enzymes for histamine degradation – DAO (diamine oxidase) and HNMT (histamine-N-methyl transferase). This is either congenital of acquired problem, and can be easily solved by avoiding food containing a lot of histamine, or by substitution of DAO in a form of supplement.

Autoimmune processes

Immune system tolerates own antigens and this is a part of the ability of immune tolerance. These antigens may be modified by many factors – e.g. by a virus, mutation, or by the process of ageing. Now the antigens have been changed and the immune system tolerance does not protect them any longer. They are being recognized as strangers and may become an easy target for immune responses. Autoimmune diseases are affecting many tissues and literary there is not a system that would not be affected by autoimmunity. **Endocrine system** is frequently affected by autoimmune disease – like Graves' disease, autoimmune thyroiditis, primary myxoedema, DM type 1, Addison's disease, idiopathic hypopituitarism and many more. **Skin diseases** involve pemphigus vulgaris, vitiligo, dermatitis herpetiformis, **neuromuscular diseases** caused by autoimmunity include dermatomyositis, sclerosis multiplex or myasthenia gravis. In the GIT, the examples of autoimmune diseases include coeliac disease, ulcerative colitis, Crohn's disease or atrophic gastritis. Autoimmunity frequently affects kidneys, eyes, blood cells (anaemia, thrombocytopenia) and connective tissue.

Isoimmune processes

The target of isoimmune processes are tissues or cells of the other human individual which were administered to the recipient's body with therapeutic purpose. They include reaction against the red blood cells administered via transfusion or grafts in transplantation. Specific type of isoimmune response is the maternal response to the foetal antigens during intrauterine development – e.g. Rh system incompatibility.

CASE REPORTS

Case report 1

70-years-old woman with diabetes mellitus was admitted to the ER due to fever, hyperglycaemia and slowly progressing consciousness problem described by relatives. Patient's history documents that the patient is on PAD, has hypertension, hyperlipidaemia

and repeated urinary tract infections. According to the documentation, she was repeatedly treated by antibiotics for the urinary tract infections; however, the effect of the treatment was only temporary and the infection keeps coming back. The cultivation showed repeated infections by *E. coli, Enterobacter sp.* and *Proteus sp.*

On admission, the patient is conscious, self-aware, but she replies with delays to given questions. She gives one-word answers. BP 90/60 mmHg, heart rate 80/min, breathing rate 20/min, skin is warm, well perfused. Chest without pathological findings, abdominal palpation is painful mainly in the lower parts, with palpable distended urinary bladder. Catheterization of the bladder evacuates approx. 400 mL of cloudy urine. Lower extremities without oedema and signs of deep venous thrombosis.

Laboratory findings: Na 158 mmol/L; K 4.6 mmol/L; creatinine 180 μmol/L, urea 14 mmol/L, TnI less than 0,2 ng/mL; pH 7.27; BE -4 (-2- +2); HCO_3^- 17 mmol/L; pO_2 13.3 kPa; pCO_2 4.1 kPa, glucose 53 mmol/L, albumin 27 g/L (32-45), WBC 13×10^9/L; HGB 116 g/L, PLT 310×10^9/L

Questions & Tasks

1) Which laboratory findings are not physiological? Explain how these parameters were changed and why in this particular case.
2) What acid-base disturbance is present in our patient? What is the cause?
3) What mechanisms contribute to the increased blood glucose level in our patient?
4) What is the cause of repeated infections of the urinary tract in our case?
5) Why diabetes leads to immunodeficiency?
6) Why the patient only has mild elevation of the body temperature in spite of massive infection?

Case report 2

35-years-old, obese woman is one day after the laparoscopic cholecystectomy. She is at the surgical ICU, BP 110/70 mmHg, heart rate 70/min, breathing rate 14/min, diuresis per hour is normal and the drainage sucks haemorrhagic fluid. She is still bit sleepy after the anaesthesia and the doctor prescribed her antibiotics, because the gallbladder during the surgery showed the signs of phlegmon. Within 2 mins after the i.v. antibiotics were administered, the patient became restless, wakes up and reports chest pain, pressure over the chest, tongue itching, breathlessness. Her skin becomes red – orange and starts to swell.

Vital signs: BP 80/55, heart rate 140/min, breathing rate 25/min, audible wheezing all over the lungs. She was given epinephrine (EPIPEN) immediately and hydrocortisone 120 mg i.v., antihistamines and oxygen. Her condition improved immediately.

Questions & Tasks

1) Describe the type of reaction present in this patient. Explain the mechanisms responsible for this reaction.

2) Explain the mechanisms of 1st type, so-called immediate hypersensitivity and the effects of the histamine on the body.

3) Which mechanisms lead to the decrease of the BP in anaphylactic reaction?

4) Explain the given medication, what are the primary targets of epinephrine, hydrocortisone and antihistamine in this case? What effects of the treatment are expected?

5) What mechanisms can be responsible for the chest pain or chest pressure in this case? Define the autoregulation interval of the coronary circulation.

Case report 3

36-years-old woman with histologically verified discoid lupus in 1992. In 2008, the patient complained about arthritis of the small joints on the hands and feet – the status was evaluated as rheumatoid arthritis and the treatment with prednisone was initiated. In February 2009, the patient was admitted to the hospital due to fever, weight loss of 12 kg. Gastroscopy verified haemorrhagic gastritis, anaemia and thrombocytopenia. The progression of disease led to the manifestation of skin vasculitis, with fever 39°C, X-ray verified fluidothorax, ultrasonographically verified ascites and oesophageal candidiasis. Throat swabs were positive for polyresistant strains of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

Laboratory tests showed high level of humoral inflammatory activity (blood sedimentation 97/147; CRP 50.7 mg/L), pancytopenia (HBG 76 g/L; WBC 3200/mm^3; PLT 20000/mm^3), hypoproteinaemia (total protein 61.3 g/L; albumin 18.3 g/L), positive D-dimers, ATIII 62.1 %, high level of autoantibodies – ANA 4z, anti-DNP 113,8 U/mL, anti-dsDNA 300 U/mL, ENA SSA/Ro 300 U/mL, SSB/La 300 U/mL, CH50 43, parameters of cellular immunity: expression of HLA-DR on monocytes 25 %. Urine was positive for RBC 70; PLT 45; protein 1.26 g/24 hours, with reduced glomerular filtration without retention of creatinine.

Based on the clinical presentation and laboratory work, the patient was diagnosed with SLE, pancytopenia, polyserositis, nephritis, hypercoagulation state, secondary immunodeficiency and secondary infections.

Questions & Tasks

1) Explain mechanisms leading to the loss of immune tolerance and onset of autoimmunity.

2) Which laboratory findings confirm that the patient has high inflammatory activity? Which of them confirm autoimmune process?

3) Explain the mechanisms leading to renal problems. Which laboratory findings confirm the kidney damage?

4) Changed levels of PLT suggest the presence of consumption coagulopathy. Explain the process.

Chapter 4

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Local inflammatory response

Inflammation is a stereotypic, mostly local response of the body followed by systemic signs of different magnitude, induced by tissue damage or destruction. Its ultimate goal is to destroy and eliminate provoking factors (viruses, bacteria, necrotic tissue, damaged tissue) and to repair the defect of previously affected tissue.

There are several possibilities how to classify inflammation

- Based on the time course – acute, peracute, chronic
- Based on the main manifestation of the inflammation – alterative, exudative, proliferative
- Based on the extent of the damage – superficial, deep, restricted to certain area spreading into the surroundings, etc.

Inflammatory reaction is initiated by identification of "strange molecular patterns" by antigen presenting cells (APCs) in tissues. PAMP – pathogen-associated molecular patterns (bacterial, viral surface identification signals) or DAMP – damage-associated molecular patterns (alarmins – signals expressed on the surface of damaged cell) are signals, which are recognized as "not mine" and initiate further immune response. APCs activate other immune cells and they start production of inflammatory cytokines (IL-1, IL-2, IL-6, TNFα, IFNγ) via activation of nuclear transcription factors – mainly NFκB. There are many more transcription factors in the nucleus of the immune cells (GATA, STAT) but the NFκB is the best known and most studied one.

The cascade of humoral signals (cytokines, NO, acute phase proteins) start to orchestrate the inflammatory response at the local level, which is characterized by the Latin words *calor* (heat), *dolor* (pain), *rubor* (redness), *tumor* (oedema) and function laesa (dysfunction). What are the mechanisms leading to these signs and symptoms?

1. **Vasodilatation** – dilation of blood vessels brings heat and redness to the affected area, so the focus is warmer and red. Vasodilatation is necessary to increase blood supply into the target tissue and enhance the supply of the inflammatory cells,

mediators, factors necessary for the optimal course of inflammatory process at the local level at first. Inflammation always starts at the local level.

2. **Increased permeability of the capillary wall** – leads to oedema of the affected area and it allows the immune cells to cross the endothelial and capillary basement membrane to move further to the tissue, where they act. Increased permeability also allows other diffusible components of the inflammatory response to move into the target tissue
3. **Transmigration of the cells (macrophages, lymphocytes, neutrophils) into the target tissue –** contributes to the expansion of the affected area (infiltrate). Infiltration is caused and regulated upon chemotactic stimuli and depends on the character of the insult that induced tissue damage.
4. **Changes of biosynthetic, metabolic and catabolic profiles of many organs** (liver, spleen, lymphatic tissue) are not local actions, but small number of cytokines released in the inflamed area circulate in the body, therefore they can affect different organs (OVLT – mechanisms of fever, liver – production of acute phase proteins, etc.). Inflammation is still LOCALIZED, but the body has been informed already via the cytokine signals about the "danger" and this will initiate acute phase reaction; this will also activate stress cascade with its neuroendocrine complexity to increase the chances of the body for survival. This includes also activation of complement, coagulation system etc.

The local signs of inflammation – calor, rubor, tumor, dolor, functio laesa are consequences of mechanisms mentioned above

Reaction of acute phase

Eukaryotic organisms have developed defensive and adaptive mechanisms necessary for the maintenance of homeostasis of internal environment after impairment of its integrity. These physiological processes of defensive and reparative nature induced by tissue damage, infectious causes, nociceptive insults (burns, trauma, haemolysis, excessive physical activities) are termed as acute phase reaction.

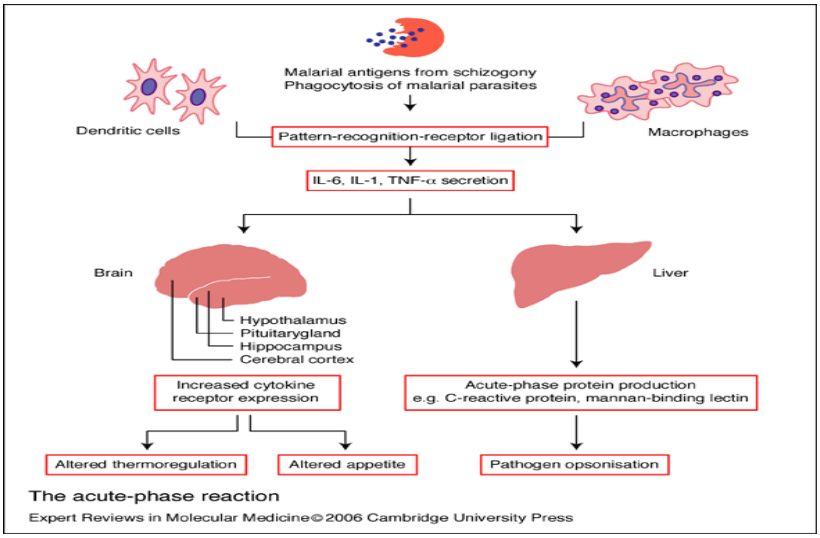
The acute phase reaction is innate uniform adaptive response to disturbance of the integrity of the body. Acute phase is a group of reactions elicited by humoral factors, especially proinflammatory cytokines **(IL-1, IL-2, IL-6, TNF α)** and axis **hypothalamus-**

pituitary gland-adrenal cortex – which is a part of stress reaction. All diseases, infections, traumas, although small and unnoticed, activate the stress axis. The question is to what extent. Acute phase reaction involves:

- **Immune processes** (production of proinflammatory cytokines, activation of innate non-specific immunity)
- Changes of hormonal and metabolic profile at systemic level (change of the metabolic profile of liver cells; decrease of plasmatic levels of zinc, iron; insulin resistance; muscle catabolism)
- **Synthesis of acute phase proteins** - C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin and many more
- **Change of water and ion balance** - activation of RAA system
- **Pyretic reaction (fever)**.

The acute phase reaction is limited in time – proinflammatory cytokines are cleared from plasma within several hours, APP are present in the serum for 48 hours at least). The main goal of the acute phase reaction is:

- **Maintenance of water, ion and temperature homeostasis,**
- **Boost of antiinfectious/immune processes**
- **Perception of pain as a signal of tissue damage**
- **Elimination of irreversibly damaged tissue**
- **Offer of optimal energy supply**
- **Optimal supply of structural molecules, mainly amino acids for the production of antibodies, hormones, regenerative and reparative processes**



Systemic inflammatory response syndrome

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions for systemic inflammatory response syndrome (SIRS), sepsis, sepsis-induced hypotension, septic shock, and multiple organ dysfunction syndrome (MODS). The idea behind defining SIRS was to define a clinical response to a non-specific insult of either infectious or non-infectious origin. SIRS is defined as presence of 2 or more of the following criteria:

- **Body temperature higher than 38°C or lower than 36°C**
- **Heart rate more than 90 beats per minute**
- **Respiratory rate of more than 20 breaths per minute or a $PaCO_2$ level of less than 32 mmHg**
- **Abnormal white blood cell count (>12,000/µL or <4,000/µL or >10% bands)**

Extremes of age (both young and old) may not manifest with typical criteria for SIRS; therefore, clinical suspicion may be required to diagnosis a serious illness (either infectious or non-infectious). Patients receiving a beta-blocker or a calcium channel blocker are likely unable to elevate their heart rate and, therefore, tachycardia may not be present.

Although blood pressure is not one of the 4 criteria, it is still an important marker of possible progression of disease.

SIRS is non-specific reaction elicited by acute body danger, defensive reaction of the human body which lost the main character of local process and it could be understood as a systemic reaction to localized inflammation. However, it must be precisely regulated, because it may lead to the damage of the endothelium, other organs etc. **SIRS is more complex and more intensive reaction in comparison to acute phase reaction.** SIRS might lead to complex disturbance of homeostasis with potentially destructive action - the body is affecting itself due to its defensive reaction. SIRS is non-specific and can be caused by ischemia, inflammation, trauma, infection, or a combination of several insults. SIRS is not always related to infection. Therefore, it is important to define several terms related to these problems.

SIRS	Two or more of: Temperature > 38°C or < 36°C Tachycardia > 90 beats/minute Respiratory rate > 20 breaths/minute or $PaCO_2$ < 4.3 kPa White blood count > 12×10^9/L or < 4×10^9/L or > 10% immature (band) forms White blood count > 12 x 10^9/L or < 4 x 10^9/L or > 10% immature (band)
Sepsis	SIRS due to severe infection, positive evidence for the presence of bacteria within the bloodstream, confirmed by cultivation
Bacteraemia	Presence of bacteria within the bloodstream, but this condition does not always lead to SIRS
Sepsis-induced hypotension	Presence of systolic blood pressure of less than 90 mmHg or a reduction by more than 40 mmHg from baseline in the absence of other causes of hypotension
Septic shock	Clinical syndrome caused by sepsis, characterized by persistent hypotension and perfusion abnormalities (mostly in microcirculation) despite adequate fluid and vasopressor resuscitation
MODS	Multiple organ dysfunction syndrome – dysfunction of kidneys, liver, lungs, heart, GIT caused by severe hypoperfusion and other complications of SIRS – physiological derangements in which organ function is not capable of maintaining homeostasis

Causes of SIRS

The most common causes of SIRS related to infectious disease are as follows - bacterial infection, wound infection (burns, surgical wounds, diabetic foot and other infectious complications), cholecystitis, cholangitis, other abdominal infections, pneumonia both nosocomial or community acquired, urogenital infections, meningitis and other less frequent conditions

Non-infectious causes as underlying conditions for SIRS involve acute intestinal ischemia, pancreatitis, GIT bleeding, autoimmune diseases, burns, aspiration, cirrhosis, inadequate reaction to drugs, cocaine, amphetamines, theophylline in high dose, myocardial infarction, trauma and other causes.

Pathophysiology

SIRS, independent on aetiology, has the same pathophysiologic mechanisms, with minor differences in initiating cascades. Inflammation is the body's response to non-specific insults that arise from chemical, traumatic or infectious stimuli. The inflammatory cascade is complex process that involves humoral and cellular responses, complement and cytokine cascades. Bone best summarized the relationship between these complex interactions and SIRS as the following three stage process:

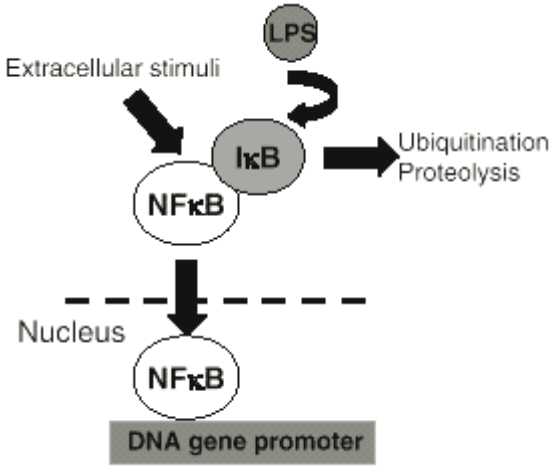
- Stage I: Following an insult, **local cytokines are produced with the goal of initiating an inflammatory response,** thereby promoting wound repair and recruitment of the reticular endothelial system.
- Stage II: **Small quantities of local cytokines are released into circulation to improve the local response.** This leads to growth factor stimulation and the recruitment of macrophages and platelets. This acute phase response is typically well-controlled by decrease in the proinflammatory mediators and by the release of their endogenous antagonists. **The goal is to maintain homeostasis.**
- Stage III: **If homeostasis is not restored, a significant systemic reaction occurs**. The **cytokine release leads to destruction rather than protection**. A consequence of this is the activation of numerous humoral cascades and the activation of the reticular endothelial system and subsequent loss of circulatory integrity. **This leads to end-organ dysfunction.**

Initiation of SIRS

Trauma, inflammation or infection leads to the activation of the inflammatory cascade. When SIRS is mediated by an **infectious insult**, the inflammatory cascade is often initiated by **endotoxin or exotoxin.** Tissue macrophages, monocytes, mast cells, platelets, and endothelial cells are able to produce a spectrum of cytokines. The cytokines **tumour necrosis factor-α (TNF-α)** and **interleukin (IL)–1** are released first and initiate several cascades. The release of **IL-1** and **TNF-α** (or the presence of endotoxin or exotoxin) leads to cleavage of the **nuclear factor-κB (NF-κB) inhibitor**. Once the inhibitor is removed, NF-κB is able to initiate the production of mRNA, which induces the production other proinflammatory cytokines. If the SIRS is induced by viral infection, the main stimulus is **interferon gamma (IFN-γ)** released from cells infected and destroyed by virus.

IL-6, IL-8, and interferon gamma are the primary proinflammatory mediators induced by NF-κB. *In vitro* research suggests that glucocorticoids may function by inhibiting NF-κB. TNF-α and IL-1 have been shown to be released in large quantities within 1 hour from an insult and have both local and systemic effects. *In vitro* studies have shown that these two cytokines given individually produce no significant hemodynamic response but cause severe lung injury and hypotension when given together. TNF-α and IL-1 are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system).

The figure shows activation of NFkB, primary transcription factor pre-existing in the cytoplasm in the form of inactive molecule linked to the inhibitor complex subunit. The answer to external stimuli or presence of lipopolysaccharide is the cleavage of the inhibitory subunit, transport into the nucleus and initiation of transcription of target genes.



Other cytokines, especially IL-6, stimulate the release of acute phase reactants such as **C-reactive protein (CRP).** Infection has been shown to induce a greater release of TNF-α than trauma, which induces a greater release of IL-6 and IL-8. This is suggested to be the reason for **higher fever associated with infection than trauma.**

The proinflammatory interleukins either function directly on tissue or work via secondary mediators to activate the coagulation cascade, complement cascade and the release of nitric oxide, platelet-activating factor, prostaglandins and leukotrienes.

Numerous proinflammatory polypeptides are found within the complement cascade. Protein **complements C3a and C5a** have been the most studied and are felt to contribute directly to the release of additional cytokines and to **cause vasodilatation and increasing vascular permeability**. **Prostaglandins and leukotrienes initiate endothelial damage, leading to multiorgan failure.**

The **correlation between inflammation and coagulation** is critical to understanding the potential progression of SIRS. IL-1 and TNF-α directly affect endothelial surfaces, leading to the expression of tissue factor. Tissue factor initiates the production of thrombin, thereby promoting coagulation, and is a proinflammatory mediator itself. **Fibrinolysis is impaired** by IL-1 and TNF-α via production of plasminogen activator inhibitor-1 (PAI-1). Proinflammatory cytokines also disrupt the naturally occurring anti-inflammatory mediators antithrombin and activated protein-C (APC). If unchecked, this coagulation cascade leads to complications of microvascular thrombosis, including organ dysfunction. The complement system also plays a role in the coagulation cascade. Infection-related procoagulant activity is generally more severe than that produced by trauma. The cumulative effect of this inflammatory cascade is an unbalanced state with inflammation and coagulation.

Signs and symptoms of SIRS – mechanisms involved

Fever

- Effects of the pyrogens in the hypothalamus
- Central thermostatic set point is shifted to the new set point, usually much higher than normal body temperature
- Mechanisms responsible for the heat production are enhanced, but heat loss is inhibited to conserve heat to reach this new set point temperature
- Production and loss of heat are regulated at this increased point until the level of pyrogens is decreased either spontaneously by action of immune system or by treatment

Hypotension – is a consequence of decreased peripheral vascular resistance due to vasodilatation induced by cytokines and other proinflammatory agents and partially is a consequence of the cardio inhibitory effect of proinflammatory molecules. The main role is played by NOS (NO synthase). Cytokines activate inductive isoform of NOS (iNOS) and this enzyme produces very high levels of NO – which is the main vasodilating substance in the body. The difference between the action of eNOS and iNOS leads to the huge hypotension, frequently resistant to the treatment.

Tachycardia

- Decrease of blood pressure inhibits the firing activity of baroreceptors in the aortic arch; therefore, natural high activity of sympathetic centre within the brainstem becomes dominant

- The effects of sympathetic system on the heart involve **increased heart rate – tachycardia** and **increased strength of myocardial contractions**
- Apart from these mechanisms, also another could be involved – fever increases the metabolic rate; therefore, the tissue oxygen requirements are increased to enhance oxidative processes
- Tachycardia is powerful compensatory mechanism able to increase oxygen supply

Increased breathing rate and hypocapnia

- Stimulation of breathing is **complex process**, with many mechanisms involved
- Example – fever – **increased oxygen consumption;** therefore, it is necessary to increase ventilation **to intake more oxygen**
- Change of $PaCO_2$ depends strongly on the **type of breathing pattern,** for example – panting as a thermoregulatory response is characterized by rapid shallow breathing with rebreathing, ventilation of death space – does not lead to change of partial pressure of CO_2
- Hyperventilation - when alveolar space is ventilated, it leads to hypocapnia which may further lead to the respiratory alkalosis

Changes of leucocytes (WBC) count

Increased count of WBC

- Proinflammatory cytokines stimulate the white blood cell population in bone marrow, they proliferate and mature to provide optimal immune defence
- If stimulation of the WBC line is strong, then younger "immature" cells are released from the bone marrow into the blood stream – bands

Decreased count of WBC is a consequence of rolling, adhesion and transmigration into the tissue and are responsible for the progressive decreasing of WBC count in blood; also, blood pool of WBC is not optimally substituted by the bone marrow production if the disease is e.g. long-lasting or aggressive.

The balance between inflammatory and anti-inflammatory response

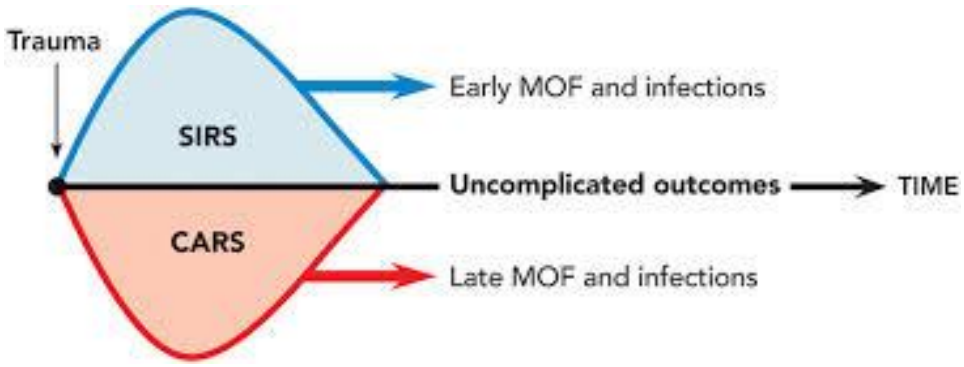
The intensity and time course of SIRS is influenced by a balance between pro-inflammatory and anti-inflammatory systems at local and systemic level. To counteract the

acute inflammatory response, the body is equipped to reverse this process via **counter inflammatory response syndrome (CARS)**. This antagonistic system is induced by the same stimuli as the SIRS and both processes **are running simultaneously**. CARS represents the system of negative feedbacks in cytokine and endocrine network (including the axis hypothalamus-pituitary gland-adrenal cortex) and limits the extent and duration of systemic inflammatory response. **The balance between SIRS and CARS course represents the balance between optimal inflammatory response and the extent of immunosuppression.**

IL-4 and IL-10 are cytokines responsible for decreasing the production of TNF-α, IL-1, IL-6, and IL-8. The acute phase response also produces antagonists to TNF-α and IL-1 receptors. These antagonists either bind the cytokine, and thereby inactivate it, or block the receptors.

Counter inflammatory response involves:

- Cytokines with anti-inflammatory action IL-4 and IL-10 - responsible for the decrease of TNF-α, IL-1, IL-6 and IL-8 production
- Production of receptor antagonists for TNF-α and IL-1. These antagonists can bind directly to the molecule of cytokine and inactivate it, or can bind to the receptor resulting into the block of the cytokine-induced biological signal
- Activation of the hypothalamus-pituitary gland-adrenal cortex axis with overproduction of glucocorticoids – their effect is inhibition of cytokine release; therefore, it leads to immunosuppressive effect



Comorbidities and other factors can influence the patient's ability to respond appropriately. The balance of SIRS and CARS determines a patient's prognosis after an

insult. Some researchers believe that because of CARS, many of the new medications meant to inhibit the proinflammatory mediators may lead to deleterious immunosuppression.

As it was described above, both SIRS and CARS are induced at the same time and the main idea of these antagonistic reactions is to maintain a balance within the cytokine network; therefore, to maintain the balance in action of proinflammatory and anti-inflammatory cytokines. The disturbed balance might result into two extreme situations:

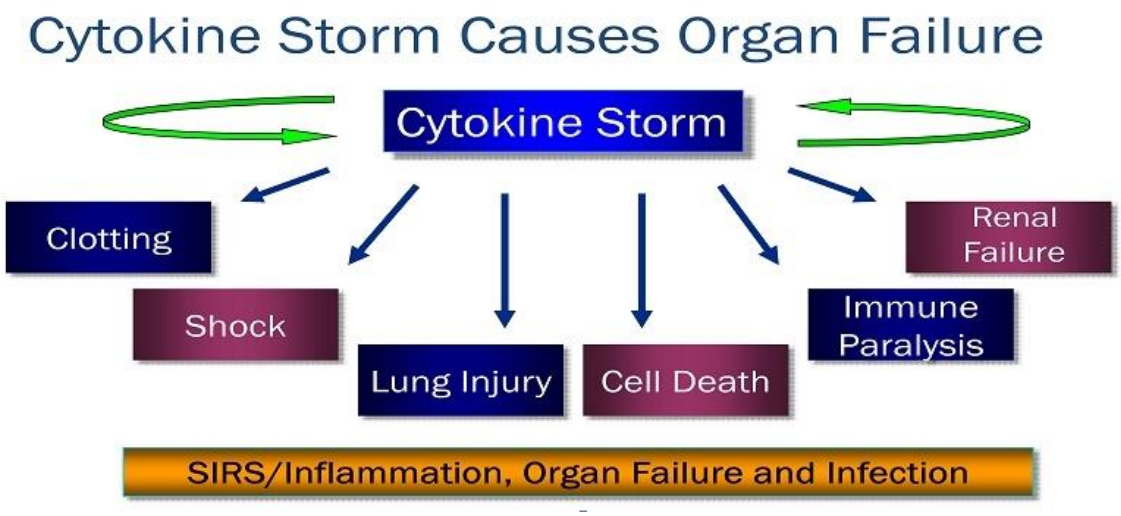
1. **Excessive activity of proinflammatory cytokines leads to severe SIRS with potential risk of organ dysfunction and death**
2. **Excessive anti-inflammatory response leads to immunosuppression and risk of increased mortality in later phases of clinical course**

Organ dysfunction as a consequence of severe SIRS

Multiple organ dysfunction could be a consequence of dramatic clinical course of SIRS; the dysfunction is mostly related to the kidneys, liver, lungs, central nervous system and heart.

Mechanisms responsible for the development of organ dysfunction:

1. Vasodilatation – abnormal distribution of circulating volume - tissue hypoperfusion
2. Increased vascular permeability - impairment of Starling's mechanisms – displacement of fluids into the interstitial space
3. Endothelial damage with expression of cell adhesion molecules and small thrombi formation in microcirculation - disseminated intravascular coagulation
4. Production of reactive oxygen species by neutrophils
5. Production of proteases by neutrophils
6. Production of NO by inductive NO synthase – refractory vasodilatation



Respiratory dysfunction

Pulmonary dysfunction is common in patients with SIRS and manifests as tachypnoea, hypoxaemia and respiratory alkalosis. When severe, it may progress to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The primary pathological process is pulmonary capillary endothelial dysfunction resulting in interstitial and alveolar oedema of protein and phagocytic immune cell rich exudative fluid. Endothelial permeability is increased in response to pro-inflammatory cytokines with progression to alveolar denudation and basement membrane destruction. Other mechanisms employed in ALI are destruction of surfactant molecules with formation of microatelectatic areas in lungs.

Cardiovascular dysfunction

Both the heart and the blood vessels are sensitive to the effects of pro-inflammatory cytokines as well as vasoactive substances present in excessive amounts in SIRS. Nitric oxide is synthesized by inducible nitric oxide synthase (iNOS) from L-arginine in the vascular endothelium and smooth muscle in response to pro-inflammatory cytokines. Nitric oxide is the mediator responsible for the decrease in systemic vascular resistance underlying the hypotension in SIRS. This hypotension may be refractory to treatment with fluids, inotropes and conventional vasoconstrictors.

The response to decrease of blood pressure is an increase in cardiac output. Baroreceptors mediate pronounced tachycardia and stroke volume increases due to decreased afterload but hypovolaemia may decrease preload and thus cardiac output. Independently of the effects of preload and afterload, intrinsic myocardial depression is present within 24 hours

of SIRS onset. Endotoxin and pro-inflammatory cytokines have both been shown to induce myocardial depression. These effects are probably mediated through nitric oxide. Constitutive NO in the heart is responsible for leucitropy - the ability of myocardium to relax, thus maximizing end-diastolic filling and coronary artery perfusion. Inducible NOS is expressed in cardiomyocytes in response to cytokines and increases NO production. Nitric oxide reduces myocardial contractility and responsiveness to β-adrenergic agents mediated through increased cGMP.

Renal dysfunction

Several mechanisms have been proposed for the pathogenesis of acute renal failure occurring in SIRS. In normal condition, the kidney maintains renal blood flow and glomerular filtration through autoregulation dependent on the tone of the afferent and efferent arterioles, an auto-regulation is disturbed in SIRS. The cytokine-induced systemic vasodilatation and relative hypovolaemia in SIRS are responsible for renal hypoperfusion. Therefore, it is difficult to predict renal blood flow from systemic blood pressure parameters. Kidneys produce intrinsic vasoconstrictors in response to cytokines and the renin-angiotensin-aldosterone system. In particular, the arachidonic acid metabolites thromboxane and leukotrienes both reduce renal blood flow and antagonists of these substances have been shown to have renal protective effects. In common with other tissues, the kidneys are susceptible to leucocyte mediated tissue injury with neutrophil aggregation in response to chemokines and production of proteases and ROS.

Gastrointestinal dysfunction

Gastrointestinal system suffers from hypoperfusion as well; and the barrier function of the intestinal wall is compromised due to hypoperfusion. After that, translocation of intraluminal bacteria or their endotoxin might occur, leading to the worsening the haemodynamic parameters primarily disturbed due to SIRS. There is a possibility for the development of septic complications in patients with SIRS as a response to non-infectious causes – based on the mechanisms of bacterial translocation across the impaired intestinal barrier from the lumen.

Metabolic disturbances

The alteration in haemodynamic regulation produces inappropriate distribution of perfusion and arteriovenous shunting resulting in tissue hypoxia and lactic acidosis. Many of

current therapeutic approaches aim to optimize oxygen delivery to the tissues by improving perfusion and avoiding hypoxemia. Cellular hypoxia is confounded due to impaired cellular oxygen extraction. Evidence suggest this is at a mitochondrial level mediated through NO which blocks the mitochondrial electron transfer chain at its terminal receptor of cytochrome oxidase. This then causes cellular hypoxia and an increase in mitochondria-derived ROS concentrations.

Haematological dysfunction

SIRS is often associated with disorder of coagulation secondary to the cytokine-mediated activation of the coagulation pathways. This disseminated intravascular coagulation (DIC) produces both bleeding and microvascular thrombi which have been proposed as mechanisms of multiorgan dysfunction. The cytokine-mediated activation of coagulation in SIRS occurs via the tissue factor-dependent extrinsic pathway. Tissue factor is the activator and cofactor for factor VIIa activation of factors IX and X of the extrinsic pathway. Monocytes and endothelial cells express tissue factor in response to endotoxin, complement fractions, IL-6 and IL-8. Attenuation of the anticoagulant systems worsens the procoagulant state. Antithrombin III (ATIII) is an inhibitor of the serine proteases responsible for coagulation factors IXa, Xa, XIa, XIIa and thrombin. Thrombomodulin is an endothelial cell derived inhibitor of clotting and activator of fibrinolysis. It acts as a thrombin binding protein, reducing the effects of thrombin. The thrombin-thrombomodulin complex has further anti-coagulant properties as an activator of protein C which, with co-factor protein S, inactivates factors V and VIII. In sepsis, the production of thrombomodulin by endothelial cells is downregulated by pro-inflammatory cytokines and circulating free levels of protein S are reduced.

CASE REPORTS

Case report 1

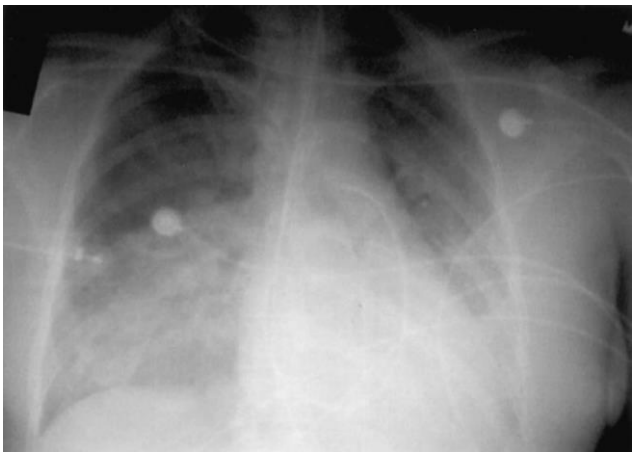
SIRS with shock and ARDS in patient with Still's disease (form of juvenile idiopathic arthritis)

29-years-old woman complained about shivering, high fever during last 4 months with arthralgia, myalgia and petechial rash. Personal history: pharyngitis and fevers of unknown origin during last 9 years. Extensive diagnostic procedures did not provide sufficient answer to her problems and following possible diagnoses were determined:

juvenile idiopathic arthritis or acute rheumatoid fever. She was treated by penicillin. Reasons of FUO were extensively investigated prior to admission. Medication: for longer period of time, she was taking combined oral contraceptives, APC (acetylsalicylates, paracetamol, caffeine), ibuprofen

Physical examination: Body temperature: 40°C, Heart rate: 118/min, BP: 85/56 mmHg, Breathing rate: 22/min, Saturation: 80% (100% O_2 mask). Petechial rash present on lower extremities, diffuse crackles in chest examination, slight tenderness in right upper quadrant of abdomen with slight hepatomegaly. Her condition deteriorated quickly and due to respiratory distress and hypotension she required endotracheal intubation, ventilation support and vasopressor therapy.

Laboratory examination: Leucocytes 16 600/μL, 38% bands; Haemoglobin 101 g/L; FW sedimentation > 100 mm/h; Platelets 142 000/μL; LDH 508 IU/L (105-330); AST 28 IU/L (10-34); ALT 32 IU/L (10-40); Bilirubin total 13μmol/L; Lactate 0.555 mmol/L. **Astrup** (artificial ventilation, 100% O_2, PEEP 10 cm H_20): pH 7.40; $PaCO_2$ 3.5 kPa; PaO_2 6.5 kPa; Bicarbonate 17 mmol/L; $SatO_2$: 85%



Questions & Tasks

1) Are all of criteria for SIRS present in this patient?

2) How would you explain the presence of 38% immature neutrophils?

3) If the patient would hyperventilate for longer time, what kind of acid-base balance disturbance could develop?

4) What respiratory system disturbance is frequently seen in SIRS patients?

Case report 2

SIRS after autovaccination

18-years-old woman was admitted to Department of Infectious Diseases with prolonged high fever (up to 41.5°C) from the day before admission, progressive malaise and maculohaemorrhagic rash. Prior to admission, she has subfebrilities and pharyngitis. Two months before, bacteriologic tests were performed – haemoculture negative, in throat swab *Staphylococcus aureus* and *Citrobacter freundii* present. Department of Microbiology prepared an autovaccine from Staphylococcus culture and it was administered in 4 doses (day 0– 0.1 ml, day 7 – 0.2 ml, day 14 – 0.3 ml, day 21 – 0.3 ml). She received the last dose 3 days prior to symptom onset. During the ages 7-12 years she had atopic dermatitis.

Physical examination: BP: 70/40 mmHg, HR: 130/min, BT: up to 38.6°C, patient was pale; generalized haemorrhagic rash on skin (diameter 5 to 25mm), also present on oral mucosa, without itching. Pharynx showed signs of inflammation, lymph nodes on neck and under mandible were enlarged. Apart from malaise, she reported pain of muscles on calf.

Laboratory examination: WBC 18 000/μL (15% bands), creatinine 177 μmol/L; PLT 299 000/μL; 219 and 189, antithrombin III 72%; INR 65%, Na^+: 132 mmol/L, FW sedimentation 140/h; CRP: 147 mg/L

After 15 min of admission her condition deteriorated rapidly (BP: 70/40 mmHg, HR: 130/min), skin was covered in cold sweat, this resulted into syncope. Hydrocortisone (100 mg) was administered, 500ml of saline, 0,5g of metronidazole twice daily. Diuresis was supported by administration of approx. 1300ml of electrolytes. During two following days, 6 units of fresh frozen plasma were administered. All haemocultures, cultivation of urine and pharyngeal swabs were negative; HBV and leptospirosis were ruled out. Chest X-ray and echocardiography did not reveal pathologic changes.

Questions & Tasks

1) Are the SIRS criteria met in this patient? What is the possible cause?

2) Why the platelet count is repeatedly examined and why does it decrease on second and third day?

3) Why is it important to maintain diuresis in patients with SIRS?

4) What wat the reason for corticosteroid (hydrocortisone) administration? What effect was expected?

5) What is NFκB and what is its role in initiation of inflammatory response?

Chapter 5

DISTURBANCES OF THERMOREGULATION
FEVER

Thermoregulation, as one of the aspects of homeostasis of inner environment, maintains constant body temperature of organism. Thermoregulatory mechanisms are activated when dynamic equilibrium between heat production and heat loss is disturbed. Body temperature is regulated exclusively by neural feedback loops and works via thermoregulation centre in preoptic area of hypothalamus, which includes specific thermosensitive neurons – central thermoreceptors. These are sensitive to temperature of blood flowing in nearby vessels. Signals from peripheral thermoreceptors (thermoreceptors for heat and cold in skin and visceral organs) are transduced to posterior hypothalamus and together with signals from *area preoptica* are integrated into final efferent signal dedicated to regulation of heat production and heat output. Overall control mechanism of thermoregulation in hypothalamus is often described as *"hypothalamic thermostat"*. Autonomous and motor nervous system, as well as endocrine system, contributes to thermoregulatory mechanisms.

In increase of body temperature the mechanisms which **increase heat output** are activated (by activation of cholinergic nerve fibres, increased activity of sweat glands, inhibition of sympathetic centres – vasodilation in the skin which increases elimination of heat from organism by radiation, conduction, convection and evaporation; increased cardiac output and respiration (through mouth); **intensity of heat production is decreased** (inhibition of hormonal influences, inhibition of metabolic processes in the liver, decrease of muscle tone).

In decrease of body temperature the mechanisms which **increase heat production and limit heat loss** (activation of sympathetic nervous system via alpha adrenergic signals leads to peripheral vasoconstriction, sweating is decreased, piloerection is present; in new-borns there is increased metabolism in brown adipose tissue mediated by stimulation of beta adrenergic receptors; muscle tone increases – muscle shivering may occur; metabolism is increased due to activation of endocrine system – release of adrenaline – plays important role in new-borns with brown adipose tissue, increased production of thyroid hormones connected with so-called calorigenic effect; in low temperatures also the effects of glucocorticoids and glucagon are important – they increase production of glucose – Fig. 5.1.

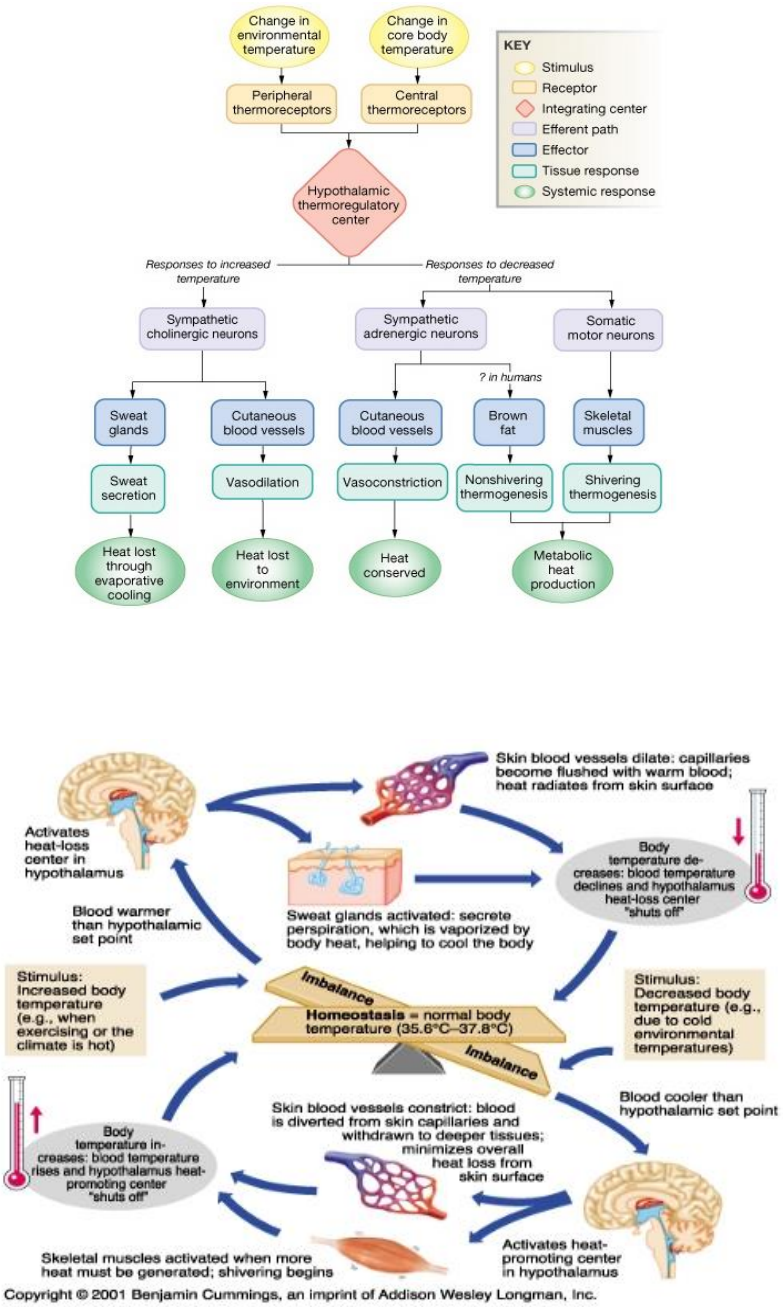


Figure 5.1: Mechanisms of thermoregulation (schematic)

Disturbances of thermoregulation

Disturbances of thermoregulation occur when inner or outer conditions exceed thermoregulation limits. These include hyperthermia and hypothermia.

Hyperthermia

Hyperthermia is process in which the organism is not able to eliminate excessive heat due to thermoregulation failure.

Causes of hyperthermia

1) Inadequate heat output due to following reasons:

- Increased temperature of environment with high humidity (affected individuals exercise excessively without replenishing fluids; physical mechanisms of heat transfer are dysfunctional due to high temperature and humidity of surrounding air – sweat does not evaporate, but flows on skin),
- Failure of peripheral thermoregulation mechanism: inadequate/ineffective vasodilation, insufficient sweat production (blockage of sweat glands) and its evaporation, cardiac insufficiency, dehydration

2) Metabolic diseases – e.g. pheochromocytoma (neuroendocrine tumour producing catecholamines), hyperthyroidism, hyperpituitarism – leading to increased heat production

3) Medication – e.g. amphetamine – increases metabolism; inhalation anaesthesia – development of malignant hyperthermia (in genetically determined disease of skeletal muscles can inhalation anaesthesia combined with suxamethonium lead to uncontrollable release of calcium ions followed by muscle rigidity and hypermetabolism). From pathophysiologic point of view, it is disturbance of intracellular calcium metabolism on level of ryanodine receptor – activation of which leads to increased and prolonged release of Ca^{2+} from sarcoplasmic reticulum to cytoplasm. Also, increased concentrations and metabolism of inositol-3-phosphate were found, which causes release of Ca^{2+} from cytoplasmic vesicles as a second messenger.

4) Disturbances of CNS – lesion of hypothalamus: bleeding, tumour, surgery

Pathophysiology of hyperthermia

Hyperthermia occurs when organism produces more heat or more heat is inputted than can be eliminated. In initial phase, the regulatory mechanisms divert blood from central circulation into skin (splanchnic and renal vasoconstriction accompanied by vasodilation in

skin). Later, the thermoregulatory mechanisms begin to fail. Elimination of heat from the centre will stop, body temperature will increase and heatstroke develops.

General effects of hyperthermia

Hyperthermia manifests with increase of cardiac output, peripheral vasodilation and sweating. Intense sweating leads to massive loss of fluids and electrolytes followed by dehydration, decrease of blood pressure, which can eventually lead to collapse. Hypovolemia causes insufficient blood supply to the skin which limits heat output via vasodilation and sweating. Due to significant loss of fluids, hypertonic dehydration develops with subsequent renal failure.

In high temperatures above 41°C due to direct effects of increased temperature, as well as secondarily due to disturbances of fluids and electrolytes, irreversible brain damage develops – therefore rapid treatment is necessary – cooling of patient!

Signs and symptoms of hyperthermia

- Red, warm skin (vasodilation, active hyperaemia) dry or wet depending on severity of hyperthermia, sweating is present – decreased sweat production is characteristic for heatstroke as a late sign of hyperthermia
- Nausea, vomiting, headache, weakness (result of dehydration and direct effect of increased temperature)
- Orthostatic changes of blood pressure (dehydration and decrease of BP), weakness and vertigo in sudden change in position
- Tachycardia and tachypnoea with respiratory alkalosis; severe dehydration leads to decrease of BP which reflexively activates sympathetic nervous system leading to peripheral vasoconstriction and skin colour changes from red to pale
- Functional changes of CNS – muscle spasms (even opisthotonos), changes of mental state, confusion, hallucinations, disturbances of balance, delirium, coma
- Increased filling of cerebral vessels (hyperaemia), cerebral oedema, increased intracranial pressure followed by compression of cerebral vessels and decreased perfusion – dysfunction of CNS
- Damage of tissues occurs in temperature higher than 42°C. Damage of proteins (denaturation) and increased permeability of membranes occurs
- Urinary tract: haematuria, oliguria to anuria as signs of acute renal failure

Injuries caused by increased temperature

Overheating, collapse

It is acute damage of organism by heat, occurs in high temperature of surrounding environment. Thermoregulatory effort with significant vasodilation and profuse sweating plays an important role in its pathogenesis – it leads to dehydration with decreased plasma volume and hypotension. Hypotension decreases stimulation of carotic baroreceptors which leads to disinhibition of central sympathetic system with development of vasoconstriction. Dehydration and hypotension can cause decrease in blood flow through brain. Accompanying symptoms include weakness, vertigo and nausea. Haemodynamic response to hypovolemia is aforementioned activation of sympathoadrenal system with vasoconstriction (also in kidneys), decrease of renal blood perfusion followed by activation of renin-angiotensin-aldosterone system – which compensates loss of body fluids and electrolytes.

Heat convulsions

Severe spasmodic cramps of skeletal muscles caused by profuse sweating accompanied by severe loss of sodium during exercise in increased temperature

Heatstroke

It is a form of overheating of organism accompanied with thermoregulation failure in body temperature above 40°C. Activation of compensatory mechanisms leads to increased blood flow through area of head – both in intracerebral and extracerebral circulation and in face with increased sweating as a defence mechanism against overheating. In further increase of body temperature, the intensity of sweating decreases, facial skin is red and dry. Stop of sweating is characteristic for heatstroke as a result of severe dehydration; therefore, it belongs to late signs of heatstroke. Complications of heatstroke include cerebral oedema and disturbances of neurons.

Sunstroke

It is local overheating of head which leads to thermal meningitis and encephalitis (local overheating of central nervous system – heat causes cerebral vasodilation, haemorrhage and oedema). It manifests with nuchal rigidity and pain in this area in forward flection of neck – patient cannot place chin to sternum and Brudziński sign – patient lying in supine position in attempt of forward flection of neck will cause involuntary flection of knee and hip. These are manifestations of meningeal irritation.

Hypothermia

It is a process, during which the body temperature decreases below 35°C. Hypothermia is pathologic process, in which more heat is eliminated than it is simultaneously produced.

Classification of hypothermia

- mild – body temperature 33–35°C
- moderate – body temperature 29–32°C
- severe – body temperature below 28°C

Causes of hypothermia

There are many of them and in development these mechanisms/processes play a role:

1) Induced hypothermia – it is a form of managed hypothermia used in longer surgeries in cardiopulmonary surgery as well as in some severe diseases: the function of thermoregulation centre is eliminated by administration of analgesics, neuroleptics and muscle relaxers. Other techniques are used as well.

2) Caused by exogenous cold – in exposure to cold air or cold water

3) Caused by decreased metabolism – e.g. in hypothyroidism, decreased activity of adrenal glands, hypoglycaemia

4) Caused by medication and drugs – e.g. barbiturates, alcohol, general anaesthesia

5) Caused by dysfunction of hypothalamus and other parts of CNS (tumour, cerebrovascular diseases)

Pathophysiology of hypothermia

In hypothermia, changes develop on level of cells, tissues, organs and systems. Intensity of these changes depends of severity, speed of onset of hypothermia and its duration.

Cardiovascular changes

Mild hypothermia – initial tachycardia and peripheral vasoconstriction followed by increase of cardiac output; blood pressure increases slightly.

Moderate hypothermia – progressive bradycardia as a result of decreased spontaneous diastolic depolarization of cells of sinoatrial node. Decreased cardiac output is

compensated by increased systemic vascular resistance via autonomous reflex (mediated by release of catecholamines). Peripheral vascular resistance is promoted also by haemoconcentration and increased blood viscosity. J wave is manifest on ECG recording (fig. 5.2). Widening of QRS complex indicates decrease of myocardial conduction in combination with either elevation or depression of ST segment and inversion of T-wave. These ECG changes can be related to acidosis and ischemia. Delayed repolarization of myocardium manifests with elongation of QT interval. These changes persist also after restoration of normal body temperature for some hours to days; atrioventricular block can also occur in temperature correction.

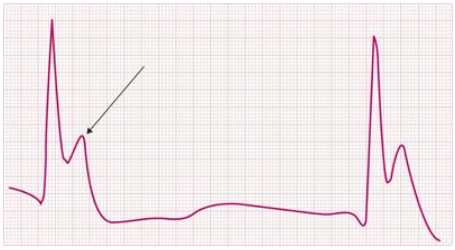


Figure 5.2: Example of J-wave on ECG strip

Severe hypothermia – is accompanied with extreme bradycardia – heart rate is approx. 30-40/min in 28°C and it progressively decreases with temperature decrease and it is only 20/min in 20°C. Peripheral vascular resistance decreases (decreased release of catecholamines, decreased reactivity of smooth muscle cells in the vessels), cardiac output decreases. It is assumed, that asystole is the result of extreme hypothermia, whereas ventricular fibrillation occurs in reheating of the patient – in restoration of body temperature back to normal values.

Hematologic changes

They include increased haematocrit and increased concentration of fibrinogen – the result is increased viscosity of blood; coagulopathy is also present. Changes of vascular permeability lead to loss of plasma into extravascular space, resulting to haemoconcentration. The resulting hypovolemia is also the result of cold diuresis. Hypothermia causes endothelial damage, which manifests with decreased synthesis of prostacyclin (PGI_2) and its inhibitory effect on platelet aggregation weakens, which in turn increases risk of thrombosis.

Neuromuscular changes

Central neurologic effects of cold clinically manifest as confusion in the beginning, sometimes they can manifest as amnesia – especially in mild form of hypothermia. With decreasing temperature, the manifestation changes – dominant features are apathy and disturbances of speech. Unconsciousness develops in temperature below 30°C. Loss of cerebrovascular autoregulation occurs in 25°C and is accompanied with decreased blood flow through cerebral arteries. Cerebral ischemia is manifest in severe hypothermia, as well as significant reduction of cerebral metabolism and loss of electrical activity of the brain. Muscle shivering is present in moderate hypothermia, but it weakens with decreasing temperature. Ataxia and motor control disturbances are observed in initial stages of hypothermia; it is followed by hyporeflexia in moderate hypothermia – pupillary reflex is weakened and loss of reflexes occurs below 28°C. Stiffness of muscles and joints is present in severe hypothermia. These changes can be attributed to disturbance of electrical conductivity of peripheral nerve fibres due to cold.

Respiratory changes

In mild hypothermia, shallow breathing with reduced minute ventilation and decreased oxygen consumption develops. Bronchospasm develops in inhalation of cold air, but decreased body temperature leads rather to "cold-induced bronchodilation". In moderate hypothermia, protective and defensive airway reflexes are decreased, as well as ciliary activity – this can lead to pneumonia. Severe reduction of oxygen production and carbon dioxide production manifest in temperature below 30°C. Body temperature lower than 34°C decreases sensitivity of peripheral and central chemoreceptors, which manifests also by decreased activity of respiratory centre – by decreased respiratory rate. Hypothermia also increases pulmonary vascular resistance, which can lead to disturbances of ventilation/perfusion ratios. Progressive hypoventilation occurs in severe hypothermia and apnoea develops in temperatures below 24°C.

Dissociation curve of haemoglobin for oxygen is shifted to the left, which explains decreased release of oxygen from blood to tissues. Lactate acidosis, which occurs in hypoxic tissues can to some extent decrease intensity of this disorder. Degree of acidosis increases as there is combination of metabolic acidosis and respiratory alkalosis – muscle shivering substantially increases production of lactic acid, but the elimination of acids from organism is limited (due to limited function of kidneys and respiratory system). High degree of acidosis is commonly seen in severe hypothermia. Mechanisms for compensation of ongoing acidosis

are activated in development of hypothermia and rapid correction of temperature (reheating) of patient back to normal values leads to severe metabolic acidosis as a result of continuous activity of antiacidotic compensatory mechanisms.

Renal and metabolic changes

Cold diuresis develops in hypothermia – it is caused by decreased production of ADH under influence of cold. In moderate hypothermia, the glomerular filtration rate decreases, as well as tubular functions, renal clearance of glucose and secretion of protons. The result is acute renal failure caused by ischemia of kidneys.

If the development of hypothermia is rapid, then the processes, which result in hyperglycaemia, are activated – insulin secretion is inhibited by increased secretion of glucocorticoids. Activation of sympathetic nervous system increases concentration of noradrenaline (norepinephrine) and concentration of free fatty acids; glycogenolysis and gluconeogenesis also contribute to hyperglycaemia.

Gastrointestinal changes

Intestinal motility decreases by 34°C and its further decrease (to approx. 28°C) can lead to manifestation of ileus. Erosions, submucosal haemorrhages and ulcerations can develop in stomach as a result of cold stress. Pancreatitis is severe complication of hypothermia, which is most likely caused by microthrombi in pancreatic microcirculation.

Fever

Fever is considered to be a defensive mechanism and it belongs to non-specific clinical signs. It is characterized by increased body temperature and an array of other signs and symptoms. Fever occurs based on the set point of thermoregulation centre to higher level. Thermoregulatory mechanisms (heat production and elimination) are preserved, but their function is shifted towards higher temperature than in physiologic conditions. This change of set point is the crucial difference between fever and hyperthermia, in which the set point is not changed.

Pathophysiology of fever

Fever is induced by substances called pyrogens. Exogenous pyrogens include bacteria, viruses, fungi; their products or parts (e.g. lipopolysaccharides from bacterial membranes), non-microbial substances (e.g. complexes of antigens and antibodies, products of non-

infectious inflammation). Exogenous pyrogens activate monocytes (macrophages), neutrophils, dendritic cells (all these cells belong to a group of cells called antigen-presenting cells) and lymphocytes, which upon stimulation synthesise endogenous pyrogens – cytokines IL-1α, IL-1β, IL-2, IL-6, TNFα and other.

Central mechanisms of fever

However, aforementioned cytokines cannot penetrate the brain-blood barrier (BBB) and directly reach neurons of preoptic area of hypothalamus (POAH). In this area, organum vasculosum laminae terminalis (OVLT) rich in capillaries is present. These parts of hypothalamus are essential for regulation of body temperature. Microbes and cytokines stimulate endothelial cells in these capillaries and upon stimulation they produce prostaglandin E_2 which can penetrate BBB. PGE_2 is synthetized utilizing an enzyme called cyclooxygenase-2, which can be effectively blocked by acetylsalicylic acid (aspirin). Endothelial cells upon stimulation by endogenous pyrogens stimulate phospholipase A_2 (PLA_2) and metabolism of arachidonic acid. PGE_2 either directly or via cAMP initiates setting of "central thermostat". Signals from reset centre are transmitted through sympathetic efferent nerves to peripheral vessels, where vasoconstriction is initiated. Thermoregulation centre also radiates efferents to cerebral cortex, where they modify the behaviour of an individual.

Stages of fever

Fever is dynamic process, which can be divided into 4 stages.

1) Prodromal stage – initial stage, without change of body temperature, thermostat is set to higher set point via pyrogens.

2) Incremental stage – increase of body temperature through activation of thermoregulatory mechanisms; the mechanisms of increased heat conservation and production prevail over opposite processes.

3) Acme stage – balance between mechanisms of heat production and elimination, but on higher level than normal.

4) Decremental stage – degradation of pyrogens leads to reset of thermostat to basal set point; mechanisms of heat elimination prevail over mechanisms of heat production

Positive effects of fever

Fever stimulates immune system, limits growth and virulence of bacteria, increases phagocytic and antibacterial activity of leukocytes, increases proliferation of T-lymphocytes and production of antibodies.

Influences of fever on organs and organ systems

1) Metabolism. Fever is accompanied with increased metabolism with increased oxygen consumption, increased CO_2 production, increased protein catabolism, hyperglycaemia; metabolic acidosis and hyperkalaemia.

2) Kidneys. Glomerular filtration rate decreases, diuresis decreases; increased contents of proteins in urine as a result of increased permeability of glomerular membrane

3) Gastrointestinal system. Production of gastric and pancreatic juices and enzymes decreases, peristalsis and resorption are disturbed. Decreased production of saliva and water resorption in large intestine is disturbed (increased or decreased) as well. Other manifestation includes loss of appetite, nausea, dyspepsia as a result of TNFα and other endogenous pyrogens.

4) Respiratory system. Respiratory system reacts to fever by increasing of ventilation – by increasing respiratory rate (tachypnoea) as well as depth (hyperpnoea) followed by development of hypocapnia and respiratory alkalosis.

5) Cardiovascular system. Fever activates cardiovascular system, which manifests with tachycardia, increased cardiac output (by increasing stroke volume as well); dysrhythmias may develop. This is especially dangerous in patients with pre-existing cardiovascular diseases (seniors!), in which fever can lead to circulation insufficiency.

Although diuresis is decreased, increased loss of fluids by sweating and respiration leads to dehydration as well as significant loss of sodium and potassium. Lot of cytokines contributing to pathogenesis of fever is able to sensitize peripheral nociceptors (nerve endings of sensory nerves), which manifests by hyperalgesia leading to headache and muscle pain. Increase of body temperature above 40°C is harmful to organism, because functional disturbances of CNS occur (increased sensitivity – cramps of skeletal muscles or apathy), muscle activity increases (general malaise, muscle fasciculations). Temperature above 41°C has a wide array of side effects and can be life-threatening, mostly because of damage of CNS.

Complications of fever

Dehydration and febrile convulsions are the most important complications of high fever, especially in children. Dehydration worsens blood flow through skin and contributes to maintenance of increased body temperature. In severe cases, the whole homeostasis can be disturbed and this can be fatal. Another specific complication of fever in children is febrile convulsions. They manifest almost exclusively in children between ages of 6 months to 5 years; most commonly between 12^{th} - 18^{th} month of age. Febrile convulsions have generalized tonic-clonic character with duration up to 15 minutes (in occurrence in series up to 30 minutes). Later in life, epilepsy can develop in these patients. Decreasing of fever by antipyretic drugs (they inhibit cyclooxygenase activity and therefore block synthesis of prostaglandins from arachidonic acid) and administration of diazepam (medication from group of benzodiazepines – sedative, anxiolytic and muscle relaxing effect) during early stages of fever is efficient prevention of recidivism of febrile convulsions.

CASE REPORTS

Case report 1

M.B. is 60 years old woman; was found unconscious by paramedics in her house with the heating turned off. There was alcohol on her breath.

History from relatives: alcoholic excesses; exclusion of diabetes mellitus, hypertension, cerebrovascular accidents and ischemic heart disease. She did not take any medication. Social history*:* widow, lives in a house, retired

Physical examination: Bradycardia, HR 44/min, BP 140/100 mmHg, RR 22 breaths/min, BT 27°C (tympanic temperature). Coma without focal neurologic defect. ECG – significant J-wave, HR 44/min confirmed; Chest X-ray normal, abdominal CT scan: obstruction of urethra and pancreatitis unconfirmed.

Laboratory examination: Glucose 1.1 mmol/L (200mg/L); Urea 22 mmol/L; Creatinine 298 mmol/L; Creatine kinase 4066 μmol/L; pancreatic amylase (pAMS) 503 U/L.

Hematologic tests: Arterial blood gases indicate metabolic acidosis with pH 7.13; BE -20; anion gap 41 mmol/L

Initial treatment: i.v. administration of vitamins B and C, 50% dextrose, mild reheating followed by 5% dextrose to maintain glucose levels. During this phase, the patient was hypotensive and oliguric. Repeated biochemical examinations showed increase in urea

(298 mmol/L) and creatinine (356 mmol/L) concentrations; creatine kinase was increased to 26833 μmol/L. Adrenaline was administered intravenously (inotropic effect) which was followed by of 20% mannitol. Biochemical markers and health state of patient improved in 10 days.

Questions & Tasks

1) What is the suspected diagnosis based on initial examination?
2) How is the pathogenesis of hypothermia influenced by alcohol?
3) What degree of hypothermia is seen in this case?
4) Sum up every relevant signs and symptoms in this patient and explain their pathomechanisms.
5) Laboratory parameters confirmed acidosis. Specify it based on laboratory parameters. What kind of changes in blood gases would you expect?
6) Which parameters do differ from normal and what kind of complications they indicate in known alcoholic ketoacidosis with hypothermia?
7) Seniors and new-borns are more prone to hypothermia than adults. Explain why.

Case report 2

45 years old woman J.P. came to emergency room with fever; she complained about diarrhoea, vomiting and general malaise.

Family history: mother had cholecystolithiasis, father diabetes mellitus type 2; children are healthy. **Personal history:** repeatedly treated for recurrent urinary tract infections. In recent years, she suffered back ache connected with spinal disc dysfunction; she took ibuprofen and diclofenac on occasion. Allergies: hay fever, which worsens during spring. **Social history:** married, lives in a house, clerk. **Epidemiologic history:** on Friday evening, she had dinner in Prague with her husband and friends. She had steak tartare (contains raw beef and raw egg yolk). **Present complaints**: the following day, on Saturday at around 4 PM she got fever 38°C and vomited. From Sunday morning, she complained about strong cramps in abdominal region, with frequent, watery stool, in the beginning it was yellowish brown in colour, later green with mucus and blood. Fever increased to 39°C. In the afternoon, she collapsed – her husband drove her to internal medicine department, from where she was referred to department of infectious diseases.

Physical examination: BT 38.8^{o}C, conscious and oriented, visibly weak, pale, slightly sweaty; eutrophic. Skin without jaundice and exanthema. Eyes, ears and nose without secretion. Throat without inflammation, oral mucosa dry; brownish tongue. Submandibular lymphadenopathy not present. Eupnoeic, RR 12/min; auscultation of heart and lungs normal. HR – 104/min, BP – 80/50 mmHg. Abdominal wall soft, with diffuse tenderness to palpation; without palpable resistance; hepatomegaly and splenomegaly absent. Meningeal signs negative.

Laboratory examinations: sedimentation of RBC 12/20; Leu 14.000; Ery 4.8; Hb 144 g/L; Hct 0.45; Plt 234.000; urea 29.3 mmol/L; creatinine 168 mmol/L; Na^{+} 129 mmol/L; K^{+} 3.6 mmol/L; Cl^{-} 95mmol/L; AMS 2.4 μkat/L (*bile ducts*), CRP (C reactive protein) 150 mg/L (reference < 5mg/L); urine: protein +, acetone +, negative: glucose, blood, bilirubin, urobilinogen

Questions & Tasks

1) Identify and sort all signs and symptoms which are present in this patient.

2) Explain pathomechanisms responsible for development of individual signs and symptoms.

3) Explain pathogenesis in this patient.

4) What aetiology of health problems is suspected?

5) Which examinations performed do support assumed aetiology of disease?

Chapter 6

GENERAL ETIOPATHOGENESIS OF DISEASES

The term **etiopathogenesis** unites the terms explaining **causes and conditions** leading to the onset of diseases – **aetiology** and mechanisms participating on the onset and progression of diseases – which is **pathogenesis**. The term "general etiopathogenesis" describes causes, conditions and mechanisms common for broad spectrum of diseases.

Aetiology of diseases

The onset and development of diseases is related to the action of certain factors, called noxae or pathogenic factors, on the body. They can be classified into several categories according to different criteria. One of aspects according to which classification of diseases is done is amount of noxae involved in its induction. When only one factor is involved then **mono-factorial diseases** are developed**.** If more than one factor participates in induction of a disease, we call them **poly-factorial diseases.**

Mono-factorial diseases, as already mentioned, are caused by **only one** factor, and their onset is facilitated by **one or several conditions**. This pattern is typical e.g. for infectious diseases; example could be tuberculosis. Tuberculosis is caused exclusively by one factor – *Mycobacterium tuberculosis* which affects the individual with reduced immune performance, e.g. subjects with immunodeficiency, malnutrition, low income and social status, alcoholism, or other conditions. **Poly-factorial diseases** are characterized by onset and progression which is caused by unfavourable orchestration of more factors and conditions. Typical example is **atherosclerosis**. **Causes** of atherosclerosis are elevated levels of LDL and triacylglycerol particles in blood, reduced concentration of HDL, smoking, arterial hypertension. **Conditions** which promote onset and progression of this process are genetic predisposition, physical inactivity and sedentary lifestyle and increased levels and duration of psychogenic stress.

While in mono-factorial diseases it is not difficult to distinguish the cause from condition, in poly-factorial diseases it is very difficult, and sometimes even impossible to say exactly what the cause was and what was the condition. If there are many factors contributing to the onset and progression of certain diseases, they are rather conditions than direct causes responsible for its development.

According to the aetiology, diseases can be classified into **aetiologically homogenous**

and heterogeneous. **Aetiologically homogenous diseases** are those, which are always caused by the same cause or the same complex of causes, e.g. pertussis, typhoid fever, carbon dioxide intoxication, *Amanita phalloides* intoxication etc. **Aetiologically heterogeneous diseases** are those which are caused by different causes, or complexes of causes. The example could be **diabetes mellitus**. There is more than one type of diabetes mellitus – DM type 1, DM type 2, gestational diabetes and other specific types of diabetes. All of these processes are caused by different factors – autoimmunity, insulin resistance or production of certain hormones in pregnancy for example, but the result is the same – inability to maintain glucose homeostasis due to absolute or relative lack of insulin. Another example is **tissue hypoxia.** This process can be caused by many factors (causes) – still leading to the same process (tissue hypoxia). Causes may be:

- reduced arterial blood supply (ischemic hypoxia)
- blocked venous blood flow (stagnation hypoxia)
- reduced saturation of arterial blood by oxygen in lungs (hypotensive hypoxemic hypoxia)
- reduced concentration of haemoglobin (normotensive hypoxia), and even more causes, which are discussed in the chapter "Hypoxia".

Provenance of causes and conditions responsible for diseases onset may be **endogenous or exogenous**. Just to mention some of the **exogenous factors** – radiation, electrical current, mechanical force, chemical and biological substances, cold, temperature, noise, vibration etc. **Endogenous causes** (related only to the subjects itself) are genetic defects, genetic predisposition to develop certain diseases, accumulation of toxic metabolites in the body, enzymopathies, vicious circles etc. Endogenous and exogenous factors usually combine in a different extent, modifying diseases in particular individuals, making them unique entities. The same diseases in three or more different subjects will provide you with individually specific clinical presentations as all the factors combine.

Main classes of exogenous causes and conditions of diseases

1) Physical factors (noxae)

a) Mechanical force
b) Acceleration, deceleration, gravity
c) Vibration, noise, ultrasound
d) Cold or heat (low or high temperatures)

e) Radiation
f) Electrical current and electromagnetic fields
g) Climate and weather

2) Chemical factors (noxae)

a) Inorganic – elements (Hg, Pb, As …), compounds (SO_2, NO_x, HCN, NH_3, CO, O_3 etc.)
b) Organic – acids, alkalis, organophosphates, toxins from plants or animals, organic dust
c) Biological – bacteria, viruses, fungi, parasites, prions, lack of nutrients or too much food

3) Social factors (noxae)

a) Psychological
b) Social

Mechanical force – mechanism of action

Extremely intense mechanical force causes damage of the structure and integrity of body tissues. Consequences could be either **direct** – wounds/injuries (scratches, abrasions, fractures, shot wounds, slashes) or **indirect** – ischemia, denervation, dislocation of organs or their parts.

Examples of diseases/pathological processes/injuries caused by mechanical energy

Crush syndrome

Crush syndrome is defined as a complex of signs and symptoms caused by exposure of soft tissues (mainly muscles) to the long-lasting intense pressure (ruins of buildings, car crashes, victims of snow-slip or land-slip). Compression of the tissue leads also to the compression of blood vessels leading to the **hypoperfusion** and further to the **ischemia of compressed tissues**. Ischemia causes damage to the cells, vessels and nerves. Hypoxia and anoxia causes lysis of muscle cells (rhabdomyolysis) leading to the leak of myoglobin, enzymes, potassium, sulphates and phosphates to the extracellular space and from this space they can pass to the blood. Hypoxic tissue also converts **aerobic metabolism** to **anaerobic,** leading to the overproduction of different types of waste products, e.g. lactic acid.

Paradoxically, release of pressure by a rescue of a person from the ruins etc. will not lead inevitably to improvement of the state of tissue of **previously compressed area** because its **reperfusion** brings **more oxygen accompanied by increased production of oxygen free radicals,** and all of the aforementioned compounds (myoglobin, acidic compounds, potassium) are spread by the bloodstream to many organs of the body, e.g. brain, heart, kidneys, causing their severe damage. For example, myoglobin, as a small molecule passes through the glomerular filter and after it reaches the tubules, **it precipitates** there due to low pH. This leads to the **decrease or complete stop of glomerular filtration with development acute renal failure**. Other mentioned "toxic" metabolites may influence **heart**, because its performance is reduced by both **acidosis and hyperkalaemia**. Vessels (capillaries) in the compressed and reperfused tissue are also damaged. The damage to the vessels manifests by **increase** of their **permeability.** This may lead to leak of plasma to the tissue – thus causing **hypovolemia. Hypovolemia** is dangerous for the body, because it has negative consequences for function of vital organs due to **hypoperfusion**. It may result in development of **circulatory shock** and **multiple organ dysfunction/failure**.

Bedsores (decubitus ulcers)

Bedsores – characterized as **damage and necrosis of soft tissues -** are caused by exposure of certain parts of the body to the **prolonged pressure due to fixed body position on bed**. Compression of soft tissue leads to the ischemia with subsequent damage to the cells, necrosis and onset of skin and further muscle defect. This wound has a tendency to be infected, and it frequently leads to the sepsis, not only due to insufficient care, but also due to conditions of patients (decreased immunity, nutrition problems, cancer patients etc.).

Commotio cordis

This term characterizes strong change of heart rate – **bradycardia** or total stop of heart beat – **asystole,** caused by huge **mechanical force applied to the sternal region** – typically strong stroke to the chest e.g. in car crash by the steering wheel, if the airbag is not present. Strong enough mechanical force may not only cause asystole (complete stop of electrical and mechanical activity of the heart) but also chaotic activity of ventricles - **fibrillation**. Both of them lead to the stop of circulation and, of course, negative consequences for perfusion of tissues.

Decompression sickness

It is a disease caused by sudden changes of atmospheric pressure. This commonly refers to problems arising from underwater diving decompression (e.g. during ascent), but may be experienced in other depressurisation events such as working in a caisson or flying in unpressurized aircrafts. The principle of this sickness can be easily demonstrated after the opening of a bottle with carbon dioxide dissolved in the liquid under pressure higher than atmospheric. After the pressure is released, the gas bubbles are released from the liquid. Divers or workers in caisson are exposed to the pressure higher than atmospheric as well, and the proportion of the gas physically dissolved in their blood increases. Since the air we breathe has highest percentage of nitrogen (if the divers are not inhaling special mixture of gases) **this is the reason why mainly nitrogen bubbles are released from the physically dissolved form during the inappropriate speed of ascent or exit out of the caisson**. With the **decrease of the pressure (decompression) nitrogen bubbles are released in the cells, tissues and blood**. These bubbles damage cells, they also cause partial or total occlusion of small diameter arteries and capillaries what leads to reduction of oxygen and nutrients supply to the tissue - **ischemia occurs**. Occlusion of circulation manifests by generalized symptoms such as fatigue, weakness, sweating, anorexia and by local manifestation in a form of pain of joints, tendons and muscles. Based on the clinical presentation, we recognize **two main forms of decompression sickness**. **Type 1** is characterized by generalized weakness and pain, abdominal pain with vomiting, whereas **type 2** is characterized by systemic dysfunctions of **cardiovascular system** (tachycardia, hypotension) and **nervous system** (with paraplegia and urinary bladder dysfunction). However, manifestation of decompression sickness may be very heterogeneous; here are examples of some symptoms and signs:

- Psychological – confusion, changed behaviour
- Ophthalmologic – double vision, eyelids paralysis, scotoma, blurred and tunnel vision
- Auditory – tinnitus, partial or total deafness, vertigo, nausea, pain in the ear, loss of orientation
- Skin – itching, marble skin
- Respiratory – dyspnoea, cough, haemoptysis
- Cardiologic – substernal sharp pain during inspiration
- GIT – cramps, incontinence, nausea, vomiting
- Urologic – incontinence or retention of urine

- Neurologic – paraesthesia located around joints, paresis, paralysis, headache, vertigo, ataxia

Effects of electrical current

Severe tissue damage is usually caused by alternating current or lightning. There are three mechanisms of interaction between the electrical energy and tissues:

- **Thermal injury** – Points of contact between the body and current are burned, because skin has very high resistance
- **Depolarisation of cell membranes** – this effect is typical for tissues with excitable membranes e.g. mainly in the heart, brain and muscles. Electrical current may cause ventricular fibrillation, coma and spasms of striated muscles
- **Mechanical injury** - current may cause rupture of the skin at the points of entry of the current to the human body

The most dangerous effects are **ventricular fibrillation** which causes stop of blood circulation and **depolarization of brain cells**, because it will lead to paralysis of important brain centres with subsequent apnoea, vasodilation and total disintegration of brain functions. Both of these pathological processes can cause death directly.

Effects of chemicals

The effect of any given chemical on the human cells, tissues, organs and systems depends on several factors:

a) Dose or concentration of the chemical
b) Duration of exposure to the chemical
c) Site of entry
d) Ability of organism to detox given chemical
e) Character and properties of the chemical compound itself

Consequences of chemical exposure at the cellular level

1) Inactivation of proteins in the cell

2) Chemical bond to active molecules in the cells – production of inactive complexes – e.g. cyanide + Fe = inactive complex which blocks oxidation processes in the cell (decreased production of ATP)

3) Induction of toxicity of primarily non-toxic chemical compound by its transformation to toxic molecule – e.g. methanol when metabolised, gives formaldehyde which is further metabolised to the **formic acid,** which is very toxic and causes irreversible damage of proteins mainly in the tissues with high activity of alcohol dehydrogenase (liver, retina and ophthalmic nerves)

4) Chemical bond to complex important molecules – e.g. CO binds to haemoglobin and turns haemoglobin molecule normally responsible for oxygen transport, into an ineffective oxygen carrier; therefore, oxygen cannot even bind to it, what leads to the hypoxemia and subsequently to hypoxia (anoxia) of tissues. Chemical bond of phenacetine, nitrite or aniline to Fe in haemoglobin leads to the production of methaemoglobin, which is also ineffective in oxygen delivery for tissues.

The consequences of the exposure to chemicals can be characterized by severity of cellular damage. The effects for the cells are described as:

a) Cytopathic effect – specific functions of cells are reduced, but its basal function remains intact
b) Cytostatic effect – the cells remain alive, functioning, but its division is stopped
c) Cytotoxic effect – all important functions of cells are compromised and it leads to the cell death

Endogenous chemical compounds

These substances are produced normally in metabolism; however, pathological circumstances lead to exaggerated production of these molecules, insufficient elimination or both. These molecules have negative effects on cells and tissues. Examples of such substances are **ketone bodies in diabetes or starvation, ammonium or false neurotransmitters in liver failure, potassium and hydrogen ions in tissue ischemia, bilirubin in jaundice** and many more.

Biological factors and their effects on human body

Biological factors such as viruses, prions, bacteria, fungi or parasites and their effects on human body are the subjects of microbiology and immunology; however, it is important to mention some effects of biological toxins – toxic compounds produced by insects, frogs or spiders (venoms). They can be classified based on their effects as:

- Vasoactive - causing vasodilatation

- Haemorrhagic – causing bleeding due to the damage of the vessel wall
- Haemolytic – causing haemolysis and haemolytic syndrome
- Thrombotic – promoting blood clotting
- Anticoagulant – inhibiting blood clotting
- Neurotoxic – causing block of neuromuscular connection or paralysis of important autonomic functions e.g. breathing
- Enzymes supporting penetration of toxins to the deeper structures (hyaluronidase) or causing proteolysis and local necrosis

Disturbance of autoregulation mechanisms and their role in pathogenesis

Homeostasis is an inevitable condition for optimal function of cells, organs and body systems. Homeostasis is precisely controlled and regulated by a**utoregulation mechanisms.** They are responsible for minimizing the differences between actual values of certain parameter (e.g. body temperature or blood glucose level) and desirable (optimal or physiological) values of this parameter. These mechanisms exist at all levels of organisation hierarchy of living organisms – sub-cellular, cellular, tissue, organs, and systems.

At the cellular level, autoregulation is performed by control of intensity of metabolic processes, activity of different enzymes, regulation and control of cellular cycle, regulation of production of certain molecules and by regulation of cell volume.

At the levels of tissues autoregulation controls count of cells, and structure, quality and function of interstitial matrix.

Organ and systemic autoregulation mechanisms participates in integration of function of all tissues in the organ and system and different parts of the same organ and system, e.g. function of the right and left ventricle, lung and cardiac functions, metabolic speed and renal functions – to maintain all biological parameters in precise dynamic balance – homeostasis. Dynamic balance means that all parameters are regulated with attempt to adapt our body to changing living (external and internal) environment.

Examples of autoregulation mechanisms:

- **Endogenous amplifying system of the cell,**
- **Antagonistic regulation of structure and function,**
- **Feedback loops (positive and negative),**
- **Regulation of acid-base balance,**

- **Regulation of body fluids, etc.**

Endogenous amplifying system of the cell and its disturbances

Endogenous amplifying system (EAS) is a system which multiplies the strength (intensity) of a signalling to particular cell. For example – insulin as a signal after its interaction with insulin receptor of effector cell initiates strong metabolic effect inside of this cell. Other example is catecholamine effect in tissues: after its interaction with adrenergic receptor, it initiates strong adrenergic effect in sensitive tissues (with high density of adrenergic receptors). This system is effective as long as the cells remain healthy and its function matches to the cell or tissue requirements. In case of cellular damage, the system will show some type of disturbances which may have **either exaggerated or attenuated function**. It means that the signal is either inappropriately strong or weak. Both these extremes can be pathogenic mechanisms leading to pathological processes.

Reduced activity of this system can be a consequence of low activity of different parts of signalling pathways, e.g. enzymes at post-receptor level – e.g. post-receptor enzyme defect in cells of diabetic subjects leads to the reduction and qualitative change of glucose utilisation. Example of **increased activity** of this endogenous amplifying multiplying system can be SIRS (systemic inflammation response syndrome), which is characterized by uncontrolled exaggerated production of pro-inflammatory cytokines caused by disinhibition of NFkB (nuclear transcription factor kappa B), which further promotes production of pro-inflammatory signals.

Antagonistic regulations and their disturbances

The main principle of antagonistic regulation of body structures/functions is that every single process in the human body has its opposite structure/function. Just to set an example for antagonistic functions/processes:

example of antagonistic functions/processes	Examples of antagonistic structures
activation – suppression	sympathetic system – parasympathetic system
depolarisation – repolarization	α-adrenergic receptors – β-adrenergic receptors
nociception – anti-nociception	flexors – extensors
stress – anti-stress	nociceptive system – anti-nociceptive system
sleep – vigilance	insulin – glucagon
muscle contraction – muscle relaxation	pro-inflammatory system – anti-inflammatory system
SIRS – CARS	stress system – anti-stress system

Antagonistic regulation

This type of regulation of certain function/structure works on the principle that both involved systems with antagonistic effects are activated by the same stimulus, e.g. stressor activates simultaneously the stress response and also initiates processes responsible for activation of anti-stress system. A manifestation of such responses can be vasoconstriction in the skin and vasodilation in the muscles during the stress response. Another example – flexors and extensors belong to the locomotion apparatus; however, they have opposite functions. Disturbance of the balance between the system and anti-system may lead to the dysfunction of the locomotor apparatus – manifesting e.g. by disturbances of movement and posture.

Anti-systems participate in the prevention of onset or progression of pathological process (bounding and reducing of its intensity). They play important role as a factor of resistance of the organism against noxae; therefore, they have significant role in the **prevention of the onset of diseases and in sanogenesis**. This is one of the reasons why some of the therapeutic methods are based on activation of "anti-system" (contra-regulatory systems).

The onset of the disease and its unfavourable course can be a consequence not only of the cause itself, but also **insufficiency of contra-regulatory systems** may contribute to it as well. E.g. mechanisms participating in the increased effects of IgE (which lead to the one type of immune hypersensitivity reactions) are **either increased production of IgE or decreased activity of suppressor cells which reduce production of IgE**, or combination of both causes. Prevention of the onset of diseases does not only relate to the elimination of the etiologic factor (etiologic prophylaxis), but also in the boosting of the function of contra-

regulatory systems (pathogenic prophylaxis – the base of the strategy "aetiology of the health").

Dysregulation diseases

These are diseases which are caused by **primary disturbance of regulatory systems of the body.** They can be classified into:

1) Diseases caused by change/disturbance of regulatory systems

2) Diseases caused by the failure (loss) of regulatory systems

The first group comprises syndromes and diseases such as Pickwickian syndrome, disturbances in regulation of cardiovascular system – e.g. essential hypertension or oncogenesis. Examples of processes which belong to the second group are characterized by the failure/Loss of regulatory mechanisms, e.g. metabolic or endocrine disorders due to deficiency of some enzymes, central type of apnoea and many others.

Regulation and dysregulation of the cell volume – importance in the pathogenesis of disease

Cellular homeostasis is the ultimate condition for proper function of the cells. Regulation of the optimal ("normal") volume of the cell is also a part of homeostasis. Under the physiological and also pathological conditions, the cell is exposed to the changes of surrounding cell environment, e.g. changes in osmotic pressure of the interstitial fluid, which may change cellular volume; therefore, this may lead to the change of the function of these cells. To fulfil all functions, cell has to maintain optimal volume and this is happening via **sophisticated system of sensors and effector mechanisms,** participating in the regulation of cell volume. This system is based on the existence of **specific intracellular metabolic or membrane transport mechanisms**. These mechanisms are able to change their activity – both increase and decrease, with changes of concentration osmotically active substances (molecules) inside or outside of cells. Mentioned volume regulatory mechanisms are able to sense **the osmotic gradient across the cell membrane**. All membranes are permeable for water, therefore, in case of any osmotic gradient develops across the membrane, the water flows to diminish it. Water flows always from the hypo-osmotic to hyper-osmotic space (to dilute the hyperosmotic one). A part of the osmotically active molecules are **inorganic osmolytes** (potassium, chloride ions), which are **available immediately, and they are quickly transported across the membranes**. Other osmolytes (**organic osmolytes** -

sorbitol, myoinositol, amino acids, methylamines) must be synthetized first and then utilized in the cell volume balancing; therefore, they are not available immediately and their synthesis leads to the delay in the cell volume homeostasis. In case of sudden shrinkage of the cell due to extracellular hyperosmolarity, the cell will react immediately by increased transport of KCl and NaCl to the cell to prevent the leak of water to the extracellular space; otherwise the cell volume would be too small. This process is called regulatory volume increase. In the opposite situation, in case of sudden swelling of the cell, the cell activates mechanism which transport potassium and chlorine outside of the cell, and the water follows this direction (regulatory volume decrease) (Fig. 1, 2, 3). In case of impairment of these mechanisms or their failure due to the lack of energy (transport mechanisms depend on ATP availability), the cell is not able to regulate its volume adequately and it leads to the considerable shrinkage or swelling of the cell.

In case of chronic, slowly developing, but progressing and permanent changes of the osmolarity of body fluids (e.g. decompensated diabetes mellitus) increasing blood glucose concentration in the extracellular compartment disturbs the volume homeostasis of cells - their shrinkage. To prevent the progressive shrinkage of cells, the cell will activate synthesis of organic osmolytes, which are not toxic for the cell and by this way keep the osmotic balance between the cell and its environment. The problem appears as soon as the extracellular hyperosmolarity is treated aggressively (quickly). Sudden decrease of osmolarity of extracellular fluid by insulin-mediated glucose utilisation or by inadequate substitution of i.v. fluids, the cell cannot eliminate the organic osmolytes quickly (these molecules cannot leave the cell across the membrane fast enough) and intracellular space now becomes hyperosmotic in comparison to the extracellular space. The flow of the water reverses and the water will now flow into the cells, leading to the dramatic cellular swelling. The main problem lies within the neurons, which are located in the skull with inability of tissue expansion in case of swelling. Oedema of brain cells leads to the intracranial hypertension with the possibility of herniation, occipital conus development and eventually death.

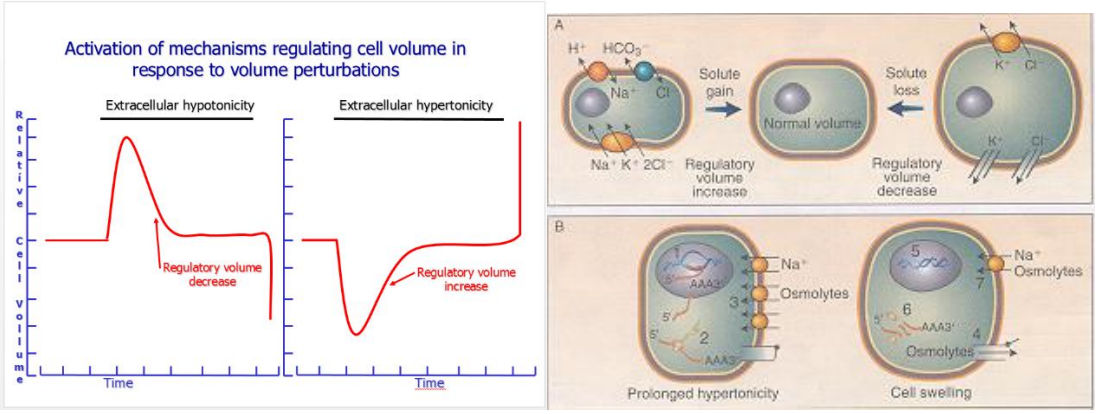


Figure 6.1, 6.2: Mechanisms of cell volume regulation

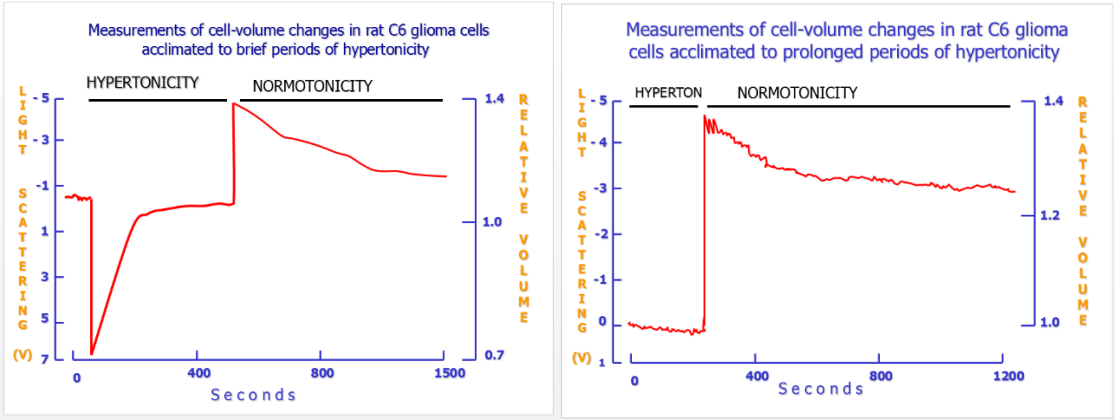


Figure 6.3, 6.4

CASE REPORTS

Case report 1

23-years-old man was admitted to emergency unit after he was found in his flat unresponsive. His mother could not reach him via phone, so she came to his flat; there was no information about him in past 24 hours. After he was found, he was lethargic and confused. GCS (Glasgow coma scale) was 7/15. He was found lying on his left side, with left leg twisted underneath his body in a very weird position, but he does not remember anything from past 24 hours; now he complains about severe pain in his left leg. Vital functions: temperature 37.2^0 C, HR 150 bpm, BP 150/70 mmHg, RR 16 bpm, SatHb with O_2 min 99% on room air.

Physical examination also showed bruises around left eye, multiple skin injuries on the left side of his chest and abdomen. Left leg is pulseless, cold and extremely sensitive to

palpation, skin facing the floor is macerated with blisters similar to burns with zero capillary refill.

Laboratory findings: WBC 26.000×10^9; Hb 19.4g/dL; Htk 59.3%; PLT $183.000/mm^3$, Na 132 mmol/L; K 5.4 mmol/L; Cl^- 105 mmol/L; bicarbonate 14 mmol/L; urea 22mmol/L; creatinine 1.4 μmol/L; glucose 12.8 mmol/L; lactate 2.8 mmol/L; CK: 41.669 IU/L. Toxicology tests: negative, CT scan of head and neck: negative.

Management: i.v. fluids 2 L of saline (0.9%), surgeon recommends fasciotomy of left lower extremity. After the surgery, arterial pulsation at extremity has been restored, and patient was transferred to ICU. Aggressive rehydration has continued – patient was given 200-500 ml of saline per hour to maintain diuresis at 200 ml/hour. This led to decrease of creatinine concentration to 0.64μmol/L; however, intensive rehydration was stopped due to breathlessness (lung oedema) and the i.v. fluids were maintained at 100 ml of saline per hour. Patient was also on vasopressors to maintain mean arterial pressure at values higher than 65 mmHg.

Laboratory tests next day: CK 50.867IU/L, myoglobin in urine 32.9μg/mL (reference value < 0.025μg/mL). Lung oedema was treated completely in three days by mannitol and diuretics medication. Instead of improved perfusion of the left leg, ischemia of the soft tissues was so severe, that the surgeon recommended amputation at the level of knee to save a life of our patient.

Questions & Tasks

1) Identify all symptoms and signs presented in this case report.
2) Explain mechanisms participating on onset and progression of symptoms and signs.
3) Try to identify possible causes leading to the condition described in the case report.
4) Try to establish a diagnosis.

Case report 2

20-years-old man was admitted to the neurology ICU with an episode of cramps and unconsciousness. He has never had this before. He came to the town from a village couple of days ago, relatives are not aware of any drugs or pills that would eventually cause his problems. Patient was restless, exhausted after an episode of cramps and sensory dysfunctions he has experienced.

Vital signs: HR 62 bpm, BP 120/80 mmHg, RR 14 bpm, body temperature was normal, with profound secretion from oral cavity (salivation?)

Neurological examination: GCS 6/15 with reduced motoric functions of all extremities, extreme narrow pupils, plantar (Babinski) reflex positive, deep muscle reflexes are delayed.

Other examinations and findings: bilateral crepitation over the lungs, renal and liver functions are normal, Na, K, Ca, Mg normal concentrations, slightly elevated WBC, chest X-ray points to respiratory distress, ultrasound revealed a collection of fluid (pus) in the arm with subsequent drainage and evacuation of fluid (250 mL of pus).

Differential diagnosis of patient's condition pointed towards metabolic encephalopathy, toxic encephalopathy caused by sepsis, brainstem lesions, organophosphate intoxication or some pills intoxication.

CT and MRI were negative, analysis of CSF was negative, ECG, myocardial markers and heart ultrasound were negative, blood, urine and pus cultures were sterile, main toxicology screening was negative. Concentration of cholinesterase in blood was 1234 IU (reference values 5000 - 9000 IU).

Second day after admission, the respiratory distress became worse (ARDS) with $PaCO_2$ 54 mmHg, and patient required external ventilator support. At that moment, possible metabolic causes were excluded, so was the structural brain lesion.

The last candidate for a cause was organophosphate intoxication: breathing problems and a lot of secretions of the mouth and airways. After treatment with atropine and pralidoxime (decreases intensity of organophosphate intoxication) and antibiotics the patient has improved slowly in 5 days. Patient was treated also by phenytoin sodium (antiepileptic drug) to stop his cramps. Even though the chest X-ray and saturation have improved a bit in 3-4 days, there were still present disturbances of sensory functions and restlessness which was treated by diazepam. Patient still required ventilation support due to persistent paralysis and weak respiratory drive. Doctors repeatedly contacted the family with attempt to discuss the organophosphate intoxication possibility; however, the result was negative. There was no intoxication with organophosphates. Plasmatic level of cholinesterase decreased to 934 IU. Restlessness and anxiety have improved, so did the paralysis. Problem was solved at the day 6 after patient's written confession of a suicidal attempt by methyl parathion on his train journey to the city. He had recovered fully after 12 days on ventilator.

Questions & Tasks

1) Identify all symptoms and signs presented in this case report

2) Explain mechanisms participating on onset and progression of symptoms and signs

3) Try to identify which symptoms are highly indicative for organophosphate intoxication

Case report 3

40-years-old man working in a construction company as a diver for many years. His job was to dive to the depth approx. 20-30 meters under the sea level to control quality of pillars holding the bridges. He is heavy smoker and he does not have any serious disease.

Patient's condition started at work, as he was controlling some pillars but his ascend was unusually fast – it took only couple of seconds. During the ascend he started to feel severe pain in his back, neck and lower extremities and in muscles all over the body. After ascend he was immediately transported to the hospital, where he was given NSAID and saline. Pain in the back, neck and extremities have continued and he started to have problems with his hearing, and also communication with the patient became worse. Later he got dizzy and nauseated with abdominal pain.

Patient was transported to the specialized clinic approx. after 10-12 hours after the onset of the symptoms. On admission, he complained about severe pain in the back, neck and lower extremities, he had urine retention. BP 80/60 mmHg, heart rate 140 bpm, respiratory rate 30 bpm, and patient was confused. There were no pathological sounds during lung auscultation, heart sounds were normal as well. There was identified low strength of reflexes at lower extremities with localized areas of lost sensitivity up to the umbilical level and mentioned urine retention. Cranial nerves were normal, cognitive functions were normal.

Laboratory findings: Hgb 14.2 g/dL; Le 14.900/mm^3; PLT 92,000/mm^3; glucose 126 mg/L, serum urea 42mg/dL, serum creatinine 0.89 mg/dL, serum electrolytes normal, serum creatine phosphokinase 1.192U/L (high), ASTRUP normal, ECG and chest X-ray normal, audiometry proved bilateral sensory – neural deafness. Electromyography showed radiculo-neuropathy, mainly axon type of neuropathy. Even after the treatment the patient outcomes were not complete recovery, but he remained deaf and paraplegic.

Questions & Tasks:

1) Identify all symptoms and signs presented in this case report.

2) Explain mechanisms participating on onset and progression of symptoms and signs.

3) Which of these symptoms and signs are the most important for establishment of the proper diagnosis?

Note: *Decreased value of platelets is a marker of severity of decompression syndrome. Platelets bind to the nitrogen bubbles in the blood what leads to thrombocytopenia. Increased concentration of creatine phosphokinase is attributed to the rhabdomyolysis. Spine damage is a consequence of damage of the white matter and/or by ischemia caused by platelets micro-thrombi in the spinal circulation.*

Chapter 7

DISTURBANCES OF FLUIDS AND ELECTROLYTES

Disturbances of the volume and composition of body fluids

Human body is exposed to constant changes of the external environment; however, homeostatic regulatory mechanisms keep and regulate the internal parameters within very precise ranges, which are necessary for optimal function of body systems and organs.

Internal environment is a liquid medium surrounding every single cell of the human body. The base is the **water with ions**, but the fluid contains also other components, which are necessary for the cell existence (oxygen, energy resources) and molecules characterized as the metabolic end-products. Homeostasis is regulated mainly by blood and cardiovascular system, lungs, kidneys and metabolism. Disturbances of homeostasis are not separate diseases, but they are rather complex pathophysiological processes and they involve disturbances of ion concentration, disturbances of hydration and disturbances of the acid – base balance.

Compartments of body fluids

Water is the main medium of the internal environment. Total body fluid (TBF) represents approximately 60% of the body weight in otherwise healthy adults. The amount of water depends on age of an individual (new-born has 75-80%, toddler has 70% etc.). Ageing reduces proportion of muscles and increases proportion of adipose tissue and TBF decreases below 60%. Proportion of TBF also depends on **gender** – (women have about 50% higher proportion of the body fat because of the oestrogen levels) and **BMI** – obese individuals have less % of the TBF than subjects with normal BMI (thus normal proportion of adipose tissue).

Major compartments of TBF

Intracellular fluid (ICF) – water and soluble particles inside the cells form 40% or two thirds of total body weight (ions – particles with electric charge, solutes – neutral molecules with no charge).

Extracellular fluid (ECF) forms approximately 20% of total body weight, and it could be further classified as:

- Intravascular fluid (IVF), which is plasma – it is approx. 4-5% of body weight
- Interstitial fluid (ISF) (fluid in the tissues), which is approx. 15% of body weight

- Transcellular fluid (TCF), this fluid is present in the serous cavities (pleural, peritoneal etc.) and in physiological conditions it does not exceed the 1% of body weight

Extracellular fluid

Main compartments of the extracellular fluid – **interstitial fluid** and **plasma** are separated by highly permeable capillary membrane and this is the reason why composition of the plasma and interstitial fluid is nearly the same – with exception of protein composition. Under the physiological conditions, capillary membrane is not permeable for plasmatic proteins. The main cation of this compartment is sodium [Na^+] and the main anions are chloride [Cl^-] and bicarbonate [HCO_3^-]. Proteins – macromolecules have negative charge, and this causes small elevation of the cations in the plasma in comparison to the interstitial fluid (about 2% - protein anions pull the sodium and the other cations as well). The opposite situation is in the interstitial fluid – there is a bit higher concentration of anions – because the proteins repel chloride and other anions.

Intracellular fluid

ICF and ECF are separated by selectively permeable membrane. Its selective permeability, together with active transport mechanisms, are responsible for considerable difference in composition of ICF and ECF. Main cations of intracellular fluid are potassium [K^+] and magnesium [Mg^{2+}], while main anions are sulphate [SO_4^{2-}], phosphate [HPO_4^{2-}] and organic anions. Cell membrane is permeable for water and relatively impermeable for ions, but the permeability is different for different ions. For example – permeability for K^+ is 50-100 times higher than for sodium and in case of excitable membranes (myocardium, nerves, muscles) permeability depends on the type of stimulation and it changes over time. Cell membrane is not permeable for organic phosphates and proteins.

Balance of the body fluids and ions

Stability of body fluids is achieved by the ability of human body to regulate intake and elimination of the fluids and ions precisely.

Water intake

1) **Water in the drinks and food** ingested via gastrointestinal system 2.0 – 2.5 L/day
2) **Metabolic water** as an end-product of chemical reactions, mainly oxidation of substrates leads to production of water and carbon dioxide – approx. 0.3 L/day

Water excretion

1) **Urine -** the most important way of excretion of fluids in resting condition - 1.5 - 2.0 L/day
2) **Stool** eliminates usually a negligible amount of fluids - 0.1 L/day
3) **Respiratory system** of an adult eliminates daily 0.3 - 0.4 L of fluids via ventilation
4) **Evaporation** eliminates 0.3 – 0.4 L of fluids daily through the skin (extraglandular elimination of water – *perspiratio insensibilis*)
5) **Sweating –** *perspiratio sensibilis* **-** elimination of the water by the activation of the sweat glands in the room temperature represents 0.1-0.2 L/day.

Intake and excretion of the salts

Salt balance (intake) depends only on the amount of the salt in food and drinks. Human cells do not produce salts in metabolism. Salts are excreted by urine, stool and sweat. Daily intake of 0.5 g of salts is usually enough for stability of the body fluids; however, the salt intake of the average population is roughly 10-15 g, which exceeds the needs, potentially leading to complications (e.g. hypertension).

Excretion of water and ions in kidneys

Kidneys represent the main way of excretion of water and ions form the body, and they are the main regulatory organ of the homeostasis of the body fluids as well.

Glomeruli: Water, ions and small neutral molecules cross freely glomerular membrane by diffusion process based on the filtration pressure. Normal glomerular filtration is **2 mL/s**, what represents 170-180 L of filtrate per day.

Tubular system: 99% of the water from the primary filtrate is reabsorbed in the tubular system. Otherwise healthy kidneys can produce less than 0.5 L highly concentrated final urine, based on the body needs, or they can excrete 18 L of hypotonic urine/24 hours if needed. Osmolarity of the urine is highly variable, ranging from 50 to 1200 mOsmol/L. Membrane of proximal tubule is well permeable for water and ions. Resorption of water is passive process governed by transtubular osmotic gradient, which is produced by the active resorption of sodium and other ions and solutes. Increased hydrostatic pressure in peritubular space induces the change in Starling capillary forces and the fluid moves to the peritubular capillaries. Resorption of water and ions is proportional (isosmotic) and nearly 70% of the primary glomerular filtrate is resorbed in the proximal tubule.

Loop of Henle: Descending part of the loop of Henle is permeable for water (resorption of 15% of GF), but it is not permeable for ions. This process is passive and is governed by hyperosmolarity of the renal medulla, which is caused by the counter-current multiplication mechanism. Ascending part of the loop of Henle is not permeable for water, but this is the site of the active resorption of sodium and chloride (Na-K-Cl-cotransport). Fluid at the top of the loop of Henle has osmolarity 1200 mOsmol/L. Resorption of ions in the ascending part of the loop represents 20% of ions present in the glomerular filtrate. Fluid at the end of the loop of Henle is hypoosmotic.

Distal tubule: First part of the distal tubule is not permeable for water, ions are actively resorbed by Na-Cl-cotransport. Straight part of the tubule (end of the tubule) is the site of facultative resorption of water and ions, depending on the hormonal signalling. Usual resorption is approximately 5%. The fluid leaving the distal tubule is hypoosmotic.

Colleting duct: This part of the nephron is responsible for the final adjustment of the urine according to the body needs. Resorption of water is controlled by ADH, which opens the aquaporins – channels for water resorption. Based on the osmotic gradient between the interstitium in the renal medulla and osmolarity of the fluids in the collecting duct water flows to the interstitium. Mainly the cortical part of the duct is under the control of aldosterone, and it stimulates resorption of sodium and excretion of potassium to the tubular lumen. Net resorption of sodium represents ~ 4% and net resorption of water in this part of the nephron represents ~ 9%.

Final composition of the urine depends on the action of end parts of the nephron. Resorption/excretion of water and resorption/excretion of ions are under separate control mechanisms. Ultimate condition for the proper function of the renal system is optimal blood flow – nearly 20-25% of the cardiac output. Kidneys, however, considerably regulate their own perfusion by autoregulation. The best perfusion is in the renal cortex which takes 90% of all renal blood flow.

Osmotic forces, total and effective osmolarity

Water is an electroneutral molecule and it moves freely across the biological membranes. The driving force for the motion of water between ECF and ICF compartments is osmotic gradient. The background for the osmotic forces is a difference of concentration of osmotically active particles in the given compartment in comparison to the neighbouring compartments. The consequence is the osmotic pressure that drags the water to the

compartment with higher osmotic concentration, e.g. if concentration of osmotically active particles in ECF increases, water will be dragged out of the cells, and this will lead to the reduction of their volume – cell shrinkage.

Osmotic forces depend only on the concentration of the particles in the given compartment**,** they are not influenced by their other characteristics e.g. charge or size. Osmolarity of 1 L of solution 1 M glucose is 1 Osmol/L, osmolarity of the 1 L of 1M NaCl is 2 Osmol/L. From this example, we can conclude that main osmotically active substances are sodium and chloride ions. Plasmatic proteins, which have incomparably higher molecular weight (in comparison to ions), represent only osmolarity 1 mOsmol/L.

Total osmolarity is determined by the sum of concentrations of all diluted solutes in the body fluid; however, effective osmolarity is only that one that causes motion of the water between compartments. It is determined by ions or solutes which cannot move easily across the biological membranes. The best example of the effective solute is sodium. It is dominant in the ECF and only minimally moves to the ICF. In case of hypernatremia, water moves from the cells to the ECF and vice versa. Ineffective solutes are those, which can increase total osmolarity, but because they move quite easily between compartments (ECF vs ICF) their concentration in the compartments is nearly equal – typically urea. Glucose has a specific position. Under the normal conditions, postprandial hyperglycaemia which is controlled by insulin does not influence the osmolarity, as glucose moves quickly to cells under the action of insulin. Different situation characterizes the DM – glucose does not enter the cells easily and remains in the ECF, thus contributing to the hyperosmolarity of the ECF – it becomes an effective solute.

Total osmolarity of plasma is normally 290 ± 10 mOsmol/L. Percental proportion of individual active particles is: ions 96%, glucose and urea 3%, amino acids and proteins 1%.
The most important solutes determining the osmolarity are ions – mainly sodium and chloride, and they are responsible for ¾ of the total osmolarity.

Common equations for osmolarity calculation in mOsmol/L:

2 × Na + glucose + urea (in mmol/L)

2 × (Na + K) + 5 (in mmol/L)

Osmolarity below 280 mOsmol/L represents **hypoosmolar state** and water moves to the cells – the volume of ICF increases. The increase of osmolarity above 300 mOsmol/L leads to **hyperosmolar state,** water moves to the ECF and volume of the ICF decreases. If

the volume of the body fluids changes, but without change of the osmolarity, it is isoosmolar disturbance, and volume of ICF does not change.

Control of body fluids volume and osmolarity

Effective osmolarity is controlled by **osmoreceptors**. Changes of the osmolarity are detected based on the change of volume of osmoreceptor cell. Central osmoreceptors are located in hypothalamus, peripheral osmoreceptors are located in the liver and they mainly monitor osmolarity of the portal blood to prevent dramatic changes of the ECF osmolarity after intake of fluids or food, because stimulation of the central osmoreceptors in hypothalamus after the ingestion, digestion and resorption of "solutes" cannot occur yet.

Effective circulating volume (effective arterial volume) – it is a part of ECF which maintains optimal perfusion of tissues and meets their metabolic demands. In physiological conditions, it is determined by the volume of the circulating blood and arterial pressure. There are no "volume receptors" that would measure directly the volume of the fluids or absolute filling of the circulatory system, there are only baroreceptors, which monitor relative filling of the circulatory system – and this is determined by the ratio between volume of the circulatory network and capacity of the network. They monitor the blood pressure. They react to the change of the tension in the arterial wall. High pressure baroreceptors change the activity of the sympathetic nervous system, low pressure baroreceptors monitor central venous pressure. Other baroreceptors are located in the organ that regulates the volume balance – kidneys. These baroreceptors are **juxtaglomerular cells in the vas afferens.** They respond to the changes of renal perfusion pressure by changes in the production of renin and by myogenic reflex that changes the tone of the vas afferens; therefore, it changes the glomerular filtration. Another possibility to monitor the circulating volume is the action of **chemosensors in macula densa**. They are sensitive to the concentration of sodium and chloride in the tubular fluid at the beginning of the distal tubule. The response to this stimulation is again the change of the secretion of renin and change of the tone in the vas afferens via tubuloglomerular feedback and this process prevents possible oscillation of the glomerular filtration.

Regulation of effective osmolarity

Antidiuretic hormone (ADH)

ADH or **vasopressin** is synthetized in hypothalamus and stored in posterior pituitary gland. Its action on V1 receptors in the resistance vessels increases intracellular concentration

of calcium and causes **vasoconstriction**. In the cells of distal tubule and in collecting ducts, ADH activates V2 receptors, and this process leads to the internalisation of aquaporins. It increases permeability of the tubular epithelium for water. Water dragged by the osmotic forces moves to the hyperosmotic interstitium in renal medulla. The result of its action is small volume of excreted urine (less than 0.5 L/day), urine is hyperosmolar (1200-1400 mOsmol/L), and this process is called **antidiuresis.**

The main stimulus for secretion of ADH is increase of effective osmolarity. Osmotic threshold for ADH release in the otherwise healthy subject is 280 mOsmol/L. The second physiological stimulus that leads to ADH release is reduction of effective arterial volume by about 5-10%. Factors as pain, stress, hypoxia and hypoglycaemia boost the secretion of ADH. ADH secretion is reduced by ethanol, cortisol and decrease of the body temperature. If the ADH is not present, renal ducts are not permeable for water and patient excretes high volume (20 L/day) of hypoosmotic urine (50-100 mOsmol/L). This process is called **water diuresis**.

Secretion and effect of ADH is the necessary condition for the renal concentration ability. Concentration of the urine further depends on the hypertonicity of the renal interstitium, which is determined by:

1) active resorption of sodium in the ascending part of the loop of Henle
2) counter-current disposition of the loops of Henle and vasa recta
3) small blood flow in the renal medulla (only 10% of the total renal blood flow), therefore solutes are not "washed away" from the medulla
4) recirculation of the urea between nephrons and interstitium

Urea enters the tubular fluid via glomerular filtration. Most parts of the nephron are not permeable for urea, therefore after resorption of water the concentration of urea increases. ADH increases permeability of the collecting ducts also for urea, and it moves across the tubular wall to the interstitium based on the concentration gradient. A part of it moves to the ascending part of the loop of Henle by diffusion and it brings it back to the collecting duct, and to the medulla again. The result of this process is that urea recirculates in the structures of the renal medulla, and contributes to the process of urine concentration.

Thirst

The thirst is second homeostatic mechanism as a reaction to increased effective osmolarity. The centre of thirst is located in the anterior hypothalamus, but it is separated

from the osmoreceptors. **The main stimulus for thirst sensation is increase of the effective osmolarity.** Strong thirst sensation appears when natremia increases about 2-3%. Osmotic threshold for the thirst sensation is 290-295 mOsmol/L. Similarly, as for the ADH, second stimulus for thirst is the reduction of effective arterial volume, but this decrease must me much deeper – about 15-20%. The thirst sensation is further enhanced by angiotensin II, and it is suppressed by the distension of stomach.

Regulation of effective volume

Correction of effective volume is achieved by two mechanisms:

1) **Change of vascular system capacity** via vasoconstriction or vasodilation. They are a part of "alarm" response related to the activation of baroreceptors, sympathetic system and catecholamines. Their responses are quick; however, limited in time, because they adapt to new haemodynamic situation.
2) **Change of the vascular system filling (volume)** via the transfer of the fluids between intra and extravascular compartments and by increase or decrease of diuresis. First mechanisms are related to Starling forces across the capillary wall, while the second are based on renal functions. The systems that participate on these mechanisms are RAA system, atrial natriuretic peptide, urodilatin and ADH. These mechanisms are intermediate or long-lasting processes with short delay of their activation; however, they regulate blood volume and blood pressure with high precision. P**ressure diuresis** belongs to this group of regulatory mechanisms as well.

Decrease of the effective volume

Neurohumoral systems respond to the decrease of the effective volume by either reduction of the capacity of vascular system, or by the increase of the filling of the system.

1) Sympathetic system and catecholamines maintain perfusion in the vital organs despite hypoperfusion of other organs – this is called **centralisation** of circulation. This system dominates and is more important than autoregulation of tissue perfusion based on their metabolic demands. Sympathetic system also increases **cardiac output** via positive inotropic and chronotropic effects on heart. This is possible only in situation when venous return is also increased – what is determined by the peripheral vascular effects of the sympathetic system. Renal effects of the sympathetic system support resorption of sodium in all parts of the nephron via:

a) increased secretion of renin from juxtaglomerular apparatus via β_1 receptors

b) vasoconstriction of vas afferents via α_1 receptors reduces GFR
c) direct resorption of sodium by tubular cells via α_2 receptors

2) Secretion of renin is stimulated by three main factors:
a) reduced concentration of NaCl at macula densa because of reduced GFR
b) increased activity of sympathetic system via β_1 receptors
c) decrease of the perfusion pressure in kidneys – juxtaglomerular cells are baroreceptors.

Production of angiotensin II takes place in kidneys and also at systemic level (mainly in the lungs vasculature by the ACE). Renal endothelial cells also have ability to produce angiotensin II, and its concentration in the renal vessels is 1000 times higher compared to systemic circulation. Angiotensin II has these effects:
a) General vasoconstriction of arteries and veins
b) Increases resorption of sodium in proximal tubules
c) Increases production of aldosterone, therefore resorption of Na^+ in the distal nephron
d) Increases resistance of vas efferens – stabilisation of GFR in renal hypoperfusion
e) Initiates thirst
f) Stimulates sympathetic system
g) Increases secretion of ADH

In summary – RAA activated by the decrease of effective arterial volume leads to the vasoconstriction (reduction of the vascular capacity) and resorption of Na^+ and water thereby increasing the volume of ECF. These processes lead to the normalisation of the effective arterial volume.

3) The most important stimulus for the secretion of **aldosterone is hyperkalaemia and angiotensin II.** Aldosterone increases resorption of Na^+ and excretion of K^+ in the distal tubule – it increases capacity of Na/K ATPase in the basolateral membrane and increases permeability of apical membrane for $Na^{+.}$ Increased resorption of Na^+ is the force enhancing excretion of K^+.

Increase of the effective volume

Neurohumoral systems react to the increase of effective arterial volume above the norm either by increase of the vascular capacity or by the decrease of the vascular filling.

1) Suppression of sympathetic activity is a reflex response to the activation of baroreceptors. Tone of the vascular smooth muscles is reduced and peripheral resistance decreases – this leads to the increased vascular capacity. Parasympathetic system is activated and it has negative chrono- and inotropic effects on the heart – it decreases the cardiac output.

2) Pressure diuresis – natriuresis represents the key physiological mechanism regulating effective arterial volume – and therefore the blood pressure. Kidneys regulate the blood pressure by the regulation of the volume to be optimal to actual capacity of the vascular bed. Increased natriuresis and diuresis occurs in 30-60 s even though the blood flow in glomerular system is maintained at "normal" levels via autoregulation. Exact mechanism of natriuresis is not clear; however, the main candidate which is considered to play a role is NO, which inhibits resorption of Na^+ in the tubule by paracrine mechanisms. In case of the imbalance between salt and water intake and excretion – the elevation of the blood pressure will be the tax to pay for maintenance of "normal" Na^+, because changes of the water/ions balance lead to death quickly.

3) Atrial natriuretic factor (ANF) is produced in the heart atria when their wall is distended by increased circulating volume. This process activates increased excretion of Na^+ and water via:

a) Dilatation of vas afferens and constriction of vas efferens increases GFR
b) Reduction of Na^+ resorption in the distal tubule and cortical part of the collecting duct
c) Reduction of renin and aldosterone secretion
d) Increased perfusion through the vasa recta decreases tubular resorption of fluids

4) Diuretic effect is caused also by dopamine and urodilatin

Summary

1. The main ion of ECF is sodium. It determines the volume of ECF, because water always follows salt. Ratio between ions (sodium) and solutes versus water determines total osmolarity of ECF.
2. Main ion of ICF is potassium.
3. Changes of the ICF are always secondary consequences to the changes of the ECF osmolarity – plasmatic concentration of sodium determines also the volume of the cells,

because sodium is osmotically active with minimal ability to move across the cell membranes.

4. Homeostasis of body fluids is regulated by many regulatory circuits. **Effective osmolarity and effective volume** are the main regulated parameters.
5. **Regulation of effective osmolarity** is achieved by the changes of the water intake and change of the secretion of water in the kidneys. Main mechanisms are ADH and thirst.
6. **Regulation of effective volume** is mediated via changes of the capacity of the vessels, and by adjustment of the volume to fit to the vascular capacity. Main mechanisms are pressure diuresis, catecholamine, sympathetic system, RAA, aldosterone, ANF.
7. **The key organ** able to provide long-lasting and effective balance in the body fluids are kidneys.

Disturbances of body fluids

Classification of these disturbances is influenced by several factors:

a) When the loss or gain of fluid and electrolytes are proportional. These are **disturbances of volume**. There is no difference in the osmotic force because water and ions are equally affected. Lack of isotonic fluid – proportional loss of water and ions affects mainly ECF, with the quick manifestation of loss of intravascular volume – **hypovolemia**. Proportional gain of water and electrolytes also does not change the osmotic forces and lead only to the expansion of ECF (**systemic generalized oedemas**).

b) If loss or gain of water is not proportional to the loss or gain of the electrolytes, it usually leads to the disturbances of **osmolarity of body fluids**. Loss of water that exceeds the loss of electrolytes leads to increase of concentration of Na^+ in ECF – hyperosmolarity of ECF drags water from the cells. This process leads to the loss of fluids from all compartments (**dehydration**). In case that loss of electrolytes exceeds the loss of water, ECF becomes hypoosmolar. Concentration of Na^+ in plasma decreases. Hypoosmolarity of ECF leads to the movement of water to the cells resulting to the **intracellular oedema.**

c) Volume and osmolarity of body fluids are not changed, but the concentration of ions – that do not contribute much to the total osmolarity changes considerably. These are **disturbances of composition of body fluids**. They are related to the loss or gain of potassium, calcium, magnesium or phosphates in ECF. This classification is useful for learning purposes, but they are frequently mixed in clinical conditions.

DEHYDRATION and HYPOVOLEMIA

Dehydration

Dehydration is defined as reduced volume of TBF. Primary change is the loss of ECF while the volume of ICF remains unchanged or it can be increased or decreased. Changes of the ICF are secondary and they happen only in case that osmotic gradient between the cells and ECF does exist and it drags the water to the cells or outside of them. Different books use different approach to the classification of these disturbances, we will use the term dehydration for hyperosmotic hypohydration – situation where loss of water exceeds the loss of electrolytes.

Dehydration is a consequence of negative water balance – loss of water exceeds the loss of electrolytes. The causes that may lead to this situation are **reduced water intake, increased loss of water (renal or extrarenal) and combination of these two.**

Ions and solutes (mainly Na^+ and corresponding anions) are responsible for "holding" the water in the body. This is the reason why loss of sodium leads to the dehydration in contrast with the loss of pure water, which does not necessarily lead to dehydration in case that ADH secretion and thirst sensation remain physiological. Dehydration is usually a consequence of loss of water and electrolytes and the proportion between the water and electrolytes further determines:

- **Isoosmolar dehydration**
- **Hyperosmolar dehydration**
- **Hypoosmolar dehydration**

Isoosmolar dehydration

Osmolarity of ICF and ECF are equal, **there is no gradient** to drag water from one compartment to another. This could be good condition, because cell volume is stable, and it does not lead to the neurological disturbances. On the other hand, isoosmolarity does not allow compensation by the movement of water from the ICF to ECF, and it leads quickly to the onset and progression of haemodynamic consequences. This type of dehydration is in clinical conditions called **hypovolemia** – reduced intravascular volume. Serious decrease of effective circulatory volume induces activation of compensatory mechanisms with centralisation of circulation. It may eventually lead to **hypovolemic shock.**

Causes:

1. **Haemorrhage:** external haemorrhage after trauma or internal haemorrhage (e.g. oesophageal varices, ectopic pregnancy). Loss of blood does not mean only effective

hypovolemia, but also reduced transport capacity of the blood to carry oxygen. Both mechanism contribute to shock.

2. **Burns:** the risk of the shock due to burns depends on the surface of the skin that was injured – the mechanisms responsible for the dehydration are (1) loss of plasma through the injured skin (2) pain (3) decrease of oncotic pressure due to lack of plasmatic proteins via injured skin surface.
3. **GIT loss:** diarrhoea or vomiting lead rather to the hyperosmolar dehydration (digestive juices are usually hypoosmolar); however, serious diarrhoea or vomiting may eventually lead to isosmotic disturbance. These disorders are usually accompanied by hypokalaemia and acid–base disturbances.
4. **Third spacing:** Isoosmolar dehydration can be caused also by iatrogenic cause – for example by the evacuation of ascites – this will lead to the imbalance of Starling forces and quick filtration of the fluids to the peritoneal cavity.
5. **Renal loss of isotonic fluids:** Polyuria of different aetiology may lead to isoosmolar dehydration – for example – polyureic phase of acute renal failure. It is important to understand that proportion between excreted sodium and water can change during the disease, and normonatremic dehydration may progress to the hyponatraemic dehydration. Diuretics blocking Na-K-Cl transport in the ascending part of the loop of Henle also lead to massive diuresis with proportional loss of electrolytes and water.

Hyperosmolar dehydration

It is dehydration with increased osmolarity of the ECF, and osmolarity of ECF is higher than that in ICF, and this osmotic force drags water from the cells to the ECF. Volume of the cells is reduced. These mechanisms partially compensate the loss of ECF; however, combination of hyperosmolarity and hypovolemia leads to intense thirst perception and to the onset and progression of symptoms caused by the exsiccation of neurons. Common causes are inadequate water intake, loss of hypoosmolar fluids (loss of water exceeds the loss of solutes).

Causes:

1. **Inadequate water intake** a) patient feels thirst but does not have access to water (babies, disabled, swallowing problems) b) reduced perception of thirst in seniors c) patient does not feel thirst (hypothalamic lesions, unconsciousness).
2. **GIT loss –** infectious diarrhoea with mild to moderate clinical course leads to loss of hypoosmotic fluid, similar situation is typical for lactase deficiency (lactose intolerance).

3. **Loss through skin and respiratory system:** perspiratio insensibilis and sweating in fever, tachypnoea, long speaking, singing.
4. **Osmotic diuresis**:
   a) **Increased glomerular filtration of osmotically active solute.** This molecule drags water as it passes alongside the tubular system and increases the speed of the flow in the distal nephron, which disables the resorption of Na^+ and water, e.g. diabetic ketoacidosis, where osmotically active solutes are glucose and ketone bodies. Hyperosmolarity of plasma is typically associated with hyponatremia, because the water flows from the cells to the ECF thus diluting it.
   b) **Disorder of physiological resorption of solutes in the tubular system** due to structural injury of the tubular cells e.g. renal ischemia, toxic influences etc.
   c) **Water diuresis –** loss of pure water in subjects with concentration disturbances, with insufficient resorption of water in distal nephron. Typical example is diabetes insipidus characterised by polyuria. If not compensated, it will lead to dehydration.

Hypoosmolar dehydration

It is a dehydration with reduced osmolarity of ECF, which is always related to the **hyponatremia**. Osmolarity of ECF is lower than osmolarity of ICF, and this is the reason why water flows inside the cells. This transfer worsens the loss of ECF with manifestation of haemodynamic symptoms and intracellular oedema leads to CNS disturbances. Causes of this type of dehydration are renal loss of hyperosmotic fluids.

1. **Diuretics** that directly inhibit resorption of salts in the tubular system - mainly inhibitors of Na-Cl-transporter in the distal tubule.
2. **Renal inflammation with the salt loss.**
3. **Deficiency of mineralocorticoids.**
4. Frequently a consequence of inappropriate treatment of iso- or hyperosmolar dehydration if they are treated only by supplementation of water.

Symptoms and signs of dehydration

Skin and mucosa: feeling of dry mouth, coating on tongue, pallor, reduced skin turgor, slow capillary filling, reduced sweating.

Neurological: hyperosmolar and hypoosmolar type of dehydration lead to the change of the volume of neurons. Restlessness, confusion, nausea, vomiting, headache, lethargy, somnolence, cramps and coma are the manifestation of dehydration. Neurons are able to

adapt to the changes effective osmolarity by changing their internal osmolarity. The background for this adaptation is the change of the concentration of main ions, mainly potassium and also change in concentration of small organic molecules – **organic osmolytes** (glutamate, glutamine, taurine and inositol). The key of this adaptation is time. This adaptation does not work in case of sudden changes of effective osmolarity in ECF; however, in slowly progressive or chronic circumstances this adaptation can have nearly 100% efficacy.

Haemodynamic: tachycardia, hypotension, tendency to orthostatic syncope, reduced filling of jugular veins, shock and unconsciousness.

Renal: depend on the causes of dehydration:

1. **Extrarenal causes –** if the kidneys are otherwise healthy, they compensate dehydration by the retention of fluids:
   a) Oliguria (diuresis less than 0,5 l/day),
   b) Hypertonic urine – usually more than 700 mOsmol/L,
   c) Centralisation of circulation may lead to renal ischemia – acute "prerenal" failure develops in dehydration states and it leads to the elevation of the plasmatic levels of urea and creatinine.
2. **Renal causes – dehydration caused by renal disturbances or regulatory mechanisms failure:**
   a) Polyuria
   b) Osmolarity of urine depends on the type of diuresis

PATHOGENESIS OF OEDEMA

Microcirculation

The main function of microcirculation is to provide optimal metabolic resources for the tissue to produce ATP (decrease of PO_2, increase of PCO_2 and decrease of pH cause arteriolodilatation, opposite changes cause arterioloconstriction) and helps to maintain optimal perfusion pressure in whole circulation.

Exchange of the fluids across the capillary membrane

Capillary membrane represents the border between IVF and ISF. IVF contains high concentration of proteins in comparison to the ISF. Exchange of molecules is realized via pores in the membrane and via transcellular transport mechanism. They are:

Diffusion: transport of the molecule driven by a concentration gradient, and it runs across the whole length of the capillary wall in both directions – to the interstitium and out of it. This is the mechanism responsible for the "mixing" of the plasma and interstitial fluid and some sort of balancing of differences in nutrients concentration, blood gasses levels and metabolites within the ECF. From the quantitative side, this is the mechanism responsible for major transport of molecules and water; however, production of the interstitial fluid is rather a consequence of other process – filtration.

Filtration/resorption is the process driven by equilibrium between Starling forces. The fluid is filtered (leaving the capillary) at the arterial side of the microcirculation and resorbed (moving back to the capillary) at the venous end of microcirculation.

Starling capillary forces

Hydrostatic pressure in capillary (Pc) supports filtration. The pressure reduces along the capillary. At the arterial end – there is **30-35 mmHg** while at the venous end only **10-15 mmHg**. Major influences are:

- Arterioloconstriction reduces Pc while arteriolodilatation increases it
- Increased mean arterial pressure increases Pc and vice versa
- Increase of the venous pressure increases Pc.

Hydrostatic pressure in the interstitium (Pi) "pushes" the fluid to the capillary. Its value fluctuates around **0 mmHg**, because most of the filtered fluid is finally going back to the capillary. Only the rest of the fluid (very tiny amount) is eliminated by the lymphatic vessels.

Oncotic pressure in the capillary (Πc) "holds" the fluid inside of the capillary. It is determined by the concentration of plasmatic proteins (80% of osmotic pressure is caused by albumin). It is the pressure of macromolecules which do not cross the membrane to the interstitium. The value of this pressure is **25 mmHg** and it is same at the arterial and venous side of the microcirculation.

Oncotic pressure in the interstitium (Πi) holds the fluid in the interstitium. This pressure is low, 5 mmHg, the reason is that plasmatic proteins do not move to the interstitium, and if any, they are eliminated quickly by lymphatic vessels.

Filtration flow (Qf) depends on the capillary filtration coefficient (Kf – determines permeability and the surface of the capillaries in given tissue) and on the gradient between hydrostatic and oncotic pressures.

$$Qf = Kf \times [(Pc - Pi) - (\Pi c - \Pi i)]$$

At the arterial side of the capillary – hydrostatic pressure is higher than oncotic pressure; therefore, the fluid moves to interstitium and at the venous side the movement of the fluid reverses, because the oncotic pressure is now higher than hydrostatic. 90% of the filtrate moves back to the capillary at the venous end, and only 10% is eliminated by lymphatic system.

Definition and classification of oedemas

Oedema is an accumulation of body fluids (fluids in the tissue). Oedemas can be classified into **localized** and **generalized** (eventually leading to anasarca).

Other classification depends on the role of the kidneys in the pathogenesis of the oedema state. **Primary oedemas** where the kidneys are the reason and cause of oedema, because they are not able to eliminate optimal amount of water and salts. In **secondary oedemas** kidneys are unaffected. They only compensate for loss of effective arterial volume/pressure in case of e.g. heart failure, hypalbuminaemia. The response to this signalling is activation of RAA system with resorption of sodium and water with a purpose to increase effective volume/pressure. However, this leads to the gain of ECF and TBF. Another classification of oedemas considers their localisation – they can be **intracellular** or **extracellular.**

Pathogenesis of intracellular oedemas

Increase of the cell volume (cell swelling) is caused by:

1. **Hypotonicity of extracellular compartment** with subsequent movement of water inside the cells based on the osmotic gradient. Typical cause is a hyponatremia, or in general, consequences of inappropriate treatment of hyperosmotic state.
2. **Depletion of intracellular ATP** as a consequence of suppression of complete block of energy production in the cell, most frequently in hypoxia, ischemia and hypoglycaemia. Decreased performance of Na/K ATPase leads to accumulation of sodium inside the cell, which drags water to the intracellular compartment.
3. **Increased permeability of cell membrane,** for example in inflammation as an effect of inflammatory cytokines.

Pathogenesis of extracellular oedema

Basic condition for development and progression of oedema is disturbance of the following equation:

FILTRATION > RESORPTION + LYMPH FLOW

There are four main mechanisms:

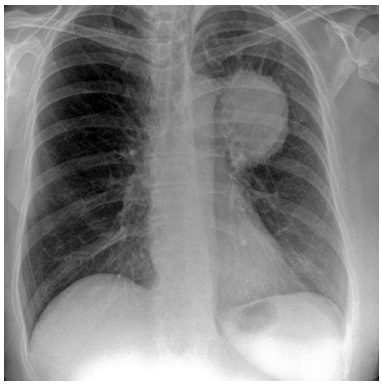
- **Increase of the difference between capillary hydrostatic pressures**
  1. **Increase of Pc**
     a) arteriolodilatation – medication, warm surroundings
     b) increased retention of fluids in kidneys – renal failure, hyperaldosteronism
     c) increase of the venous pressure – heart failure, venous thrombosis
  2. **Decrease of Pi –** exposure of tissues to the lower atmospheric pressure (decompression in the aircraft cabin)
- **Decrease of the oncotic pressure differences**
  1. **Decrease of Πc (decreased concentration of plasmatic proteins)**
     a) Protein malnutrition
     b) Reduced proteosynthesis in liver
     c) Increased consumption of proteins related to the stress, shock, MODS, catabolism
     d) Protein loss – burns, nephrotic syndrome
  2. **Increase of Πi –** typical for tissue destruction (trauma, ischemia, inflammation)
- **Increase of the capillary permeability** – typical for infectious and non-infectious inflammation, allergy, prolonged ischemia (leak of plasmatic proteins to interstitium)
- **Disturbance of lymphatic capillaries – lymphedema –** compression of the lymphatic vessels by tumours, parasites, damage to the lymph nodes and lymphatic vessels due to cancer surgery.

CASE REPORTS

Case report 1

58-years-old man, smoker for many years, was admitted to the hospital due to exacerbation of chronic bronchitis with auscultation finding suggesting pneumonia, which was also confirmed by chest X-ray. Apart from pneumonia, the X-ray shows suspicious shadow in left middle field.

Laboratory parameters and chest X-ray



Na 116 mmol/L; K 2.8 mmol/L; Cl 74 mmol/L; urea 2.4 mmol/L; creatinine 54 μmol/L; $PaCO_2$ 6.9 kPa; PaO_2 8.0 kPa; pH = 7.4; HCO_3^- 29 mmol/L

Questions & Tasks

1) Which laboratory parameters differ from physiologic values?

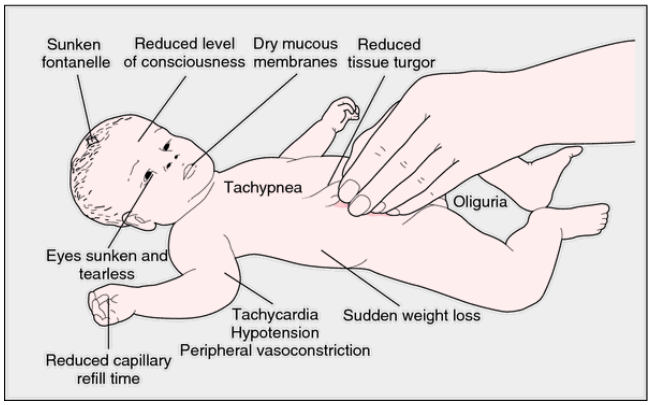
2) Explain which mechanisms contribute to development of this disorder?

3) Explain what kind of acid-base balance disorder this case report presents and explain if it is correct to talk about a disturbance given the normal pH value.

4) What mechanisms can influence K^+ in this case?

Case report 2

4-week-old baby was admitted to paediatric intensive care. The child was lethargic the whole day, did not cry (healthy new-born cries a lot, demands attention and feeding), drank only a little milk from feeding bottle (approx. 30ml in every feeding). Mother states that the previous day, the baby was all right, slightly more irritated because formula was introduced. The baby is form first pregnancy, delivery was spontaneous in 39th week of pregnancy, with good adaptation, and delivery weight was 3800g.



Objective findings

Current weight is 3000 g – weight decrease in comparison to d.w. is increased
Hypotonic
Dry skin and mucosal membranes, skin turgor is decreased
Fontanelle is sunken
Diuresis is decreased (only 2 diapers/24h)

Laboratory parameters: Na 170 mmol/L; K 4.8 mmol/L; Cl 135 mmol/L; glucose 5.0 mmol/L; Hbg 189 g/L; Htc 56.3; pH 7.29; pCO_2 5.4 kPa; pO_2 10.7 kPa; HCO_3^- 13.5 mmol/L; BE -11.2

Questions & Tasks

1) Which laboratory parameters differ from physiologic values?

2) List the mechanisms leading to development of hypertonic dehydration in this case?

3) Clinical manifestation of hypertonic dehydration is dominated by neurologic signs and symptoms. Explain which mechanism contributes to their development.

4) Explain the mechanisms leading to maintenance of cell volume in hypertonic environment activated in case of short-lasting hypertonicity.

5) Analyse what kind of acid-base balance disorder is present and which mechanisms lead to its development.

Case report 3

72-years-old woman was found unconscious in her flat. According to indirect history, the cause of unconsciousness can be stroke, as she already had one before, and she was left in her flat without any help for 2 days. The heating was on in her flat, so no hypothermia was present.

Objective findings: unconscious patient, does not react to salutation, flection responses to pain stimuli; signs of dehydration – dry coated tongue, dry mucosal membranes, decreased skin turgor; BP 140/80 mmHg, HR 100/min; diuresis – after insertion of catheter in urinary bladder oligoanuria is found

Laboratory parameters: Na 169 mmol/L; K 3.4 mmol/L; Cl 124 mmol/L; HCO_3^- 28 mmol/L; urea 37.5 mmol/L; creatinine 280 mmol/L; glucose 7.2 mmol/L. Amount of Na in urine is decreased and specific weight of urine is increased.

Questions & Tasks

1) Which laboratory parameters differ from physiologic values?

2) How would you explain the mechanism of increased values of Na^+ and Cl^-, whereas K^+ is slightly decreased?

3) How would you explain elevated concentrations of urea and creatinine? What processes in kidneys could lead to "urine concentration and decreased sodium concentration in urine"?

4) Could this patient be given 5% glucose solution for rapid rehydration? Explain why.

Chapter 8

ACID – BASE REGULATION AND DISTURBANCES

Acid-base disturbances are common clinical conditions and their manifestation varies from mild to severe, life-threatening problems. Acid-base disorders are not "diseases" per se, but rather consequences of primary diseases and dysfunctions of systems regulating acid-base balance e.g. kidneys, GIT, respiratory system, cardiovascular system and endocrine glands. Acid-base disorders are frequently associated with fluid and ions imbalance (mainly K^+). Therefore, it is important to evaluate **parameters of acid-base balance** together with the **concentration of electrolytes,** volume and composition of the **urine, blood gases values**, hemodynamic situation and respiration.

H^+

Acid-base balance (ABB) is related to the regulation of concentration of H^+ ($[H^+]$) in body fluids. It is maintained in very narrow interval, and physiological value of $[H^+]$ is around **40 nmol/L**. Since this is very low number, pH is expressed as negative decimal logarithm of $[H^+]$. From the relationship between the pH and $[H^+]$ is clear that relatively small change of pH (e.g. from 7.4 to 7.1) represents considerable increase of $[H^+]$ from 40 to 80 nmol/L (see figure in the lecture). In contrast, **concentration of bicarbonate** ($[HCO_3^-]$) is maintained around **24 mmol/L**, what is approximately 600 000 times higher concentration than for $[H^+]$. It is necessary to keep $[H^+]$ within the physiologic range, because it would bind quickly to proteins, influencing the function of enzymes, structural proteins, contractile proteins in the heart etc.

Sources of H^+

Human cells naturally produce acids in metabolic processes and "acid" in a sense of acid-base balance is any molecule, which is able to release H^+.

Volatile acid: Main end-products of oxidation of substrates in cells are the water and CO_2. CO_2 is the most important metabolic end-product in aerobic metabolic chain of glucose, amino acids and fatty acids. Daily production of CO_2 is roughly 20 000 mmol. CO_2 diffuses from cells to the body fluids and it reacts with water. This reaction is a source of volatile carbonic acid. The reaction is facilitated by the **carbonic anhydrase** in the red blood cells.

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$

Non-volatile (fixed) acids: Sulphur and phosphorus as components of amino acids and nucleic acids are metabolized to the salts of strong acids, mainly sulphuric and phosphoric acids.

Organic acids: They are end-products of the metabolism of glucose and free fatty acids – mainly lactic acid and ketone bodies. However, these are produced in low concentrations under the physiological conditions, and are incorporated back to metabolic chains via liver. Lactic acid and ketone bodies can considerably influence the acid-base balance under pathological conditions, when cells produce excessive amounts of these molecules – lactic acid as a product of anaerobic metabolism of glucose and ketone bodies in decompensated diabetes mellitus or long starvation.

Acidosis – acidaemia

Increased concentration of $[H^+]$ (decrease of pH) is commonly defined as acidosis in literature. For better understanding of acid-base balance, it is useful to distinguish between acidosis and acidaemia. **Acidaemia** is the term restricted to describe increased concentration of H^+ in body fluids above 44 nmol/L (decrease of pH below 7.34) while **acidosis** is a term that describes entire pathological process leading to acidaemia. These two usually correspond – acidosis with acidaemia and alkalosis with alkalemia; however, when the body has enough time for compensation of pH disturbances, we may have e.g. **acidosis without acidaemia** – the pathological process is still present, but the concentration of H^+ could be already normalized by the action of compensatory mechanism(s) – an example **in metabolic disorder** - acidaemia is compensated by either alveolar hyperventilation (which eliminates excess of CO_2) or by increased excretion of H^+ in kidneys what increases the concentration of bicarbonates in the blood. In respiratory acidosis, only kidneys can take part in compensation process by increased reabsorption of bicarbonates.

Alkalosis - alkalemia

Reduced concentration of H^+ in the blood below 36 nmol/L (increase of pH above 7.44) is referred to as **alkalemia,** pathological process that causes it is called **alkalosis**. Relationships between **alkalemia and alkalosis** are similar to the relationship between acidaemia and acidosis. For example, in case of metabolic disorder, alkalemia is compensated

by alveolar hypoventilation (reduced elimination of CO_2 – which is limited by the availability of oxygen to meet metabolic demands of tissues) or by reduced elimination of H^+ in kidneys, what leads to the decrease of plasmatic bicarbonate concentration. Respiratory alkalosis can be compensated only by renal mechanisms – by the reduction of plasmatic bicarbonate concentration.

Regulation of ABB

Acid base balance is precisely regulated, because metabolic processes are permanent sources of acid (and small amounts of alkalis) which are constantly influencing pH of extracellular fluid. Therefore, pH must be maintained in physiological ranges. If the pH of extracellular fluid should stay normal, it requires constant regulation of the $[H^+]$ by **biochemical processes, transmembrane ion movement (K^+/H^+ exchange), activation of buffers, alveolar ventilation and renal excretion of H^+.**

Buffer systems

Buffers are mixtures of weak acids and their conjugated basic salts, which are able to minimize changes of the pH in the blood by elimination of the H^+ from the blood by chemical bond, or by the release of the H^+ to the blood when needed. Buffer systems react as the first line defence to minimize changes of the $[H^+]$ which are normal, natural consequences of metabolic processes. Buffers are able to normalize pH in normal daily production of volatile, fixed or organic acids (or alkalis) produced in metabolism. This means that buffers are normally active even in physiological circumstances. Pathological circumstances lead to the excess of either acids or alkalis in the body, what may lead to the consumption of the buffer molecules and finally to their depletion.

HCO_3^-/H_2CO_3 buffer system

Hydrogen carbonate buffer is the main buffer system in the extracellular fluids, its function is demonstrated by the equation:

$$\mathbf{CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-}$$

This biochemical process represents the basic relationship of acid-base balance from the perspective of the hydrogen carbonate system. The effectiveness of this system is determined by its ability for quick responses, which are provided by the change of **alveolar ventilation**, regulating $PaCO_2$. In case of increase of CO_2, the direction of this biochemical

process is shifted to the right side – to the production of carbonic acid, and its further dissociation to H^+ and bicarbonate in hypocapnia, reduced CO_2 shifts this reaction to the "left side". This means that addition of an acid to the body systems will lead to consumption of HCO_3^- by forming the carbonic acid (buffering process); what subsequently increases production of water and CO_2. Since the level of CO_2 is precisely regulated and maintained at physiological levels, this will lead to the **increased respiratory drive to eliminate the excess of CO_2** that was produced in this reaction.

Renal tubular system will also regenerate the bicarbonate anions that were "used" for buffering responses. This system is therefore very effective, because both components – respiratory and metabolic (HCO_3^- a $PaCO_2$) can be regulated in separate and independent ways.

Based on this equation, the pH is not determined by the "absolute" concentration of these two components, but rather by the **ratio** between $PaCO_2$ and concentration of HCO_3^-. Therefore, if the change of both components is proportional (both are increasing, or both are decreasing) pH would not be changed. This is also the background for the compensations of pH disturbances which attempt to achieve again the "normal" ratio between CO_2 and HCO_3^-

Other buffer systems are haemoglobin system, phosphate system and system of plasmatic proteins. All buffer systems are important for assessment of total buffer activity of the blood.

The role of respiratory system and kidneys in regulation of pH

Alveolar ventilation is important regulatory mechanism influencing acid-base balance. Respiratory system reacts in a quite short time and it can compensate primary "metabolic" disturbances of acid-base balance.

Response to **metabolic acidosis** leads to the activation of the central chemoreceptors via increased concentration of H^+ in the cerebrospinal fluid. Increase of the H^+ activates specific neuronal population in the brainstem (central chemoreceptors) which initiate respiratory response, in this case **alveolar hyperventilation**. These mechanisms will eliminate excess of CO_2 which was produced in the reaction of hydrogen carbonate buffer (see Henderson-Hasselbalch equation) as a response to excess of H^+ in the body fluids. Increased ventilation drive leads to the sensation of dyspnoea and respiratory distress, and only barely can fully compensate the excess of pH. The limitation is fatigue of respiratory muscles.

One may incorrectly assume that **metabolic alkalosis** can be easily compensated by alveolar hypoventilation. Ability of alveolar hypoventilation to compensate alkalosis is partial and it is limited by the oxygen demand. Hypoventilation leads to the gain of CO_2 and lack of oxygen, which stimulates carotid bodies to optimize breathing pattern to achieve normal oxygenation. Oxygenation takes over the compensation of acid-base problems. Severe metabolic acid-base disturbances are not fully compensated by the respiratory system, and renal mechanisms must be involved to achieve full compensation of this process.

Kidneys contribute to the regulation of ABB by several mechanisms

The daily tubular secretion of H^+ is enormous, because we excrete 70 mmol of non-volatile acids and also have to match almost all of the total filtration flux of bicarbonate. At the brush border of the proximal tubule cell, carbonic anhydrase (CA) catalyses the reaction, so CO_2 is formed and can enter the cell by diffusion. Also within the cell CA facilitates production of ($H^+ + HCO_3^-$). For each bicarbonate produced in the cell from the CO_2 of the tubular fluid, one bicarbonate ion diffuses to the interstitial space and via renal venous blood back to the body. **This is resorption – what was filtered via glomerular filtration is now reabsorbed.**

Normally, most of the filtered bicarbonate flux is reabsorbed already in proximal tubules, where the luminal membrane contains a Na^+/H^+-antiporter. The **bicarbonate reabsorption** is accomplished by means of H^+ secretion. A driving force for this process is the ability of proximal tubular cells to excrete H^+ by Na^+/H^+-antiporter (see lecture). The main role of this process is to reabsorb all bicarbonates, which were filtered, so the body does not lose a component of crucial buffer system. Secretion of H^+ in the distal tubules and collecting ducts is another process through which the kidneys increase serum HCO_3^- concentration above physiological levels. The Na^+/K^+ pump in the basolateral membrane provides the energy for the secretion of H^+ into the tubular fluid by H^+/K^+ antiporter at the luminal side. This secretion of H^+ serves to reabsorb the filtered bicarbonate, which is thus not excreted in the urine (see lecture).

Another renal mechanism is excretion of H^+ in the distal tubule and the collecting duct. This process involves NH_3/NH_4^+ system. Acidosis influences the production of ammonium ions in the renal tubular cells from glutamate. One molecule of NH_4^+ is produced by deamination of one glutamine molecule by the enzyme glutaminase, and a second by oxidative deamination of glutamic acid forming α-ketoglutarate that is metabolized. The

NH_4^+ in the proximal tubule cells is in equilibrium with minimal amounts of NH_3 at the relatively low pH. The NH_4^+ secretion into the tubular fluid makes use of the Na^+/H^+ antiporter, where NH_4^+ substitutes H^+.

Last renal mechanism that participates on H^+ excretion is a phosphate urine buffer system. It consists of secondary/primary phosphate. Phosphate is filtered via glomerular filtration and it is a threshold substance, which is reabsorbed in the proximal tubules unless this resorption is blocked by the parathyroid hormone. As the primary phosphate passes along the tubular system, it accepts the H^+ and changes to the acid form, $H_2PO_4^-$. Titratable phosphate acidity in the daily urine is the amount of base (in mmol) needed to titrate an acidic daily urine back to the pH of plasma and glomerular filtrate (pH 7.4). Normally, the titratable phosphate acidity is 30 mmol in a 24-hour urine. Acidosis increases the urinary titratable phosphate acidity (towards 50 mmol daily) in order to get rid of the excessive amount of acids.

Overview of the primary acid-base imbalances

Normal range of blood pH is near 7.4 and the widest range compatible with life is from 6.8 to 7.8. A blood pH of less than 7.35 is acidaemia, and the process causing it is called acidosis. A pH of 7.25 is life-threatening and a pH of 6.8 is incompatible with life. Similarly, a blood pH greater than 7.45 is called alkalemia and the process causing it is called alkalosis. A pH greater than 7.55 is life-threatening and a pH greater than 7.8 is incompatible with life. Based on the Henderson-Hasselbalch equations, the acid-base disturbances can occur in principle in case of

1) **Accumulation of fixed or organic acids**
2) **Loss or increase of bicarbonate concentration in plasma**
3) **Hypercapnia or hypocapnia due to primarily impaired alveolar ventilation**

Metabolic imbalances are those in which the primary disturbance is in the concentration of bicarbonate - decreased bicarbonate concentration causes **metabolic acidosis** and increased bicarbonate concentration causes **metabolic alkalosis**. Respiratory imbalances are those, in which the primary disturbance is in the concentration of carbon dioxide. An increase in the $PaCO_2$ lowers the pH and is called **respiratory acidosis.** A decrease in the $PaCO_2$ raises the pH and is called **respiratory alkalosis.**

Metabolic acidosis (MAC)

MAC is a systemic disorder characterized by primary decrease of the plasma bicarbonate concentration that results in a decrease of pH. The causes of MAC are commonly divided into two groups according to whether the anion gap is normal or increased. In normal anion gap acidosis, bicarbonate loss may occur via the gastrointestinal tract or kidneys. When bicarbonate is lost from the body, decreased HCO_3^- concentration in plasma is followed by the increased Cl^- concentration as a compensation, because total number of anions and cations in the body fluid must be equal to maintain electroneutrality. The result is **hyperchloremic MAC.** The most common condition associated with **high anion gap** acidosis is shock resulting to accumulation of large amounts of lactic acid. Diabetic ketoacidosis, starvation and ethanol intoxication cause elevation of the anion gap due to the production of anions, which are normally not present in plasma, or they are present only in negligible concentrations. Renal failure with retention of sulphuric and phosphoric acid leads to **normochloremic acidosis with high anion gap**.

The main causes are

1) **Accumulation of organic acids –** from pathological metabolic processes. Lactic acid is produced in tissue hypoxia, because the metabolic switch to the anaerobic glycolysis leads to production of lactic acid **(lactate acidosis).** Starvation or diabetes mellitus lead to the oxidation of free fatty acids, with the ketone bodies as the end-product. Since they are donors of proton, their accumulation leads to **ketoacidosis**.
2) **Accumulation of fixed acids** – sulphuric or phosphoric acids, which cannot be eliminated in the case of **renal failure**. Renal diseases also reduce the ability of the tubular cells to reabsorb bicarbonate.
3) **Loss of bicarbonate from the GIT** in diarrhoea or intestinal fistula,
4) **Tubular acidosis –** can be either inherited or acquired, when the transport mechanisms that participate in the excretion of H^+ are not functioning properly.

The immediate response to the excess of H^+ is extracellular buffering by bicarbonate system. Bicarbonate reacts with the excess of H^+, thus reducing plasma **bicarbonate concentration**. Excess of the H^+ is also transported to the cells by H^+/K^+ antiporter, where it is buffered by proteins and phosphates. To maintain electroneutrality, the entry of H^+ to the cell is accompanied by movement of K^+ out of the cell resulting to the distribution **hyperkalaemia.**

The second compensatory mechanism starts to compensate with a delay of couple of minutes. Increased arterial concentration of H^+ stimulates chemoreceptors, and respiratory centre, and this leads to the increase of ventilatory drive. Increased ventilation eliminates more of CO_2 than is produced in metabolism. It shifts the balance described in Henderson-Hasselbalch's equation to the left side. Reduction of $PaCO_2$ leads to the improvement of the ratio between bicarbonate and CO_2. Metabolic acidosis is compensated by kidneys by excretion of H^+ and reabsorption of bicarbonate anions.

Patients with acidosis have usually vasodilation, low blood pressure with tachycardia, well perfused skin, they sweat, they may have high diuresis (depends on the type of acidosis); therefore, they are prone to dehydration. In case of decompensated diabetes, there is an "acetone" smell on breath and Kussmaul's breathing. Severe disturbance may lead to neurological signs and symptoms, since acidosis increases permeability of blood/brain barrier leading to brain oedema. It is responsible for headache, psychiatric or neurological manifestation (somnolence, coma). Acidosis has suppressive effect on the strength of heart contraction.

Metabolic alkalosis (MAL)

MAL is a systemic disturbance characterized by primary increase of plasmatic bicarbonate concentration, resulting in an increase of pH.

Common causes of MAL are net loss of H^+ (and chloride ions) or excessive retention of HCO_3^-. HCl may be lost from the GIT in prolonged vomiting or nasogastric suction, or through urine due to administration of loop or thiazide diuretics. The depletion of chlorides is crucial, both in the generation and in maintenance of hypochloremic MAL. Cl^- and HCO_3^- have a reciprocal relationship: a decrease in Cl^- results in an increase of HCO_3^-, the purpose is to maintain electroneutrality. MAL is commonly initiated by **vomiting,** with subsequent loss of fluids rich in chlorides. KCl, NaCl and water are lost as well. The result is an increase in the serum HCO_3^-, potassium depletion and volume depletion. Other causes of MAL are chloride depletion as a side effect of diuretic medication, hyperaldosteronism, hypokalaemia and sudden correction of MAC.

Immediate compensatory response to MAL is intracellular buffering. H^+ moves from the cells to buffer excess of extracellular HCO_3^-. This transport requires one K^+ to be transferred to the cell, what leads to hypokalaemia. Also, chemoreceptors are activated by increased pH, and the reaction to this activation is reflex decrease in alveolar ventilation. The

degree of hypoventilation and increase in $PaCO_2$ is however limited by the need for oxygen. The final renal correction of MAL requires the excretion of the excess of HCO_3^{-}.

Chloride depletion plays the major role in preventing the renal excretion of HCO_3^-. Volume depletion stimulates the RAA system. Aldosterone causes increased Na^+ and water reabsorption in an effort to restore volume of extracellular fluid. Compensation of volume depletion dominates over the compensation of alkalosis, because it would require excretion of Na^+ alongside with HCO_3^- Since the Cl^- depletion does not allow reabsorption of Na^+ and Cl^-, Na^+ is reabsorbed with HCO_3^-, what makes alkalosis worse. Aldosterone also excretes H^+ and K^+. In summary, chloride depletion, fluid depletion and hyperaldosteronism contribute to the maintenance of alkalosis and complicate its compensation.

There are no typical signs and symptoms of MAL. Signs and symptoms of volume depletion may be present. Severe alkalemia can cause arrhythmias. Occasionally, tetany may occur in patients with MAL - in a patient with the borderline serum Ca^{2+} concentration and if alkalosis developed rapidly. Calcium binds more to the albumin in alkalic pH, therefore plasmatic proportion of ionized calcium decreases. It leads to the increase in neuromuscular irritability, producing tetany or seizures. Muscle weakness, muscle cramps and also heart arrhythmias may appear in case of hypokalaemia.

Respiratory acidosis (RAC)

RAC is a disorder characterized by decrease of pH to less than 7.44 because of primary increase of $PaCO_2$ to more than 5.8 kPa. The fundamental cause of RAC is **alveolar hypoventilation.** This process leads to hypercapnia, because elimination of CO_2 by lungs is lower than its production in the metabolism. Ratio $HCO_3^-/PaCO_2$ decreases and so does the pH.

Acute RAC is usually a consequence of acute problems with ventilation (acute airway obstruction, foreign body aspiration, pneumothorax, suppression of respiratory centre etc.) In severe acute RAC, the resulting RAC is worsened by an accompanying metabolic acidosis due to hypoxia. Acute gain of CO_2 leads to the huge decrease of pH with bicarbonate deficiency, which were consumed for the buffer response. This is **acidosis with acidaemia**.

Chronic progressive retention of CO_2 leads to the chronic RAC with activation of compensatory mechanisms in the renal tubular system that lead to the resorption of bicarbonate and excretion of H^+. Resorption of bicarbonates makes the pH normal or nearly normal, with elevated bicarbonates – as a sign of good renal compensation. This is **acidosis without acidaemia**. The arterial pH and plasma HCO_3^- are different in acute and chronic

RAC. In response to acute RAC, only the buffer systems have time to be used, because the renal mechanisms will not be significant in first 12 or 24 hours. Thus, acute RAC is poorly compensated and the pH is severely reduced. Chronic RAC is well-compensated because renal compensatory mechanisms had time to become fully operational.

Main causes of chronic RAC are diseases such as COPD, kyphoscoliosis, Pickwickian syndrome, sleep apnoea, progressive atrophies of respiratory muscles and so on.

CO_2 retention is always associated with hypoxia; therefore, signs and symptoms are related to hypoxia – they are **headache, tachycardia, CNS disturbances** – **reduced consciousness or mental performance, fatigue.** CO_2 is the main regulator of cerebral perfusion, hypercapnia leads to the vasodilatation of cerebral arteries. It may lead to **increased intracranial pressure** with headache and the risk of cerebral vasogenic oedema. Acidosis in general decreases the heart contractility and peripheral arterial resistance. This process may lead to the decease of the blood pressure and influence the perfusion of tissues.

Respiratory alkalosis (RAL)

It is a primary acid-base disorder caused by the decreased $PaCO_2$ below 4.8 kPa, with the pH above 7.44. The main condition leading to the RAL is alveolar hyperventilation that leads to hypocapnia. Henderson-Hasselbalch equation shows that ratio between HCO_3^- /$PaCO_2$ increases and so does the pH. Main causes of this disorder are panic attacks with hyperventilation, stress hyperventilation, initial phases of an asthma attack, pulmonary embolism and reflex irritation of the respiratory centre in fever, sepsis, intoxications or early pregnancy.

The immediate response to an acute reduction in $PaCO_2$ is intracellular buffering. H^+ is released from cellular buffers, which minimizes alkalosis by lowering the plasma HCO_3^- concentration. When hypocapnia is sustained, renal adjustments yield a much larger decrement in plasma HCO_3^-. Renal tubular reabsorption and production of new bicarbonate is inhibited.

When symptoms are referable to respiration, the complaint is usually “unable to get enough air” despite already present hyperventilation. CO_2 is the main regulator of the **cerebral circulation,** and when it decreases, vasoconstriction in the CNS occurs. Symptoms and signs of this condition are dizziness, dull head feelings, eventually unconsciousness. The effect of alkalosis on the blood biochemical parameters leads to the **decrease of ionized calcium**. It causes perioral **paraesthesia**, numbness and tingling and of fingers and toes, and if alkalosis is severe, manifestation of tetany such as carpo-pedal spasms occur. Low $PaCO_2$

increases affinity of haemoglobin to oxygen what in combination with cerebral vasoconstriction may lead to cerebral hypoxia and transient loss of consciousness.

CASE REPORTS

Case report 1

Patient is 25-years-old woman with panic disorder (psychiatric disease characterized by anxiety, fear and accompanied with hyperventilation). During regular check-up, her blood was tested and selected laboratory parameters were as follows: Na 135 mmol/L; K 3.5 mmol/L; Cl 96 mmol/L; pH 7.42; $PaCO_2$ = 5.2 kPa.

A few days later, she was admitted to the hospital due to spasms and short-lasting unconsciousness, which occurred during one of her panic attacks.

Laboratory parameters at the time of admission were: Na 145 mmol/L; K 3.1 mmol/L; Cl 100 mmol/L; pH 7.64; $PaCO_2$ 3.5 kPa; PaO_2 13.3 kPa

Questions & Tasks

1) Which laboratory parameters differ from physiologic values?

2) What kind of homeostasis disturbance is indicated by medical history and laboratory results?

3) Explain possible mechanism of short-lasting unconsciousness development.

4) Explain the mechanism responsible for development of spasms in this patient.

5) What mechanism could explain increased concentrations of Na, Cl and decreased K concentration in second laboratory examination?

Case report 2

Otherwise healthy, 45-years-old man was admitted to hospital due to history of nausea od 4 days and vomiting due to food poisoning. He did not eat anything and drank only little water, because he “cannot hold anything in his stomach”. He is lethargic and complains about fatigue.

Objective findings: Heart rate: 110/min, breathing rate 14/ min, BP 120/80 mmHg when lying down and 90/60 mmHg when sitting, decreased skin turgor, dry coated tongue, body weight 64kg (70kg before)

Laboratory results: Na^+ 150 mmol/L; Cl^- 82 mmol/L; K^+ 3.1 mmol/L; pH 7.52; HCO_3^- 30 mmol/L; $PaCO_2$ 5.3 kPa

Questions & Tasks

1) Which laboratory parameters differ from physiologic values?

2) What kind of acid-base balance disorder developed in this patient? Why are concentrations of K^+ and Cl^- also affected?

3) How can the progression of this pathologic process be negatively influenced by kidneys?

4) Analyse possible causes of increased hear rate in this patient and why is there a difference in BP measured when lying down and sitting present?

5) How could the activation of renin-angiotensin-aldosterone system be confirmed in this patient?

Case report 3

Patient is first day after cholecystectomy in surgical ICU. Surgery was without complications and patient feels well with exception of moderate pain in surgery wound. Laboratory results ordered on this day were surprising, because they indicated severe changes in homeostasis even though that patient feels subjectively well.

Laboratory results: Na^+ 117 mmol/L; K^+ 6.0 mmol/L; Cl^- 90 mmol/L; urea 7.7 mmol/L; creatinine 92 μmol/L; glucose 18 mmol/L; HCO_3^- 14 mmol/L

Questions & Tasks

1) Which parameters differ from physiologic values?

2) Explain the mechanisms which can contribute to changes in glucose level in this patient.

3) Explain the mechanisms which contribute to increased concentration of potassium and explain why is hyperkalaemia dangerous?

4) Explain the cause of hyponatraemia in this patient.

5) Can be this finding considered as physiological to some extent?

Case report 4

56-years-old man, treated for diabetes mellitus type 2 by PAD and on diet. He complains about headaches, weakness, thirst and frequent urination. These problems got worse 2 days ago, after a traffic accident.

Objective findings: Patient sweats a lot and has warm, well-perfused skin; Objective markers of dehydration are present – decreased skin turgor, dry tongue; Acetone smell on his breath; BP 100/60 mmHg, HR 110/min

Laboratory results: pH 7.19; $PaCO_2$ 5.0 kPa; HCO_3^- 12 mmol/L; BE -7 mmol/L; Na^+ 130 mmol/L; K^+ 6.9 mmol/L; Cl^- 112 mmol/L; glucose 30 mmol/1

Questions & Tasks

1) Which laboratory parameters differ from physiologic values?

2) What diabetes complication is suggested by listed symptoms, objective findings and laboratory examinations? How would you explain the presence of this complication in patient with diabetes mellitus type 2?

3) Why is $PaCO_2$ decreased?

4) Analyse the mechanisms contributing to changes of Na^+, K^+ and Cl^- in this case.

5) How could we determine whether renal mechanisms are involved in compensation of metabolic acidosis?

Chapter 9

PATHOPHYSIOLOGY OF NUTRITION

To maintain homeostasis and to provide all necessary functions, human body needs **enough energy in the form of ATP**. ATP is produced mainly by aerobic oxidation of substrates – carbohydrates, lipids and proteins – which are the main components of nutrition. Except from these, there are so-called **essential components**, **or micronutrients,** which have nearly negligible role when it comes to the structural function or energy production, but they are necessary for optimal course of biochemical processes – they include vitamins, essential amino acids, copper, zinc, iron and other micronutrients.

Nutrition should be evaluated from two different aspects – **quantitative aspect** – which determines the amount of energy the nutrients will provide during oxidation and **qualitative aspect** – which describes the proportion of nutrients, mainly proteins, amount of essential amino acids and micronutrients.

Quantitative disturbances – malnutrition (hyponutrition)

Hyponutrition is a consequence of the lack of energy resources in nutrition or lack of the proteins in otherwise optimal energy coverage. Therefore, we can recognize two types of malnutrition. First type – characterized with **energy deficiency is called marasmus** (energy malnutrition), when the affected individual is extremely emaciated with the body weight reduced below the 60% of the expected value (based on age and gender). The layer of subcutaneous adipose tissue is reduced, skin is very thin, fragile, skin folds over the triceps are minimal and in supine position the abdomen is under the chest level, with visible rib cage and pelvic bones. On the face, the bones of jaws and chin are noticeable and eyes are sunken.

Kwashiorkor – it is the second type of malnutrition – **is the consequence of protein deficiency** with relatively satisfactory energy coverage. It is characterized by the lack of plasmatic proteins and reduced oncotic pressure with the tendency to generalized oedema. **Kwashiorkor-like syndrome** is a term describing ineffective proteosynthesis in the body. Amino acids which are meant to be used in the proteosynthesis are redirected to the gluconeogenesis process in subjects with intense stress response e.g. in critically ill patients at intensive care units even in developed countries. The real **kwashiorkor** as a protein deficiency is characterized by growth retardation in children, mental suppression, hypothermia, thin arms and legs, noticeably bigger abdomen (ascites) and liver steatosis in

starving children. Ascites and tendency to oedema is caused by disturbance of precisely regulated Starling balance at the capillary wall, leading to the leak of the fluids out of the capillary due to the decreased oncotic pressure. RAA system is also involved in this process, because the body reacts to the under filing of vessels.

Primary malnutrition – simple starvation

This is type of nutrition with considerably reduced or stopped energy intake. It can be seen frequently in the subjects trying to reduce the body weight by reduced intake of energy – subjects are not eating, because they do not want to eat. In this case, the body will use the stored energy. There is a hierarchy in the way the body uses the energy stores and it represents a physiological response to starvation. Regulatory mechanisms are working properly in this case and short-lasting starvation (less than 72 hours) or long-lasting starvation (more than 72 hours) is not followed by dramatic catabolism of proteins, which are preserved.

1) Glycogen is the first store which is used in starvation and the human body has enough glycogen to cover energy (glucose) requirements for 12- 24 hours depending on activity which is performed. Concentration of insulin decreases during starvation and vice versa, concentration of glucagon increases and it initiates mobilisation of another resources – lipids by initiation of lipolysis.

2) Lipids are split to glycerol and free fatty acids (substrates for β oxidation, with production of ketone bodies) and they are also converted to acetyl-CoA. This molecule is used as a substrate for Krebs cycle to produce energy. This is the way how body produces energy for quite long time without destruction of proteins. In case of severe and long-lasting starvation even the brain can use the ketone bodies to produce energy.

3) Proteins remain untouched so far, because the lipolysis produces enough of energy; however, if the cortisol level increases (e.g. in stress, trauma, disease etc.) the body would not protect proteins any longer and proteolysis will be initiated. This situation is common in case of secondary malnutrition and catabolic states.

The problem is that regulation of energy consumption and regulation of fat storage during starvation lead to the expression of **genes which slow down the metabolic rate** and

redirect majority of available "energy" to fat stores. After the individual starts eating normally after diet, this will lead to very rapid gain of lost weight, so-called **yo-yo effect**.

Secondary malnutrition

Secondary malnutrition is a consequence of primary pathological processes (diseases) which lead to:

1) Increased nutritional requirements (e.g. fever, surgery, trauma)
2) Increased loss of energy and/or substrates (e.g. diarrhoea, bleeding, exudative enteropathy)
3) Reduced food intake (e.g. nausea, anorexia, gastrointestinal diseases)
4) Combination of all causes

In general, we can say, that patients are not eating because they cannot eat – the underlying disease/condition does not let them and this is also the main difference between secondary and primary malnutrition where patients do not eat, because they do not want to. If there is an underlying disease, mechanisms regulating the utilisation of energy sources are impaired. This condition may lead to the proteocatabolism and eventually to the catabolic states. Remember, every single disease patient has is associated with activation of the stress axis, with the cortisol at its end, which may potentiate destruction of proteins. It is always important to maintain energy coverage as much as possible by some alternative ways if normal oral food intake is limited or impossible (e.g. gastrostomy, parenteral nutrition). Positive energy balance maintained by optimal nutrition is a part of the management of these conditions – remember that every recovery, healing, recuperation needs energy (ATP), because these all are biochemical processes depending on ATP.

Catabolic states – stress-induced malnutrition

Catabolic states are characterized by severe impairment of metabolic processes, ineffective use of energy caused usually by serious diseases or pathological processes. In contrast to the simple starvation, energy and protein deficiency develops very quickly and dramatically with very bad prognosis, because the regulation of metabolism is disturbed. Specific cases of catabolic states are oncologic diseases.

Cancer in terminal stage has specific features when it comes to nutrition. There are negative psychological factors depending on the patient's bad prognosis. Anxiety and depression are typically linked to the reduced appetite. The appetite will cease towards the

end, because the body does not need to replenish energy substrates. Anorexia, reduced appetite and nausea are common side effects of chemotherapy. The disease itself contributes to the negative energy balance by production of molecules with negative effects on metabolic regulations. The tumour itself or activated immune cells produce TNFα (also known as cachectin – molecule causing cachexia), IL-1 and IL-6. These molecules activate immune system and further they activate the axis hypothalamus-pituitary gland-adrenal cortex with the final product of this cascade – cortisol. Cortisol has catabolic effects on proteins and lipids, because it negatively influences the availability of glucose for the tissues. In the stress response (and this is a stress response – the phase of resistance or exhaustion eventually) the glucose is saved for the brain and cortisol produces insulin resistance in the other tissues; therefore, they will use lipids and proteins as alternative substrates (free fatty acids, ketone bodies).

Fever is non-specific defensive response of the human body helping to maintain homeostasis. Fever increases the oxygen consumption and the rate of basal metabolism with subsequent anorexia caused by the direct action of pyrogens on the brain centres regulating the food intake. Systemic changes during fever also supress the function of gastrointestinal tract and this leads to reduced digestion and resorption of substrates. Fever typically lasts for couple of days in case of non-complicated infections; however, when it lasts longer, it may quickly lead to the catabolic state. The most dangerous situations are **septic shock or hyperkinetic SIRS**. These patients have elevated concentration of catecholamines, cortisol and glucagon and all of these hormones have mainly catabolic effects. Similar response is present in severe and long-lasting stress response. Catabolism is present also in patients with hyperfunction of thyroid gland (thyroid hormones fasten metabolic rate and they also change the proportion of energy directed towards ATP and heat production, so we have more heat and less ATP). Catabolism is also present in patients after severe trauma, extensive burns, severe pain syndromes, wasting syndrome in AIDS and many more.

Consequences of the energy and protein deficiency

Energy and protein deficiency will lead to these changes: weight loss, shrinkage of adipocytes, tissue atrophy and protein loss with relatively stable volume of extracellular fluids may lead to this shift of the Starling forces with the tendency for the fluid leak to the interstitium. In **heart**, there is atrophy of myofibrils with reduced contraction force, which leads to reduction of stroke volume and cardiac output in general. Malnutrition influences also the function of **respiratory system** – atrophy of respiratory muscles leads to the

reduction of vital capacity. In **gastrointestinal tract**, there is reduced motility of all parts, reduced secretion of gastric juices, atrophy of the intestinal mucosa and atrophy of the villi with reduced proliferation of enterocytes. Exocrine function of the **pancreas** is reduced, while the endocrine function remains untouched. **Kidneys** are losing their *capsula adiposa*, they are atrophic and concentration function in kidneys is reduced because of the ineffective osmotic gradient in the renal medulla. **Liver** is atrophic as well, with reduced stores of the liver glycogen, protein synthesis is reduced and in patients with protein deficiency – kwashiorkor – have hepatomegaly, which is a consequence of steatosis. **Endocrine system** reduces production of hormones, testosterone levels decrease in men and FSH and LH production in women, there is also impaired conversion of T4 to T3. **Immune response** is also attenuated, both in cellular and humoral pathways; granulocytes have reduced ability to migrate and kill bacteria with relatively intact ability of phagocytosis. **Barrier functions** are impaired, because of atrophy of skin layers and atrophy of intestinal mucosa. **Wound healing** is considerably reduced.

Obesity

Statistical data point to the importance of the obesity and they document that approximately 65% of population lives in countries, where the mortality to diseases associated with obesity is higher than the mortality to consequences of malnutrition. Obesity leads to the onset and progression serious consequences and it influences somatic, psychological and social aspects of human life. Therefore, it is important to study pathogenesis of obesity and the consequences of this disease for the body.

Definition of overweight and obesity

Obesity is defined as abnormal accumulation of adipose tissue in the body caused by imbalance between high energy intake (food intake) and low energy consumption (physical exercise). The proportion of fat in the body of more than 30% in women and more than 20% in men is considered obesity (calculated as a proportion to total body weight). This disturbance usually lasts long enough to cause severe problems in regulation of food intake, energy consumption and pooling of the fat in the body, because all of these processes are otherwise precisely regulated. The balance is then shifted towards pooling of the fat in the body. Pooled adipose tissue is distributed either under the skin (**subcutaneous adipose tissue**) or among the visceral organs (**visceral adipose tissue**).

Obesity is defined as multifactorial disease with genetic predisposition and this disease represents strong risk factor for multiple organ dysfunctions – obesity influences all systems of the body. There are methodical approaches how to evaluate the amount of the adipose tissue in the body to categorize patients into certain groups according to the severity of the problem, which predicts the risk for later complications.

BMI – **body mass index** calculation is frequently used in clinical settings. Also the measurement of the **waist to hip ratio** is also important, because it indicates the type of obesity related to the distribution of adipose tissue. Accumulation of fat in the abdomen around the waist is called android (apple shape) obesity, whereas accumulation of the fat at the hips and gluteal region is called gynoid (pear shape) obesity. It is also possible to measure the skin folds at defined points on the body or to use more sophisticated methods; they are however used mainly for research purposes, while BMI and waist to hip ratio are used routinely in clinical settings.

$$BMI = \frac{body\ weight\ [in\ kg]}{height\ [in\ m]^2}$$

Malnutrition – BMI <18; underweight – BMI 18-19; normal value – BMI 19-25; overweight – BMI 26-30; obesity – BMI > 30; severe obesity – BMI > 40

Classification of obesity recognizes **primary and secondary obesity**. **Primary obesity** is a result of abnormal balance between intake and consumption of energy, while **secondary obesity** is usually a consequence of some other disease(s) or medication influencing the appetite or energy consumption.

Histological classification recognizes **hypertrophic type** of obesity, where the count of cells in the adipose tissue is normal, but their size is increased and **hypertrophic-hyperplastic** type of obesity, which indicates that obesity has started in the childhood and there is increased count and increased size of the cells as well. During the reduction of body weight, the count of cells does not reduce, only their size is reduced with the reduction of the pool of fat. Clinical significance points to the type of obesity with accumulated fat around the waist, which is called **android type or "apple shape" obesity**. This type is typical for men and testosterone is responsible for this type of fat distribution. This type represents higher cardiovascular risk, because the "visceral" fat has much higher lipolytic response than subcutaneous fat and there is also higher risk of development of insulin resistance in this type of obesity. Deposition of fat at thighs and hips leads to the so-called **gynoid or "pear shape"**

obesity and is typical for women. Oestrogen production is responsible for this type of fat distribution. It is frequently seen after the menopause that the "pear" shape changes into the "apple" shape obesity. This change is caused by oestrogen decrease.

Pathogenesis - primary obesity

Pathogenesis of primary obesity is complex and multifactorial process. The underlying condition is imbalance between intake of calories (energy) and consumption of energy. The partial mechanisms are

a) **high intake of calories in food (caloric food)**
b) **low physical activity**
c) **combination of both**

Genetic predisposition plays an important role in the pathogenesis of obesity. Genetic predisposition is related to the expression of variable genes regulating the food intake, energy consumption and fat stores – they will manifest in the phenotype only in case of permissive effect of environmental (exogenous) factors. According to literature, genetic predisposition contributes to obesity in about 25% of obese people. **Genetic factors** are also related to the expression or lack of genes leading to the **leptin deficiency** or **leptin resistance**. There are exactly defined syndromes, where obesity is constant finding, e.g. Prader-Willi syndrome, Bardet-Biedl syndrome and many more. In majority of cases there is polygenic determined predisposition. It means that mutations affect more than one gene coding enzymes, receptors and signal molecules in the pathways regulating the food intake, fat pooling and consumption of energy.

Primary obesity is strongly associated with unhealthy life style and the socio-cultural changes related to the nutrition. Nowadays, there are many **fast foods** providing junk food with a lot of calories, people are busy during the day, so they do not eat during the day and they compensate it by **night eating (huge dinners)** when eating is uncontrolled. Another factor is **nibbling** – typically while watching TV, and after all, food became one of the most frequently used factors reducing anxiety/depression. Another negative factor is a **lifestyle with low physical activity** of adults and even children who prefer watching TV or playing computer games to going to playing outside or doing sport on regular basis.

Secondary obesity

Secondary obesity is caused by imbalance between food intake and consumption of energy, but this is determined by some primary disease, pathological process or medication.

For example, inflammation, tumours or other lesions located in the ventromedial hypothalamus may lead to the changes of appetite and increasing the food intake; hyperfunction of adrenal cortex (Cushing's syndrome) may lead to "apple shape" type obesity caused by increase of cortisol levels; DM type 2 with insulin resistance, hypothyroidism (this disease particularly leads to hypometabolic state with low rate of basal metabolism), Stein – Leventhal syndrome in women etc. can be also causes of secondary obesity.

So-called **iatrogenic obesity** is specific, which is caused by medication influencing the appetite – antipsychotic drugs, antidiabetics, insulin, beta blockers or corticosteroid treatment may lead to weight gain.

Regulation of food intake

Food intake is regulated by multiple mechanisms and under physiological circumstances it is always in balance with the rate of metabolic processes and physical exercise of particular individual. These are under control of autonomic centres located in the **ventromedial hypothalamus** (VMH). Experimental studies in animal models document that the lesions of the *ncl. arcuatus* in the VMH lead to hyperphagia and to weight gain. This is very likely associated with increased "set point" in the hypothalamus which controls fat storage. There are two main types of neurons in the VMH related to the food intake with reciprocal activity. First population - **anorexigenic neurons** are sensitive to **ghrelin, leptin and αMSH;** they suppress the food intake and they are responsible for the signal "stop eating" for the CNS. The second group are **orexigenic neurons**, which are activated by the decrease of blood glucose and amino acids levels, decrease of ATP in the neurons and they are responsible for the signal "eat" in general. They also respond to neuropeptide Y.

There is **short and long-lasting regulation of food intake**. Short-lasting regulation, so-called **"from meal to meal"** regulation, depends directly on the availability of the substrates for neurons. After food intake, the concentration of glucose and amino acids is high, substrates enter the neurons, they are utilized thus the neurons have enough ATP. After some time interval after the food intake the concentration of substrates decreases, so does the ATP in the orexigenic neurons, and they start to produce the signal EAT; therefore, the individual will perceive hunger and will eat again. Similar time intervals are seen in the regulation by **signal molecule ghrelin**, which is produced by distended stomach after food intake. Ghrelin will activate anorexigenic neurons, producing the satiety sensations and they

will prevent additional eating and further stomach distension. As the food moves slowly from stomach to duodenum, the production of ghrelin decreases, so does the satiety feeling and the balance between the neurons will be shifted again to the dominance of orexigenic neurons and the feeling of hunger will replace slowly the sensation of satiety. Cholecystokinin has similar effects.

In the long-lasting regulation of food intake and fat stores, **leptin** plays the most important role. It is a peptide and its structure is coded by "ob" gene – obesity gene, which is located at the 7^{th} chromosome. Leptin has character of a hormone and it is produced by the adipose tissue in case there is enough fat in the body stores. This peptide is transported by the blood to the hypothalamus, where it acts. If there is enough fat in the body stores, then it produces certain amount of leptin, which inhibits eating and maintains the balance of food intake and energy dispense. If the fat stores are reduced, the concentration of leptin decreases and the body will experience the sensation of hunger, followed by eating and making the new stores of the fat. This regulation obviously **does not work in obese individuals**, as they have huge fat stores, but they still keep on eating, which is not in agreement with the leptin signalling concept. They have very high leptin concentrations, but the hypothalamus does not seem to respond to it properly, which is called **leptin resistance**. There are also individuals with **mutations of the ob gene**, leading to the **leptin deficiency** and also **mutations of leptin receptor** which may contribute to the failure of leptin as a signal. Regulation of food intake and energy utilisation is influenced also by signals from the vagus nerve and nucleus of the solitary tract and higher centres of the CNS – e.g. I am not going to eat more, because I had a dinner already – some kind of conscious regulation, which does not work well in children.

Obesity and its impact on human body

As it was already mentioned, obesity represents important risk factor for many diseases; however, sometimes, in advanced processes, it is very difficult to see whether present pathological processes are direct or indirect consequences of obesity.

1) **Cardiovascular diseases** (mainly **ischemic heart disease, hypertension, stroke)** as direct consequences of atherosclerosis. Obese patients typically have high levels of plasmatic lipids, what exaggerates the process of plaque formation much faster than in individuals with normal BMI. Growing plaques and their complications (e.g. thrombosis) lead to the clinical manifestation.
2) **Diabetes mellitus type 2** is caused by insulin resistance and disturbance of insulin secretion from B cells. Adipose tissue is massive source of molecules (one of them was

named resistin) which influence the sensitivity of tissues to insulin and glucose utilisation in the insulin-sensitive cells. Therefore obesity, mainly the "apple shape", type is associated with this disease. This type of obesity also modulates the "first pass" effect of glucose through liver and it also decreases tissue sensitivity to insulin.

3) **Hypercholesterolemia and dyslipidaemia** – patients with high BMI usually have elevated plasma level of cholesterol and disturbed balance in the spectrum of plasmatic lipoproteins. There is high concentration of LDL cholesterol particles and triacylglycerides – what increases atherogenic index and a risk of formation of atherosclerotic plaques.
4) **Sleep apnoea** – disturbances of breathing during sleep are common consequences of obesity together with the syndrome of hypoventilation called Pickwickian syndrome. Accumulation of the fat on the abdomen and chest limits the movement of the rib cage and diaphragm, thus limiting the gas exchange in lungs. This leads to the disturbances in the oxygen and carbon dioxide levels.
5) **Gall bladder diseases** – patients with obesity have increased turnover of lipids – mainly cholesterol and high concentration of it in bile leads to the production of "lithogenic" bile with high tendency for precipitation and formation of crystals, which may grow to bile stones.
6) **Steatosis** – increased intake of caloric food leads to accumulation of lipid storages inside of hepatocytes, what leads to steatosis. This may however initiate inflammatory changes in liver.
7) **Gout –** patients with high BMI have also increased turnover of purines, what leads to increased production of uric acid – the final metabolic end-product. Uric acid may precipitate in joints and form salts (crystals of urates), which cause arthritis. This type of inflammation is very painful and further limits the physical activity of obese individuals.
8) **Gastroesophageal reflux disease (GERD)** – increased amount of fat in abdominal cavity and abdominal wall leads to insufficiency of anti-reflux mechanisms. This leads to the very frequent and long-lasting episodes of reflux of gastric juices into oesophagus, eventually the refluxate may be of duodenal origin. Refluxate with acid or bile causes chemical damage to oesophageal mucosa what initiates inflammation, with particular clinical presentation. Chronic GERD may lead to further complications, such as metaplasia with cancer.
9) **Depression, psychological and emotional problems** – they are usually caused by negative emotions associated with low esteem of obese individuals, mainly caused by

generalized and society-approved ideals of human body and later also by diseases, which are caused by obesity – obese patients may see them as consequences of their failure in their weight control.

10) **Musculoskeletal diseases** – mainly degeneration and osteoarthrosis of knees and coxae due to high body weight.
11) **Certain types of cancer** seem to be associated with obesity (carcinoma of endometrium, breast or colon cancer)
12) Other conditions as menstrual cycle and fertility problems.

CASE REPORTS

Case report 1

Patient is 48-years-old man, obese since childhood. He is 167 cm tall and he has 150 kg. Within couple of last weeks, he reports extreme fatigue, he cannot even move from one room to another, he is not able to perform normal daily activities, because they make him breathless. He feels extremely sleepy, but he does not feel to sleep well lately, because he cannot lie on bed normally - he can only sleep while sitting. Lying on the bed makes him extremely breathless. He suffers from headache as well.

Physical examination: Heavy obesity, patient is oriented, neurologically normal findings, breathless during examination, heart action regular 87/min, no murmurs, blood pressure 160/100 mmHg, breathing rate 24/min, on auscultation – normal vesicular breathing, no pathological phenomena. Abdomen above the chest level; palpation not possible because of obesity; lower extremities without oedema, thrombosis or varices.

Lung function tests: moderate restrictive ventilation disorder with VC at 65% of predicted values

Astrup: pH 7.35; $PaCO_2$ 8.8 kPa; PaO_2 7.6 kPa; $SatO_2$ 88%; Hbg 168 g/L, Htk 0.48

Questions & Tasks

1) What do you think is the problem with breathing during patients' sleep in this case? Why is it happening?
2) What is the ventilation problem presenting during the day (and probably also during the night)?
3) What are the mechanisms responsible for hypoxemia and hypercapnia in this patient?
4) Calculate the BMI.

5) Explain elevated haemoglobin concentration and elevated haematocrit.

Case report 2

75-years-old woman was admitted to emergency room after history of haemoptysis. She had gastric ulcers 15 years ago, then resection of a part of the intestine because of vascular ileus 8 years ago and she has had hysterectomy at the age of 45 because of cancer with following radiotherapy. Now regular gynaecological examinations, osteoporosis. When asking about appetite, she replies she lost 4 kg in last 3 months and she is having diarrhoea sometimes, mainly after milk or milk products. Chronic medication: inhibitors of proton pump, calcium supplementation, vitamin D.

Objective findings: height 174 cm, weight 50 kg, lucid, oriented, walking forward bend, asthenic, dry skin, pallor, pink conjunctival mucosa, cardiovascular and respiratory systems without pathology.

Laboratory results: Hbg 86 g/L, RBC 3.1×10^{12} microcytes, albumin 30 g/L, coagulation parameters normal, Fe in plasma 7.9, total iron binding capacity elevated, microscopic blood in stools – negative, fat, and muscle fibres in stools positive.

Chest X-ray: no pathology found; **Abdominal ultrasound:** no pathology found; ENT: reason of haemoptysis unrecognized; **Gastroscopy**: atrophic gastritis with achlorhydria; **Stomatology**: ulcers of the gingiva caused very likely by not properly made dental prosthesis one ulcer inflamed, signs of bleeding

Questions & Tasks

1) Calculate BMI

2) Which clinical and laboratory findings indicate problems with nutrition?

3) Analyse the reasons of bad nutrition in this case.

4) What type of anaemia is present in this case? What is the role of nutritional factors in pathogenesis of anaemia?

Chapter 10

PATHOPHYSIOLOGY OF DIABETES MELLITUS

Diabetes mellitus (DM) is chronic metabolic disorder caused by absolute or relative lack of insulin due to its abnormal (low) secretion or due to reduced sensitivity of tissues to insulin as a signal. It leads to impaired metabolism of carbohydrates, fats and proteins and also to mineral and water imbalances. Long-lasting and not optimally compensated DM leads to multiple organ dysfunction and damage.

Blood glucose level is precisely regulated within the interval 3.9 -5.6mmol/L – which is the normal physiological fasting level of blood glucose. It is a result of two processes. On one side, it is the **blood glucose supply** that is balanced with the other process, which is **glucose transport to tissues and its utilisation**.

Blood glucose supply follows food intake, when cleaving of polysaccharides and disaccharides in enterocytes releases glucose and enables its resorption and transport to blood. Also, glucose supply may be present in a form of intravenous administrations for treatment purposes and finally, blood glucose supply increases by endogenous production of the glucose in glycogenolysis and gluconeogenesis.

Transport of glucose to tissues is performed by insulin-dependent and insulin-independent processes. Transport of glucose by facilitated diffusion via transporters GLUT 1, 2, 3, 5 does not depend on insulin concentration/action. These transporters are located in the red blood cells, endothelial cells, testicular cells or neurons. Transport dependent on insulin is typical for postprandial phase (after the food intake) via insulin dependent activation of GLUT 4 transporter in hepatocytes, adipose cells and striated muscles.

Insulin is synthetized as the proinsulin and it is stored in the secretion granules in the β cells of the islets of Langerhans in the pancreas. During the secretion process, the proinsulin is cleaved to insulin and C peptide, which is then present in plasma in equimolar concentrations and is used as a diagnostic marker of the insulin blood concentration. The main stimulus for insulin secretion is the increase of blood glucose level. Insulin, as an anabolic hormone, is a signal for tissues and it mediates immediate, intermediate and finally delayed actions (hours). From immediate actions, the most important one is the transport of glucose to cells via GLUT 4 and transport of the amino acids to the cells as well. It is critically important to note that insulin facilitates the transport of the potassium to cells and this can have therapeutic applications in case of hyperkalaemia. This information should be

considered anytime when patient receives i.v. infusion of glucose with insulin – because of risk of hypokalaemia. Insulin has intermediate effects mainly on the muscle cells, adipocytes and hepatocytes. They are listed in the boxes below:

ADIPOCYTES

↑ Glucose uptake
↑ Synthesis of free fatty acids
↑ Synthesis of glycogen
↑ Synthesis of TAG
Activation of LPL
+
↑ Uptake of K
Inhibition of hormone sensitive lipase

MUSCLE

↑ Glucose uptake
↑ Synthesis of glycogen
↑ Amino acids uptake
↑ Proteosynhesis
↓ Proteokatabolism
↓ Release of AA for gluconeogenesis
↑ Uptake of ketone bodies
+
↑ Uptake of K

LIVER

Reduced ketogenesis
↑ Proteosynthesis
↑ Synthesis of lipids
↓ Glucose release to the blood

Long-lasting effects are mainly prolipogenic – facilitation of enzymes that participate on lipid synthesis and also growth action of insulin (mainly on smooth muscle cells in the vessel wall). Insulin in tissues binds to its receptors. It is a tetrameric protein located in the membrane of insulin-sensitive tissues, and insulin activates it. It causes phosphorylation in the tyrosine kinase part of the receptor, what further activates subsequent intracellular signalling cascades, leading to the "effects of this signal". The main effect mediated by this signal is translocation of GLUT 4 and its connection with the membrane, which allows for glucose transportation to cells.

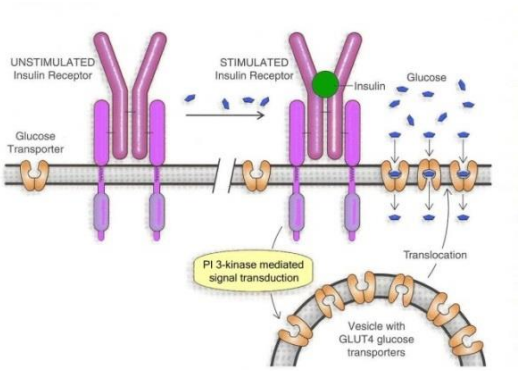


Figure 10.1: Unstimulated and stimulated insulin receptor

Lack of insulin or tissue insensitivity to it will cause diabetes mellitus. Nowadays, these complex metabolic disturbances are classified into the 4 categories:

1) **Diabetes mellitus type 1** which can be either autoimmune or idiopathic,
2) **Diabetes mellitus type 2** caused by combination of impaired secretion of insulin and insulin resistance,

3) **Gestational DM,**
4) **Other, specific types of DM**

Pathogenesis of DM type 1

Diabetes mellitus type 1 is characterized by absolute deficit of insulin, which is caused by autoimmune destruction (inflammation) of β cells, or the process is idiopathic, where we are unable to prove the presence of autoimmune process. Autoimmune type affects **genetically predisposed individuals** – who express HLA antigens type HLA DR, DP, DQ. It is supposed that genetic factors in combination with environmental factors, such as **viruses** (Coxackie B, EBV and many more) **certain food components** (stabilizers, dyes which act as toxins), **cow milk albumin** and some other factors damage the β cells surface antigens of internal components to the extent when immune system starts to recognize them as foreign and initiates the immune response towards these "new" unrecognized antigens, which in fact are the modified structures of β cells.

The first stage of disease is latent, when child has no symptoms and signs and parents are completely unaware that something is wrong. However, there is already an autoimmune process (yet unrecognized) which slowly destroys β cells. Since this process has all features of inflammation, it was given the name insulitis. Immune system is destroying cells that have been damaged by aforementioned viruses or food components. Immune cells are producing antibodies against β cells (ICA – **islet cells antibodies**), against insulin (IAA – **insulin autoantibodies**) and even against some of the intracellular components of the β cells – for example glutamate decarboxylase (GAD – **antiGAD**). These antibodies can be detected in the blood of a child and can be used as a diagnostic tool). The inflammation – insulitis – is not destructive process from the very beginning; however, later it changes to destructive type of inflammation and this leads to the destruction and, of course, deficit of β cells. The onset of clinical manifestation of insulin deficiency appears when the destruction exceeds **90% of β cells.** There is **lack of insulin, lack of C peptide and presence of antibodies in blood**.

Absolute deficit of insulin leads to onset and progression of signs and symptoms typical for DM type 1. As the typical patient with DM type 1 is a child (10-11 years of age), the first manifestation of DM type 1 is **fatigue, tiredness, decrease in school performance, polyuria, polydipsia, loss of body weight in spite of normal or even increased appetite**. Frequently, the first manifestation of DM could be straight ketoacidosis with serious metabolic condition and disturbed homeostasis, which develops due to absolute deficit of insulin

Interesting example of autoimmune type of diabetes is **LADA (latent autoimmune diabetes of adults**). It usually starts in the childhood; however, the destruction is very slow and takes years or decades to the full manifestation. LADA can manifest at any age in the adulthood, and in fact it is frequently misdiagnosed, because it is atypical to have autoimmune DM in adults. As it was described, all depends on how slow is the destruction of β cells. Therefore, not all adults have DM type 2 as it would be expected, some have type 1 LADA.

Mechanism of signs and symptoms

a) Fatigue, tiredness, decrease of school performance - these symptoms are related to energy depletion. There is a lot of glucose in the blood; however, cells are not able to utilize it properly what leads to the depletion of ATP

b) Weight loss in spite of normal or increase appetite – it is also a consequence of energy depletion. The lack of the glucose in cells leads to the utilisation of alternative resources for oxidation, which are lipids. This leads to lipolysis and reduction of the store of adipose tissue in the body. Adipose tissue is the source of important hormone leptin, which regulates food intake. In this case depletion of the leptin will activate the hypothalamic centre for food intake. Hunger and increased appetite are consequences of this signal. The subject will eat more to replenish the missing energy. Another reason for losing weight is that glucose – important energy substrate is excreted out of the body via osmotic diuresis.

c) Polyuria – glucose is osmotically active substance, which is present in glomerular filtrate at the same concentration as it is in blood. Mechanisms of tubular cells are effective in glucose resorption only to the level of 10 mmol/L – which is the tubular maximum for glucose resorption. After the glucose exceeds this concentration, tubular cells cannot uptake more glucose; therefore, it stays in tubular fluid, drags the water to the tubular lumen (osmotic process) and increases the total volume of excreted urine.

d) Polydipsia – glucose as osmotically active molecule increases osmolarity of extracellular fluid. This is detected by hypothalamic osmoreceptors which signalize “thirst” as a signal responsible for increase of water intake (pure water intake will lead to the decrease of osmolarity of extracellular fluid). Also ADH will be released; however, it will not influence the concentration process in kidneys much.

Pathogenesis of DM type 2

DM type 2 is characterized by hyperglycaemia**, insulin resistance** and **impaired secretion of insulin.** Diabetes mellitus type 2 affects mainly individuals with high BMI and genetic predisposition for this type of DM is even stronger than for type 1 and it is mainly of polygenic affection (affection of many genes coding enzymes, receptors, intracellular signals etc.).

The main pathogenetic mechanism of DM type 2 is **insulin resistance**. It is defined as a process where transport of glucose to cells requires higher concentration of insulin than normally, because tissues are less sensitive to insulin. Sensitivity of tissues to insulin can be measured by clamp technique (euglycemic clamp). In this technique, it is measured how many units of insulin we need to give to a patient with 10% glucose infusion to maintain euglycaemia. Logically in subjects with insulin resistance it will be higher than normal. However, this is not a routine test and it is not necessary to establish a diagnosis.

Reduced sensitivity of tissues can be a problem at **pre-receptor, receptor or eventually post-receptor level.** Mechanisms responsible for insulin resistance are not entirely understood, but there are several hypotheses trying to explain why and how this signal cascade is less effective. One of these claims, that individuals with IR have mutation of insulin receptor itself or mutation of the genes that encode the molecules participating on the intracellular signal processing. Mutation may relate also to the GLUT 4 molecule as well.

There is one very important relationship in pathogenesis of DM type 2. It is the link between **IR and obesity**. Obesity, mainly the apple shape type is a strong risk factor for onset of IR and DM type 2. Reduction of the body weight in obese individuals leads to considerable improvement of tissue sensitivity to insulin. Adipose tissue is a source of many molecules with signal roles. One of them is **resistine.** This is a molecule which causes IR at post-receptor level. In obese individuals with android type of obesity there is increased offer of free fatty acids for liver cells, because the visceral localisation of adipose tissue has enormous lipolytic and metabolic activity. Once hepatocytes uptake FFA, they do not need glucose any longer and this process decreases their sensitivity to insulin that would activate GLUT 4 and let the glucose to enter hepatocytes because they have enough energy already. This process decreases sensitivity of liver cells to insulin. Glucose remains in blood (it is not picked up by liver - **first pass effect**) and high glucose level reaches systemic circulation. Long-lasting hyperglycaemia leads to the “down regulation” of insulin receptor in tissues what further worsens the glucose homeostasis – mainly glucose transfer via GLUT 4 and its utilisation.

Reduced sensitivity of tissues to insulin leads to hyperglycaemia, what constantly stimulates β cells to produce more and more insulin. This situation is characterized by paradoxical hyperglycaemia and hyperinsulinemia. Exaggerated stimulation of β cells leads to **impaired secretion of insulin,** sooner or later.

Impaired secretion of insulin can be explained by several possible mechanisms. One simple mechanistic theory explains that increased demands of the body to produce more and more insulin to beat the resistance lead to exhaustion of β cells. Exhaustion (inability of β cells to produce insulin any longer) leads to absolute deficit of insulin. Another hypothesis explains that impaired insulin secretion is a consequence of deposition of a peptide amylin which is released from the islets with insulin. It is believed that amylin precipitates in interstitial space of islet tissue between the cells and capillaries, thus creating a barrier between the cells and capillaries. This barrier disables contact between cells equipped with the glucose sensor and blood in the capillaries. This process may lead to attenuated insulin production. In DM type 2, as we may understand, we are fluently going through the stage of hyperinsulinemia to hypoinsulinemia caused by the "damage or exhaustion" of β cells with impaired insulin production.

Association of **hyperglycaemia, hyperinsulinemia, hyperlipidaemia, hypertension hirsutism** (increased facial hair in women) **and apple shape obesity** has been for long considered a random pattern in subjects with DM type 2. The research clearly showed that association of these clinical and laboratory findings is not random, but they have one causative factor, which is insulin resistance. These "hypers" were given a name **"syndrome of 5H"** or **"syndrome of insulin resistance"** or **Reaven's metabolic syndrome**. In subjects with insulin resistance **hyperglycaemia** is a consequence of inappropriate action of insulin, what is logically compensated by increased production of insulin from islet cells – **hyperinsulinemia.** Hyperlipidaemia is a result of the changes present in metabolism; more precisely, body changes the order of energy resources, in case it cannot utilise glucose properly, it will activate lipolysis, to utilise free fatty acids as an alternative source of energy. **Hypertension** develops as a consequence of diabetic vascular damage – vessels are damaged by hyperglycaemia and hypertension, as it will be explained later. Vascular damage leads to the increase of peripheral vascular resistance, therefore the blood pressure. Hirsutism appears in women with "apple shape" obesity as a result of increased concentration of male sexual hormones. They are produced by the enzyme aromatase, which is abundantly expressed in the adipose tissue in visceral location. Therefore, the precursors for steroidogenesis are metabolised to produce testosterone and DHEA. Presence of the Reaven's metabolic

syndrome considerably increases risk of serious cardiovascular complications in these subjects, namely myocardial infarction and stroke.

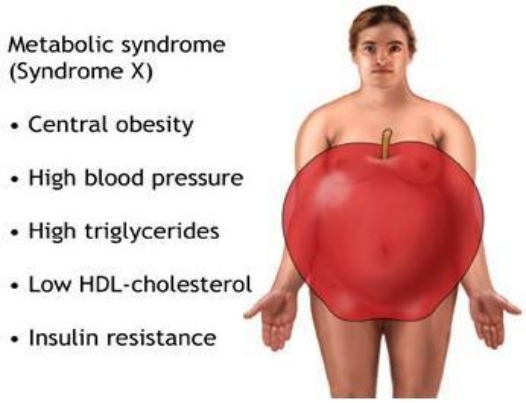


Figure 9.2: Main findings in Reaven's metabolic syndrome

Subjects with DM type 2 have some insulin in the body and even low concentration of it inhibits ketogenesis; these patients are not prone to ketoacidosis unless they have high levels of contra regulatory hormones (for example catecholamine or cortisol), which may be a result of stressful situations such as trauma, surgery, difficult life situations etc. **Symptoms and signs** in type 2 diabetics are not typical. Instead of presence of **polyuria and polydipsia** in some of the patients, majority diabetics are diagnosed only after a myocardial infarction or a stroke. A typical history may be also a presence of **repeated urogenital infections** due to immune problems these patients have (secondary immunodeficiency). Sometimes the **annual check-up by the GP** can diagnose **impaired fasting glucose levels**, leading to further tests and eventually a diagnosis.

Gestational DM

Impaired glucose tolerance or gestational diabetes itself develops typically in pregnant women with higher BMI. All pregnant women are examined in the 20th week of gestation using the oral glucose tolerance test to exclude this condition. This problem is of hormonal origin, because in pregnancy, there are hormones with the contra regulatory action when it comes to insulin. They antagonize effects of insulin. The main hormone with this ability is human placental lactogen, which causes this condition. These women have higher risk of development of regular DM type 2 later in life, but remember that impaired tolerance of glucose is a risk factor for both the mother and the foetus and if this condition has been detected, mother and foetus require more attention till the end of pregnancy.

Other specific types of diabetes

This is quite heterogeneous group of disorders which contains diseases with impaired glucose homeostasis, which cannot be otherwise classified to the type 1, type 2 or gestational group classification. This group contains conditions such as genetic defects of β cells, mutations of the insulin receptor (MODY) or diseases affecting the exocrine parts of the pancreas.

Acute complications of diabetes mellitus

Ketoacidosis is typical complication of DM 1 with absolute lack of insulin. Glucose cannot be utilised in cells and this leads to hyperglycaemia. Cells however need to cover their metabolic demands. This is the main reason that lipolysis in the body starts and it provides free fatty acids as a secondary source of energy. Their oxidation is massive source of ketone bodies – **acetoacetic acid**, **β–hydroxybutyric acid and acetone.** These molecules can release H^+; therefore, they have character of "acids" and their accumulation in ECF leads to acidosis with increased anion gap and disturbed ion and water balance. Clinical presentation includes **polyuria, dehydration, thirst, vasodilation of skin, acetone smell on breath and Kussmal type of breathing pattern,** which is necessary to compensate for the excess of the acids in body. This serious disturbance to the homeostasis may also lead to unconsciousness (acidosis impairs the permeability of the blood-brain barrier). Laboratory findings will confirm **hyperglycaemia, hyperkalaemia, presence of ketone bodies in blood and urine and presence of metabolic acidosis.**

In DM 2, where there is a bit of insulin present, this complication is rare, because insulin inhibits ketogenesis; however, it may appear as a consequence of high levels of so-called contra regulatory hormones – e.g. epinephrine, cortisol – during the stress response. In DM 2 slow increase of extracellular concentration of glucose leads to the increase of the osmotic force of ECF – hyperosmolarity. Dehydration (caused by osmotic diuresis) contributes to this state considerably. Hyperosmotic ECF leads to osmotic motion of water out of the cells, leading to cell shrinkage (intracellular dehydration). The most serious consequence of this state is **hyperosmotic hyperglycaemic non-ketogenic coma**.

Complication not of the DM itself, but rather its treatment by insulin or PAD (per oral antidiabetic drugs) is **hypoglycaemic coma**. Management of glucose level is based on the balance between the food intake, physical activity and insulin supplementation which must be perfectly learned and used by the patient to optimise his/her blood glucose level. When these three do not match (the most frequent cause is high dose of drugs or high dose of insulin)

hypoglycaemia may occur. Decrease of blood glucose level below 3 mmol/L leads to strong activation of the sympathetic nervous system, because hypoglycaemia is a strong stressor. **Sympathoadrenal stage** of hypoglycaemia is characterized by **intense feeling of hunger, sweating, palpitations, pallor, shivering and blurred vision.** These symptoms represent a warning that more serious situation may develop if the patient does not increase the glucose level – because after 10-15 min so-called **neuroglucopenic stage of hypoglycaemia** will start and this one is characterized by **unconsciousness. Hypoglycaemia unawareness phenomenon** is a relatively frequent reaction of the patients with diabetes – patient does not obtain the warning signals, mainly because of sympathetic neuropathy which develops in long-lasting or poorly compensated hyperglycaemia.

Chronic complications of diabetes mellitus

Chronic complications of diabetes are consequences of bad compensation of hyperglycaemia. The overview about the long-term compensation of DM can be evaluated according to the levels of **glycated haemoglobin HbA1c**, levels of which are high in diabetic individuals. It shows the average glucose levels in past 4 months (120 days is the life span of red blood cells). Healthy individuals have typically 2.8 to 4%, while diabetics have elevated values, and they also indicate a higher risk of chronic complications. Level below <6.5% indicates common risk, 6.5 to 7.5% indicates the risk of macrovascular complications and level above 7.5% of HbA1c indicates increased risk of microvascular complications.

Glucose cannot enter the cells via insulin-sensitive GLLUT 4 transporter; therefore, it will be utilized in other processes, which do not depend on the presence and level of insulin. **Extracellular biochemical processes** are characterized mainly by the glycation – which is non-enzymatic addition of the glucose to the amino acids in structural proteins – the products of these reactions are given the name **AGEs - advanced glycosylation end-products**. These products damage the endothelium in vessels, initiate inflammation with the subsequent migration of immune cells with "reparation" processes as well. Those unfortunately lead to overproduction of the extracellular matrix, hyalinisation, fibrotisation and sclerotisation. All of these may lead of the multiple organ damage.

Some cells (neurons, Schwan cells, endothelial cells) do not need insulin; because they have other than GLUT 4 transporters and they will utilise glucose from ECF by facilitated diffusion. In case of the **permanent hyperglycaemia**, there will always be a concentration gradient pushing glucose to cells. Many enzymes participating in "traditional"

pathways of glucose utilisation are also insulin-sensitive; therefore, in the case of its lack some other alternative metabolic processes will be activated. One of them is "polyol" pathway, in which glucose is metabolized by the enzyme **aldose reductase** – turning the glucose to **sorbitol** and further to **fructose.** Both products are osmotically active and the increase of osmolarity inside the cells drags the water to intracellular space. Although the cells have adaptive and defensive mechanisms, this process leads to permanent osmotic swelling at one side, which can cause damage, and also they have a lot of glucose but only a bit of ATP (processes leading to the ATP production are inhibited) and the cells are starving. Osmotic swelling and the lack of energy lead to the multiple organ damage.

Diabetic angiopathy

Damage to the vessels in DM patients is complex. The most important and very first process in vascular damage is the endothelial dysfunction, which is caused by the non-enzymatic glycation and the osmotic swelling of cells. The vascular damage could be classified into **diabetes-specific and diabetes-nonspecific damage.**

Diabetes-specific damage is **diabetic microangiopathy** – damage to the capillaries and the arterioles of small diameter. In the initial phase of this process, permeability of vessel wall is increased and plasmatic proteins have the tendency to leak out of them. However, they are simultaneously glycated (AGEs formation) and this leads to the deposition of the AGEs to the vessel wall. This induces inflammatory reaction with the excessive production of the extracellular matrix, hyalinisation, sclerotisation etc. At the level of capillaries, this process leads to the impaired tissue supplementation with oxygen and energy resources, which in combination with the damage of major arteries may seriously **compromise the tissue nutrition**. At the level of arterioles, mainly hyalinisation is seen and this damage is typical for vas afferens and vas efferens leading further to impaired glomerular filtration. Damage of the large diameter arteries is called **macroangiopathy.**

Macroangiopathy could be understood as extremely exaggerated process of the atherosclerosis, which affects all arteries in the body; however, the highest clinical significance is related to the cerebral and coronary arteries. Macroangiopathy belongs to the non-specific complications of DM. Of course, we can see here also deposition of AGEs and osmotic damage; therefore, this process is more complex than a simple atherosclerosis. Growth of plaques is further promoted by severe **hyper and dyslipoproteinemia**, which are also consequences of lack of insulin.

The plaques reduce the oxygen supply, may be a source of some complications such as thrombosis, and specifically in the lower extremities this problem promotes serious atrophy of skin and soft tissues and of course problematic wound healing.

Diabetic nephropathy

Nephropathy is one of the most serious microvascular complications of diabetes. Glomerulus (which is the net of the capillaries) together with the vas afferens and vas efferens are damaged by the processes explained above. Once it appears, it tends to progress through several stages to chronic renal insufficiency/failure. DM is number 4 in the list of causes leading to end-stage kidneys with the need of kidney transplant or dialysis. Progression of this process depends heavily on blood glucose levels and blood pressure, because it determines ultrafiltration pressure across the glomerular membrane. Therefore, normoglycemia and normotension are ultimate conditions in the prevention of its progress. Hyperglycaemia and hypertension facilitate the progression of nephropathy.

Main manifestation of diabetic nephropathy is **microalbuminuria**. This is a result of increased permeability of damaged glomerular membrane and with the progress of nephropathy, microalbuminuria changes to **proteinuria.** Damage to the glomerular membrane initiates "reparation" of the tissue; however, this leads to **fibroproduction and sclerotisation** of affected glomerular units. It can be diffuse or nodular, which is typical just for diabetes. Reduction of the number of fully functioning nephrons leads to the decrease of preglomerular resistance with hyperfiltration in residual nephrons. **Hyperfiltration** further contributes to the damage of the glomeruli. As it was mentioned before, this condition may lead sooner or later to the chronic renal insufficiency or failure with the need of dialysis treatment.

Diabetic retinopathy

This complication is a result of affection of small vessels providing oxygen and energy resources to the retinal tissue. Lack of oxygen and energy in retina leads to vision impairment or blindness, eventually. There are three types of retinopathy, depending on the response of the vessels to the retinal hypoxia – **non-proliferative, pre-proliferative and proliferative** type of retinopathy. Hypoxia of retina leads to production of factors, which promote growth of new vessels and branching of already existing vessels to provide more oxygen and substrates to retina. This process is called **neovascularisation**. However, these vessels are usually poorly made, with imperfect vessel wall, what predisposes them for future

ruptures. Therefore, retina of diabetic patients has parts with poor nutrition and parts with haemorrhages. It is also important to note the damage to the lens, which gets its nutrition by diffusion – glucose accumulated inside of it, or eventually sorbitol or fructose accumulation may lead to the cataract development. This changes the optical properties of the lens, decreasing the quality of the vision.

Diabetic neuropathy

Diabetic neuropathy is a specific type of diabetic complication affecting autonomic, sensory and motor nerves. There are two critical factors contributing to the damage of the nerves – **metabolic consequences of hyperglycaemia and damage of the vasa nervorum** (small arteries supplying the nerves). Vasa nervorum – small arteries are damaged by the diabetic microangiopathy (swollen endothelial cells, production of AGEs etc.); therefore, the substrate and oxygen supply of the nervous tissue is inappropriate. Lack of ATP leads to the reduced performance of affected nerves. It is supposed that the peripheral nerve damage is also influenced by the damage to the Schwan cells. These cells operate insulin-independent transporters; therefore, they have plenty of glucose. Abundance of glucose leads to the activation of so-called polyol metabolic pathway, which produces sorbitol and fructose. They are osmotically active and lead to osmotic swelling of affected cells. Swelling of the Schwan cells may considerably reduce conductivity of nerve fibres. Impairment of the **autonomic nervous system** manifests with lack of respiratory sinus arrhythmia, changes of the cough reflex sensitivity, disorders of GIT motility, problems with micturition, erectile dysfunction etc. Sensory neuropathy manifests by reduced sensitivity to tactile stimulation, later also nociceptive signalling may be reduced. It is usually symmetric and affects peripheral parts of the legs and hand (sock-like and glove-like patterns). Very dangerous aspect of sensory neuropathy is unnoticed trauma (even small injury) on the lower extremities, which may in turn lead to complicated, infected deep wounds without response to treatment. Motor nerves dysfunction is less frequent and it usually manifests as asymmetric paresis of peroneal or ulnar nerves.

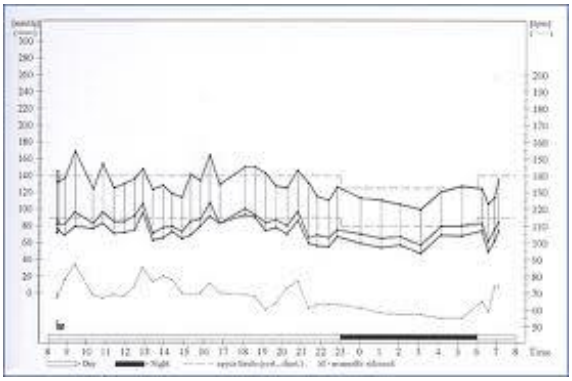
CASE REPORTS

Case report 1

45-years-old man with BMI higher than 33 attended regular check-up at his physician, who had measured increased BP (160/100 mmHg). Even though the patient does not

complain about any subjective health problem, given positive family history (mother had died due to MI and father due to stroke) the GP ordered blood tests and recommended repeated BP measurements.

Laboratory results: Na 146 mmol/L; K 4.5 mmol/L; Cl 97 mmol/L; AST, ALT normal; GMT and ALP slightly increased; glucose 8.4 mmol/L; creatinine 97 μmol/L; urea 4.8 mmol/L; cholesterol 6.7 mmol/L; TAG 3.2 mmol/L. 24h blood pressure monitoring (Holter) revealed increased BP during the day with decrease during sleep.



BP recording

Due to android obesity, high BP, hypercholesterolemia and hypertriacylglycerolaemia and increased fasting glucose levels the patient was referred to diabetes specialist for further examination.

Questions & Tasks

1) Define insulin resistance syndrome.

2) Explain how hyperinsulinemia can contribute to increased BP.

3) What consequences can combination of increased levels of lipids and high BP have on organism as a whole? What type of vascular complications would be expected in given patient?

4) Does the finding of fasting glucose level 8.4 mmol/L mean that the patient has diabetes mellitus?

5) Define relationships between obesity – insulin resistance and hypertension.

Case report 2

Patient is 56-years-old man, is being treated for DM type 2, taking his PAD and on diet. Recently, he reported headaches, fatigue, thirst and frequent urination. Intensity of these problems increased 2 days ago after a traffic accident.

Physical examination: patient is sweating, has warm red skin; objective signs of dehydration, decreased skin turgor, dry tongue; acetone smell on breath; BP is 100/60 mmHg, HR 110/min

Laboratory examination: glucose 30 mmol/L; Na 130 mmol/L; K 6.9 mmol/L; Cl 112 mmol/L; pH 7.19; $PaCO_2$ 5.0 kPa; HCO_3^- 12 mmol/L; BE = -7 mmol/L;

Questions & Tasks

1) Which laboratory parameters are outside their reference values?

2) What complications of diabetes mellitus is indicated by manifestation, objective findings and laboratory examination results? How would you explain the presence of this complication in patient with DM type 2?

3) Why is partial pressure of CO_2 decreased?

4) Analyse which mechanisms contribute to changes of Na, K and Cl levels in this particular case.

5) How could we determine if kidneys are involved in compensation of metabolic acidosis?

Chapter 11

PATHOPHYSIOLOGY OF THE STRESS RESPONSE

The term stress is frequently used nowadays in the modern society, because it is a part of everyday life of millions of people and reducing their quality of life. Many factors affecting the human body from the outside are considered to be innocent or having positive effect, supporting development or skills and health of an individual. People are looking for many of those, because they induce joy, happiness, success from the achievement of designed objectives. Anyways, there are still factors influencing the human body in an opposite way, because of the character or strength of these factors, which appear to be inappropriate for the particular individual; however, these factors can be absolutely normal for other individual. These factors are perceived as unpleasant and to cope with them, one needs to mobilize his/her intellectual and energy resources and also to change the behaviour to survive given unpleasant conditions.

These factors influencing the body in a negative way are called **stressors** and the reaction they induce in the body is **stress**. From the type of the response of the body we can distinguish **eustress** (good stress), which is characterized by the positive cognitive response to the stressor, with positive physical and psychological effects (e.g. preparation for an exam and passing it with the good results). The "eustress" – positive response to the stressor depends on the individual's perception of stress. Negative impact of the stressor, if it has high magnitude or exposure to it is long-lasting, is called **distress** – and this is actually the type of stress response, which has adverse effects on an individual (in case it is not compensated).

The field of the stress response was systemically studied by American physiologist Walter B. Cannon and in 1915 he described the reaction **"fight of flight"**. The objective of his study was the function of autonomic nervous system during stress. Hans Selye continued and extended those studies and he described **"general adaptation syndrome"** as a non-specific response of the body to considerable exogenous factors. He was the first one who used the term **stress** to name and explain changes in the body of an individual exposed to "potentially dangerous" exogenous factors. These factors were aptly named **stressors.**

Stressors and stress

Searching for the exact definition of stress may not be successful, because there are many definitions, mainly partial and subjective definitions. The reason is that stress is highly subjective phenomenon. Selye has defined stress as a complex of non-specific regulatory mechanisms and responses of the body which are activated in case of the risk of homeostasis disturbance by stressors. The final response is determined by the integrated function of central nervous system, endocrine system and immune response.

Types of stressors

- **Somatic** (physical – cold, heat, noise, vibrations and pathological processes – hunger, thirst, immobilization, haemorrhage, inflammation, extreme physical exercise, hypoglycaemia and others)
- **Psychological** (transient tension, public speech, sleep deprivation, work overload, unemployment, fear, frustration, death of close relatives, retirement, political issues, serious life events, painful memories etc.)

Majority of somatic stressors also includes the psychological component. The final response to stressors depends on the quality (nature) and quantity (strength) of stressor, age, physical and psychological condition of an individual, his/her personal experiences, abilities and actual health status.

Classification of stressors

There are several classification criteria of stress. According to the duration of exposure, **acute** or **chronic stress** can be distinguished. Based on the type of the stressor that has caused it, stress could be **somatic** or **psychogenic**. In the phylogenetic process, early humans were exposed mainly to acute and somatic stress. This response was necessary to survive in dangerous conditions (climate changes, long distance moves, lack of food, water etc.) Today, people are exposed mainly to psychogenic chronic stress related to lifestyle. However, changes and reactions of our bodies are the same despite the character of stressor.

Stress response

Stressors from outer environment are detected via sensory organs or exteroreceptors, stressors from the inside of the body are detected via interoreceptors – chemosensors,

baroreceptors, nociceptors etc. Information about the exposure to stressor is conducted by afferent nerve fibres (pathways) to central nervous system, where it activates particular sensory areas (noise activates acoustic cortex, pain activates somato- or viscerosensory cortex etc.) and simultaneously, this information is integrated in **amygdala**. This is the structure of CNS which participates in perception of emotions, and if the information is identified as "dangerous" it is sent to **hypothalamus,** which is the centre of the stress response. It communicates with all body structures via the autonomic nervous system, which consist of two partially antagonistic parts – **sympathetic** and **parasympathetic systems.** Sympathetic part of autonomic nervous system initiates the flight of fight response and it provides the body with the energy resources to handle this demanding situation. Parasympathetic part works as a brake, which is activated when the exposure to stressor is terminated and it supports the achievement of the previously established "homeostasis" which has changed according to sympathetic signalling. Homeostasis during the stress response is called **allostasis** and some values are temporarily changed for a purpose – for example – normal glucose level is up to 5.6 mmol/L in normal condition, whereas during stress the glucose level is elevated – this is not considered to be pathological, but necessary; as the body needs more resources.

After the activation of the sympathetic system achieved its peak, another powerful system is activated – and this is the axis **hypothalamus – pituitary gland – adrenal gland**. This axis represents integrated neuro-endocrine response and it plays the key role in the coping during the stress response. Nerve system integrates and regulates the interaction between the individual and the neighbouring environment. The main role of endocrine system is to maintain homeostasis (allostasis). Both systems work with the purpose of maximization of the body response to stressors. **The main role of the nervous, endocrine, circulatory and metabolic changes during the stress reaction is mobilization of energy resources, their transport to tissues with the predominant supply for the brain, heart and muscles and to maintain volume of circulating fluids – homeostasis (allostasis)**.

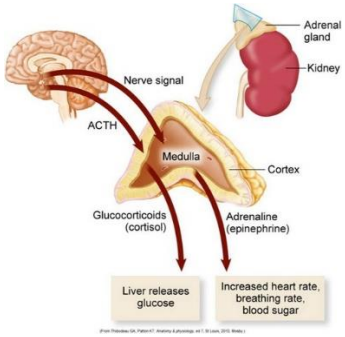


Figure 11.1: Alarm stage of the stress response

During the stress response, cortisol released from adrenal cortex is transported to liver, where it stimulates production of glucose and epinephrine released from the adrenal medulla increases heart rate, breathing rate and also increases the glucose level.

Neuroendocrine stress response

First stage of the stress response is **alarm stage**. Dominant feature of this stage is the activation of sympathoadrenal system with production of catecholamines – epinephrine and norepinephrine, which are released form adrenal medulla and also postganglionic sympathetic nerve terminals. They are the most important mediators of this stage. Level of catecholamines increases not only in peripheral tissues, but also in the CNS. Majority of cells express adrenergic receptors and the final effects of catecholamines depend on the type of receptor activated by catecholamines – leading to changes of the many physiological functions. Increased concentration of epinephrine in the CNS has the effect on the neurons located in the **paraventricular nucleus of hypothalamus** and it leads to the release of CRH. This signal molecule is transported via the portal hypothalamo-pituitary circulation to the anterior pituitary gland, from where it releases proopiomelanocortin (POMC). This is a precursor for ACTH; however, ACTH is not the only active signal produced by fragmentation of POMC. Circulating ACTH binds to membrane receptors of cells in adrenal cortex and it regulates production of glucocorticoids – main representative in humans is cortisol.

Sympathetic nervous system (SNS)

Catecholamines released by activation of SNS mediate their effects via adrenergic receptors distributed in tissues. They produce constriction of vascular smooth muscles in the peripheral circulation what leads to vasoconstriction and this increases peripheral vascular resistance and blood pressure. On the contrary, muscular arteries are well perfused. They have relaxing effect on smooth muscles in respiratory system, increase respiration, cause mydriasis and they considerably influence the action of heart – they increase the cardiac output via increasing contractility and heart rate. In metabolism, catecholamines induce glycogenolysis, lipolysis and release of free fatty acids from the pool in adipose tissue. This is another important resource for energy production. They also decrease production of insulin, increase concentration of glucagon and they block uptake of glucose by muscles and peripheral tissues (Fig. 11.2).

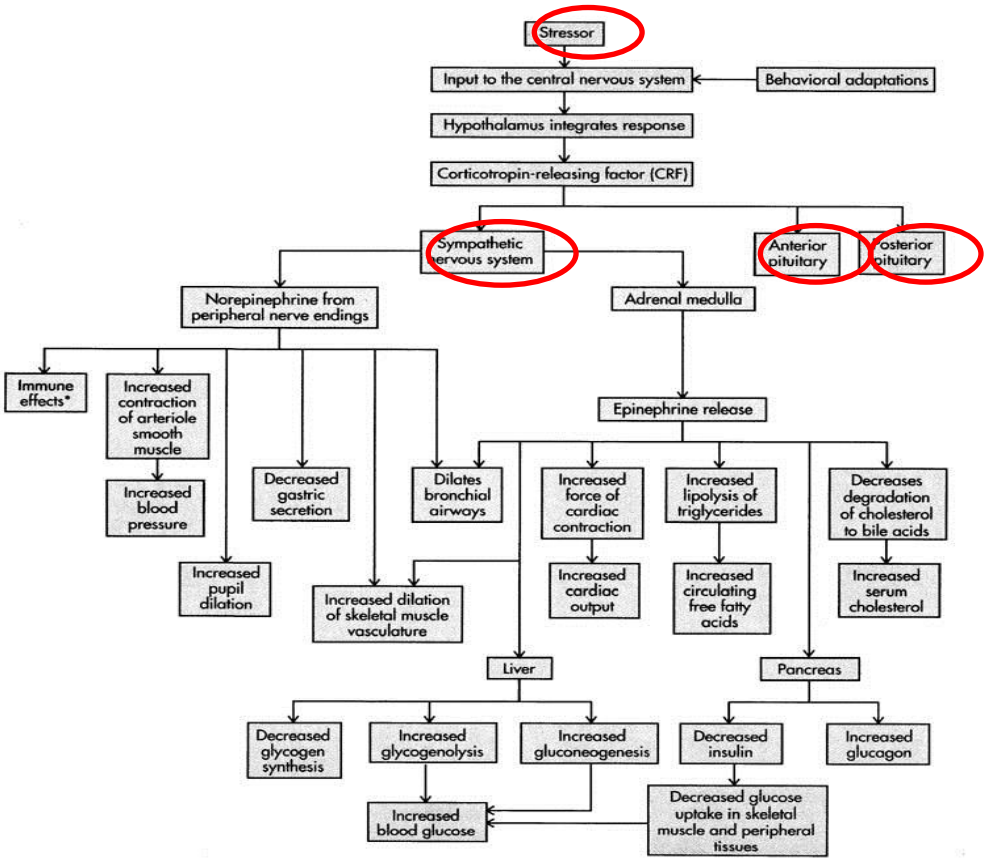


Figure 11.2: Neuroendocrinne response during the stress – part 1

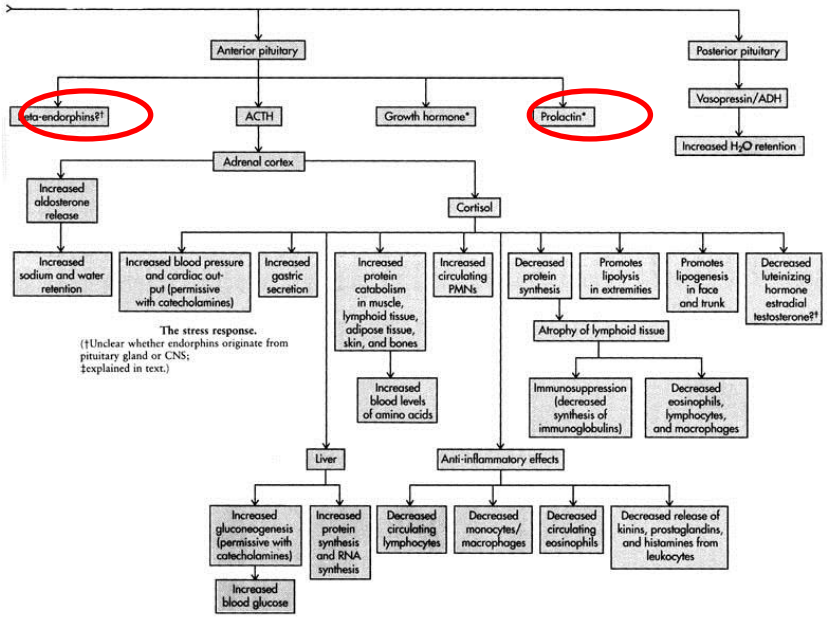


Figure 11.2: Neuroendocrinne response during the stress – part 2

Special type of stress response could be seen in animals, which is called **"Freeze or Feigned Death".** This can be also a form of adaptation/alarm stage in an individual who can somehow avoid "stress response" or be able to cope with it with successful outcomes.

Role of pituiary gland in stress response

Anterior pituitary gland produces **ACTH** during stress response and as it was mentioned already, this is one of the active fragments of the POMC molecule. Another active molecules produced by anterior pituitary are beta endoprhins, STH (growth hormone) and prolactine. **ACTH** binds to membrane receptors at cells of adrenal cortex and increase their activity. The main action achieved by the ACTH is production of **glucocorticoids** – mainly **cortisol,** and partially they induce production of mineralocorticoids. Their main action is resorption of Na^+ and water in renal tublar cells – therefore hormones of adrenal cortex in stress also contribute to the positive water balance. The main action of cortisol, however, are effects important in the second stage of the stress – **stage of resistance**. Cortisol increases blood pressure and cardiac output with permissive effect of catecholamins. Primary effect of cortisol is stimulation of gluconeogenesis (production of glucose from aminoacids and glycerol in liver). Cortisol contributes to the elevation of blood glucose level supported by epinephrin, glucagone and growth hormone. Cortisol further influences metabolism of proteins – increases production of proteins in liver, but on the other side it has catabolic effect on muscles, lymphatic tissue, skin and bones. This may lead to the nagative nitrogen balance with increased level of circulating ammino acids. The suppressive effect on imunity is mediated via supression of proteosynthesis including immunoglobulins; cortisol reduces population of eosinofils, lymphocytes and macrophages; it inhibits release of kinins, histamine and prostaglandins. In GIT, cortisol stimulates secretion of the gastric juices, it also has an effect on lipolysis of adipose tissue in extremities; however, it promotes lipogenesis in the face and in abdominal visceral region. Cortiol also supresses the release of thyroid hormones, LH, estradiol and testosterone.

Another hormons released during the stress response are **beta endorphins**. They belong to the group of endogenous opiates, which have mainly protective effcet, increase treshold for pain; they also have analgetic effect, stimulate positive mind and mood, even leading to euphoria.

Glucagone, the hormone of the energy deficiency, antagonist of insulin, increases gluconeogenesis and glycogenolysis. STH **(growth hormone)** increases the transport of

ammino acids to musles and proteosyntheis in muscles. It is important protective factor, as it protects muslces aginst proteocatabolism. Prolactin has effects similair to growth hormone; however, it cnsiderably supresses the function of gonades. The newest data showed that prolactin has an effect on production of immunomodulatory cytokines and factors activating lymphocytes, therefore prolactine has imunoprotective effect during the stress response.

Posterior pituitary gland in the stress response

Activation of posterior pituitary gland during the stress response is asociated also with the release of the **ADH** (vasopresin) and its release is modulated by corticoliberin. This hormone increases resorption of water in distal nephron and increases peripheral arterial resistance. Optimisation of the water balance has significant effect on subjects in stress.

Intensity of the stress response is regulated

Intensity of the stress response is regulated by the principle of **antagonism.** It means that stress response must have its limits. Strength of the stress response represented by the axis **hypothlamaus - pituitary gland - adrenal gland** is regulated by neural and hormonal mechanisms, which can be called **"antistress" system**. This system is activated simultaneously with the stress response and the result of this antagonism is the control of levels of corticosteroids at a tolerable level. Antistress system consists of these three negative feedback loops:

a) inhibition of pituitary gland, hypotalamus and hippocampus by the levels of cortisol in blood

b) inhibition of hypothalamus by increased level of CRH in blood

c) inhibition of hypothalamus by the direct action of CRH

Stress and allostasis

Allostasis is the term which was introduced to the stress field in the 1988 and it means "adaptational change" (or modulation) of the stress response with the purpose of achievement of stabilisation state of the organism. Term allostasis characterizes the process which maintains the "homeostasis" by its adjustment to the new requirements (adaptation). It is a basic process which organism uses to actively adapt to the currently exisitng situation and also to expected and unexpected processes. It is the stage of resistance, just termed differently. Allostasis means that body is adapted to the extra load and can normally operate in it even without serious problems or tissue damage. **Allostatic load** means that

adaptation to the given stressor is not possible any longer wihout considerable danage to the tissues or body systems. The result is the onset and progression of pathophysiologcal processes, which may possibly lead to diseases (dysregulation).

Stress as the risk factor of diseases

The main role of the stress response is to increase preparedness of the organism and its ability to perform huge physical activity, activate defensive mechanisms and to provide optimal and satisfying energy resources in case of energy depletion which is for example typical for animals in the nature during intensive physical activity and starvation.

Humans in modern society are mostly exposed to the **chronic mental stress** with elevated concentrations of certain hormones, glucose and lipids in blood – however, without propper compensation of these conditions. Frequently, mental stress is followed by the **unhealthy lifestyle** with lack of physical exercise, smoking, alcohol abuse, and lack of sleep. These factors are responsible for progressive failure of defensive and compensatory mechanisms, what leads to the all spectrum of so-called civilisation diseases. Stress is not the main pathogenetic factor; however, it plays an important role in their pathogenesis.

Cardiovascular diseases

They are for example ischemic heart disease, systemic hypertension, dysrrhythmias, and many more. Mechanisms leading to cardiovascular problems are complex. It is a combination of the **catecholamin effect** on heart what increases inotropic and chronotropic state of the heart. Oxygen consumption and oxygen demands of myocardial cells working under catecholamin signalling is increased and tachycardia may lead to the relaxation impairment of cardiomyocytes. Majority of patients with chornic stress have **advanced atherosclerosis**, not only because endothelial damage caused by elevated blood pressure (typically in the chornic stress subjects), but also due to accumulaiton of lipids in the vessel walls (hyperlipidemia as a part of metabolic consequences of the stress response). Catecholamines are responsible for the increased risk of **thrombosis,** because they shift the balance in coagulation system in a direction to “trhombogenic” state.

Systemic hypertension is caused not only by catecholamines as it would seem, but also by high level of cortisol. Since cortisol is a glucocorticoid, 10% of its action is mineralocorticoid – meaning that cortisol participates in resorption of Na^+ and water in distal tubules.

Long-lasting stress may also lead to hemoconcentration (stess polyglobulia) and high hematocrit is an independent risk factor for cerebral ischemia and/or stroke. Psychosocial stress may be a trigger of heart attack (myocardial infarction) in subjects with ischemic heart disease.

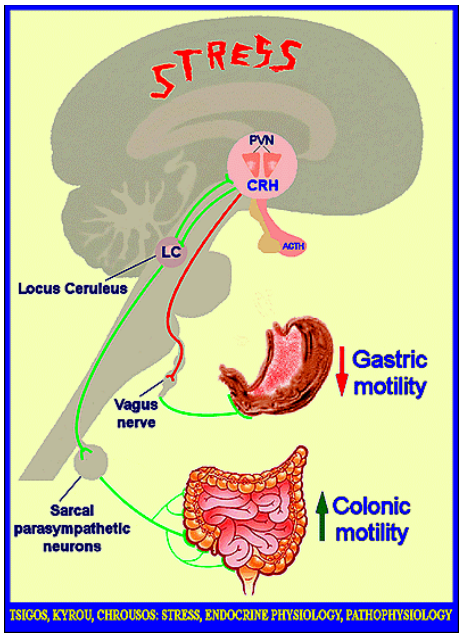
Disorders of musculoskeletal system

Chronic stress leads to mucles problems, because stress response increases the muslce tone (for fight or flight), including postural muslces (back, shoulders, neck muscles) what in turn reduces the blood supply of these muscles. This leads to their stiffness and pain.

Immune disorders

Chronic stress has nagative influence on the immune system. Dysfunction manifests by repeated infections of the upper or lower airways, urogenital infections, allergies, autoimmune disordes, eventually infected skin leasions and impaired healing – immundefficiency. The main reason for the onset and further progressin of immune problems is high level of cortisol, which is known to have supressing effects on imune system.

Gastrointestinal disorders



Stress induces short-lasting and long-lasting changes in the GIT. Exposure to stressors leads to the activation of so-called “brain-gut axis” what results to series of pathological changes in the GIT, for example inflammatory diseases, irritable bowel syndrome, peptic ulcer, GERD and many more. Stress reduces gastric motility what may lead to the delayed emptying, but it increases motility of the bowels.

Figure 11.3: Stress impact on GIT

Mental stress increases production of HCl; however, this response is strongly influenced by the personality of an individual. Choleric people usually react with the increase of acid production, which is not usually seen in subjects with phlegmatic type of personality.

Stress also reduces production of mucus covering and protecting the gastric mucosa against gastric juices (pepsin and HCl) and it reduces regeneration ability of epithelium as well. Stress reduces perfusion in gastric mucosa via sympathetic receptors, which is very important protective factor and also influences microbial flora. Imbalance between aggressive factors and protective factors usually leads to mucosal erosions in stomach or stress peptic ulcers. Majority of the GIT problems "caused" by stress are the manifestation of "brain-gut" axis. Mast cells are able to transduce the stress signal to the GIT by production of neurotransmitters and pro-inflammatory cytokines.

Gonadal dysfunction

Gonadal dysfunction is the consequence of stress impact on the axis hypothalamus – pituitary gland – adrenal gland. In general, it is known that **activation of this axis suprsses the reproduction system.** This response has a sense, because unfavourable or dangerous conditons (climate changes, hunger, stravation etc.) which generally induce stress, would not represent a good environment for reproduction. In men, chornic stress supresses and in most serious situations completely inhibits spermatogenesis (hypogonadism). In women, functional **hypothalamic amenorrhoea** is very frequent disorder, as well as infertility, premature labour and other sexual/reproductive dysfunctions.

Endocrine diseases

Other diseases pathogenesis of whose is considerably influenced by chronic stress is for example DM type 2 – this disorder is characterized by impaired utilization of glucose due to **insuline resistance and dysfunction of beta cells**. Cortisol is the hormone, which is "**contraregulatory"** hormone to insulin and its main action is to stimulate gluconeogenesis and reserve the glucose as energy resource for brain, which is mediated by "prevention" of the glucose up-take by peripheral tissues. Insensitivity of peripheral tissues to insulin is called **insulin resistance**.

Chronic stress related disorder with the endocrine background is also **obesity.** It is characterised by the **gain of body mass index with increased amount of fat**. Stress may contribute to the obesity by sevral mechanisms. **Beta endorphins**, which are produced from the pituitary gland have **"polyfagic"** effect in general (polyfagia means increased food

intake), and this is further promoted by **cortisol.** The main fucntion of this increased eating is to provide the energy for the body which will either **fight or flight**. Unfortunatelly, stress nowadays does not represent physical type of reaction, so the energy cannot be utilized for the muscle work. It is therefore stored in the body in a form of adipose tissue. Mental stress is usually associated with negative emotional background (e.g. fear, anxiety). According to the newest studies, food is one of the modern "anxiolytics" or antidepressants people use to supress these negative emotions, even though it may lead to the obesity, bulimia, anorexia nervosa or other serious diseases.

Disorders of CNS

Stress has both **positive and/or negative effect** on the CNS. **Acute stress** of mild-to moderate intensity with only slightly elevated levels of cortisol in the blood leads predominantly to activation of corticosteroid receptors type 1 (located mainly in hippocampus). This process promotes **long-lasting potentiation** of the synaptic transmission (LLP – long-lasting potentiation) and there are studies showing that this process is important in consolidation of memory. However, **chronic**, mainly mental stress with very high level of cortisol leads to the activation of the corticosteroid receptors type 2 in the hippocampus and it leads to the inhibition of LLP and **memory problems**. LLP is considered to be important mechanism responsible for memory and learning. Therefore, chornic stress influences mainly thy hippocampus – the structure of the brain responsible for memory and learning, because hippocampal neurons express high amount of corticosteroid receptors. **Corticosteroids in very high concentration appear to be "toxic" for these neurons and lead to their irreversible damage**. Chronic stress is further characterized by the loss of congnitive functions in subjects with Cushing syndrome, post-traumatic stress disorder, hypothyroidism, Alzeheimer disease and depression. Chronic stress in certain professions may lead to the burn out syndrome - more info available on www.hindawi.com/journals/isrn/2013/806104/

CASE REPORTS

Case report 1

Submissive university graduate has her first public talk at a conference. Although she did prepare for the talk, immediately before the talk itself she is anxious and frightened. She had diarrhoea in the morning, was urinating quite often and she lost her appetite. She was stiff during her talk, heart was racing; her hands were cold, she was sweating profusely, her

hands were shaking and she stuttered a few times because she had trouble remembering the text of her slides. She also had dry mouth and after the talk she did not remember the discussion. She has also digestive problems with stomach ache for quite some time and also acne – which is a big handicap for her.

Questions & Tasks

1) Describe all signs and symptoms in this patient.

2) Explain the pathomechanism of her stress reaction.

3) During stress response in this patient, disturbances of focus, memory and speech occur as well as trembling. Explain the mechanisms of these signs.

4) What other signs and diseases are of high risk in this patient?

5) Hyperventilation syndrome with chest pain is frequent functional disorder in acute stress. Describe the mechanism of this syndrome and its influence on acid-base balance disturbance with its consequences.

Chapter 12

PATHOPHYSIOLOGY OF CIRCULATORY SHOCK

Shock condition, whatever its cause, is characterized as a syndrome initiated by acute systemic hypoperfusion, which leads to tissue hypoxia and acidosis and subsequently to the dysfunction of vital organs, if shock is not treated.

Definition

All types of shock are characterized by inadequate tissue perfusion, compared to their metabolic requirements. Organ hypoperfusion causes cellular hypoxia, accumulation of metabolites that cause **metabolic acidosis** and later organ damage, which is referred to as multiple organ failure.

The development and progression of shock depends on disorders of the cardiovascular system, which can be characterized as an **imbalance between the volume of circulating fluid and capacity of vasculature.** The disparity may arise either from a sudden loss of intravascular fluid volume or sudden expansion of blood vessels caused e.g. by vasodilation. Progressive and final phases of shock are mainly related to disorder and **disintegration of microcirculation**. However, damage affects not only cardiovascular system, but also other body systems are affected by generalized hypoperfusion. Progressive stage of shock is characterized by severely damaged kidneys, lungs, intestinal system, brain and heart.

The **severity of the shock** results from a situation where progressive shock that is not corrected, results in the disruption of energy and metabolic processes (shock itself produces more severe shock) and ends with death. Metabolic changes such as energy failure (↓ ATP), metabolic acidosis (lactate↑) and dominance of catabolism develop.

It is important to distinguish two different situations – **collapse (syncope)** and **shock.** Collapse is also caused by acute circulatory insufficiency. The difference is that in collapse, failure of circulation leads to hypoperfusion of central nervous system with short-term self-limiting loss of consciousness. After the body fall, circulation returns to norm and consciousness is regained. Compared to the shock, **there is not sufficient time to develop a tissue hypoxia and metabolic acidosis**. The most common causes of collapse are reflex collapses or so called **non-cardiogenic** - (vasovagal, or orthostatic collapse – a sudden

change from lying down to standing, where the insufficient vasomotor regulation holds blood in the lower extremities, thereby reducing venous return.) E.g. short-lasting disturbances of cardiac rhythmogenesis cause **cardiogenic collapse**, which is more serious, and must be carefully examined.

Clinical manifestation of shock

The patient in shock is typically ash-pale, has sweaty cold skin, the pulse is weak and very fast, superficial veins are collapsed. The patient is very weak (often unable to sit up from a lying), complains of thirst, disorientation, shallow and fast breathing is present and body temperature falls. The patient has low blood pressure, low urine output and metabolic acidosis develops. In advanced stages, patient gradually loses consciousness, the heart is weakened, kidneys cease completely to produce urine, the lungs lose their ability to oxygenate arterial blood and excrete CO_2, stomach and intestines do not function properly and barrier function of gastrointestinal system is lost.

Classification of shock

Shock is identified in most patients by hypotension and inadequate organ perfusion, which may be caused by either low cardiac output or low systemic vascular resistance. Circulatory shock can be **subdivided into four distinct classes** based on the underlying mechanism and characteristic hemodynamics, as follows:

1) **Hypovolemic shock**
2) **Distributive shock**
3) **Cardiogenic shock**
4) **Obstructive shock**

Despite the different mechanisms of hemodynamic disorders and different types of shocks all lead to one serious consequence - **progressive failure of microcirculation.**

Shock	Mechanism	Main hemodynamic problem
hypovolemic	loss of intravascular fluid	↓ venous return & therefore ↓ cardiac output
septic (distributive)	generalized vasodilation	hyperdynamic circulation with low peripheral resistance

cardiogenic	failure of the heart pump	↓ cardiac output
obstructive	sudden obstruction of the large vessels close to the heart (e.g. vena cava, aorta)	↓ cardiac output

Hypovolemic shock

It is a consequence of the loss of more than 30% of the body fluids, specific type of hypovolemic shock is haemorrhagic shock. Hypovolemic shock results from an absolute deficiency of intravascular fluid volume.

1) Intravascular volume loss - gastrointestinal loss, burns, diabetes insipidus, severe sweating, third spacing.
2) Loss of plasma or interstitial fluids in extensive burns.
3) Haemorrhage - blood loss – trauma (external or internal bleeding).

Physiologically, rapid **loss of intravascular volume reduces ventricular preload**, resulting in decreased stroke volume and cardiac output. The result is a reduction in blood pressure (mainly systolic). The involvement of compensatory sympathetic vasoconstriction in the initial phase of shock keeps blood pressure at a level to **protect coronary and cerebral blood flow** (centralization of circulation). By contrast, there is significantly worse perfusion and oxygen supply in other tissues.

In addition, a haemorrhagic component may reduce haemoglobin, resulting in decreased oxygen content (CaO_2). **Haemorrhagic shock reduces both CaO_2 and preload**, resulting in decreased oxygen delivery to the tissues. Specific type of hypovolemia is third spacing or capillary leak syndromes. These two lead to the leak of the fluid out of the intravascular space into the interstitial space. Aetiologies include burns, crash syndrome, sepsis, and other systemic inflammatory diseases. Patients with such aetiologies may appear "puffy" and **total-body fluid overloaded while actually being significantly intravascularly depleted** with inadequate preload and in significant shock.

Cardiogenic shock

Cardiogenic shock is caused by the failure of the heart as a pump with severe reduction of cardiac output in subjects with normal vascular volume and normal preload. The most common causes are e.g. **myocardial infarction when more than 40% of the left ventricle** is affected. Other causes are represented by **severe tachycardia** (180-200 bpm),

severe bradycardia (30 and less bpm), and **sudden severe heart valve problems**. Cardiogenic shock has high mortality, because the organ, which usually compensates for impaired circulation, is affected, therefore the compensation is not possible or severely limited. Moreover, compensatory mechanisms such as tachycardia, vasoconstriction or volume retention in kidneys are unsuitable, because they have negative effect on heart already affected by primary pathological process.

Obstructive shock

Obstructive shock is caused by obstruction of vessels close to the heart not the heart itself, however, cardiogenic and obstructive shock have very similar clinical presentation with the severe reduction of cardiac output. In obstructive shock, the heart is not primarily affected, decreased preload or increased afterload limit its optimal performance. Causes leading to the obstructive shock are for example **occlusion of vena cava inferior** (compression or clamping by tension pneumothorax), then **pulmonary embolism** affecting more than 50% of pulmonary vasculature, **pericardial tamponade, or aortic dissection.** Major obstruction in the central heamodynamics influences either preload or afterload, therefore the cardiac output becomes considerably reduced.

Distributive shock

In certain clinical states, normal peripheral vascular tone becomes inappropriately relaxed. Common causes include **anaphylaxis, neurologic injury, sepsis, and drug-related causes**. Such vasodilation could **increase venous capacitance**, resulting in a relative hypovolemia even if the patient has not actually lost any fluid. However, the common physiologic disturbance that affects oxygen delivery in all forms of distributive shock is a **decrease in preload** resulting from **inadequate distribution of effective intravascular volume as a result of massive vasodilation**. Some types of distributive shock are characterized by vasodilation and **drop of resistance in arteriovenous anastomoses** (meta-arterioles). Blood flow is redirected through these vascular structures instead of capillaries. Since the blood is passing-by microcirculation, tissues do not have enough oxygen.

Common causes of distributive shock are **anaphylaxis** - immediate hypersensitivity reaction mediated by IgE crosslinking with the antigens, leading to the massive systemic degranulation of the mast cells with release of histamine, **neurologic causes –** injury of the CNS that disables vasomotor regulation, which leads to the vasodilation (e.g. head injury, spinal shock).

Septic shock (the most important subtype of distributive shock)

Systemic inflammatory vasodilation due to sepsis causes a decrease in peripheral vascular resistance and opening of arteriovenous anastomoses. The most common causes leading to sepsis is a bacterial infection of burned tissue, cholecystitis, peritonitis, pyelonephritis, and gangrene. The patient has red warm skin due to fever (to be distinguished from other types of shock). Despite the increase in cardiac output patient is hypotensive (notably the reduction in diastolic pressure). Hypotension persists despite adequate intravascular volume replacement, which is another typical feature of septic shock. Systemic inflammatory involvement of the microcirculation rapidly progresses to intravascular coagulopathy (disseminated intravascular coagulation), and following **severe tissue hypoxia leads quickly to multiple organ failure**.

Stages of shock

Following phases are characteristic for hypovolemic shock and they differ significantly e.g. from phases of septic shock. The causes of shock lead to a critical insufficiency of microcirculation, which would lead inevitably to death without compensatory responses. In the phase of shock when compensatory reactions become insufficient, shock progresses and without anti-shock therapy leads to a fatal outcome.

Initial phase (compensated response)

The human body responds to acute volume loss by activation of compensatory mechanisms in the cardiovascular, renal, and neuroendocrine systems. These responses act to systematically divert circulating volume away from non-vital organs so that **blood volume may be conserved for vital organs.**

Acute volume loss causes **decreased cardiac output** and decreased blood pressure. These changes are detected by baroreceptors in the aortic arch and atrium. With a decrease in the circulating volume, weakened arterial baroreflex cause an **increased sympathetic outflow** to the heart and other organs. The cardiovascular system initially responds to hypovolemic shock by **increasing the heart rate and myocardial contractility, and constriction of peripheral arteries/arterioles.** The cardiovascular system also responds by redistribution of blood. Heart and central nervous system are rather well perfused, while other organs are hypoperfused due to vasoconstriction.

It is important to note that vasoconstriction may considerably reduce hydrostatic pressure in the capillaries mainly in the GIT and according to the Starling balance, fluid **will move from the interstitial space to the capillaries compensating for the volume loss.**

Concurrently, a **multisystem hormonal response occurs.** Corticotropin-releasing hormone is stimulated directly. This leads to glucocorticoid and beta-endorphin release. **Vasopressin** from the posterior pituitary is released, causing water retention at the distal tubules, the collecting ducts, and the loop of Henle. **Renin is released** by the juxtamedullary complex in response to decreased mean arterial pressure and increased sympathetic tone, leading to increased aldosterone levels and eventually to sodium and water resorption.

In addition to these global changes, many **organ-specific responses** occur. The brain has remarkable autoregulation that **keeps cerebral blood flow constant** over a wide range of systemic mean arterial blood pressures. The kidneys can tolerate a 90% decrease in total blood flow for short periods of time. With significant decreases in circulatory volume, intestinal blood flow is dramatically reduced by splanchnic vasoconstriction.

The main compensatory mechanisms are **vasoconstriction with redistribution of the blood to the vital organs, tachycardia, thirst, resorption of water from the interstitial space to the capillaries, resorption of water in the kidney** mediated by **aldosterone** (Na^+ and water) and **vasopressin** (only water). These compensatory mechanisms can only occasionally improve the circulatory volume. The fluid resuscitation is usually necessary to restore the circulation through all capillary beds in the body.

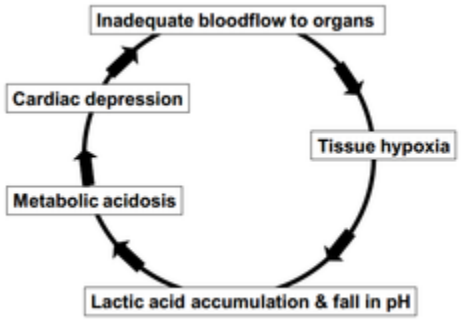
The main purpose of compensatory responses is to maintain the circulation in vital organs, however, the rest of the tissues is exposed to the hypoperfusion. Systemic vasoconstriction persists and after some time leads to severe tissue hypoxia, and accumulation of metabolites of anaerobic metabolism. These substances belong to the local blood flow regulation system, which dominates over the sympathetic system. This will lead to weakness and progressive insufficiency of compensatory mechanisms (local hypoxic vasodilation overcomes sympathetic vasoconstriction) and shock gradually deepens.

Progressive phase (reversible decompensation)

Accumulation of acid metabolic end-products lead to the passive dilatation of the precapillary sphincter (it overcomes the neurogenic sympathetic regulation) and the blood will be redirected back to the capillaries which were hypoperfused during the compensated stage.

Now, the **ischemic hypoxia** changes to the **stagnation hypoxia**, because the post capillary sphincter still holds the blood in the tissue. The gain of the blood in the tissue and the increase of the hydrostatic pressure lead to the disturbance of Starling forces. Forces governing the move of the fluids across the capillary membrane will suddenly change and the **fluid and proportion of proteins will leak from capillaries through the damaged endothelium to the interstitial space.** Proteins enhance the water leak by oncotic forces. This will further worsen the disproportion between the **fluid volume and capacity of the vascular bed.** At this stage, the compensatory mechanisms failed (decompensation, however, still reversible phase) and shock can be treated only by intensive anti-shock therapy.

Progressive phase of shock is characterized by presence of as **vicious circles**, which deepens the shock by a series of positive feedback loops. Many of these loops are initiated by presence of acid metabolic end-products, hypoxic tissue damage, nitric oxide, cytokine and endotoxin. They usually have **cardio-depressor and vasodilating effect**. Leak of intravascular fluid out of the capillaries in progressive stage worsens perfusion of the heart and brain. Hypoperfusion of the heart leads to the decrease of cardiac output, while hypoperfusion of the brain weakens the central compensation mechanisms (cardio-motor centre is localized in the brainstem) and it becomes a part of vicious circle as well.



Hypoperfusion of the GIT plays important role in the progression of shock. Intestinal mucosa becomes ischemic, and therefore damaged. Bacteria, their toxins and waste products cross this impaired barrier (translocation) – the most important is **endotoxin.** Endotoxin has **cardio-inhibitory effect, it worsens vasodilation and it also increases tissue oxygen demands**. Excessive GIT hypoperfusion is therefore considered to be the "engine" worsening the shock leading to the multiple organ dysfunction syndrome. This stage is critical however **treatable by intense anti-shock treatment**.

Irreversible phase

Irreversible stage is characterized by deep tissue hypoxia (therefore also cell necrosis due to the lack of oxygen) and acidosis. Endothelial damage together with the capillary basal membrane damage is now severe, so the proteins and the red blood cells can escape out of the lumen to the tissue (bleeding to the tissues). **Loss of the integrity in microcirculation is one of the determinants of irreversible condition, so does the necrosis of considerable numbers of cells in tissues.**

Capillary function is further compromised by the formation of the small clots and this process is a part **of disseminated intravascular coagulation**. Coagulation cascade is activated by endothelial damage and other signal molecules, unfortunately, it leads to the consumption of coagulation factors. It will manifest by uncontrollable tissue bleeding. DIC contributes to the **failure and disintegration of microcirculation**. There is not therapeutic approach which would save the patient in irreversible phase of shock and patient will die due to **multiple organ failure**, which is characterized as a failure of at least two organ systems. It is a consequence of generalized vasodilation, hypoxia, metabolic acidosis, ion disturbances and disseminated intravascular coagulation.

Organ dysfunction in shock

Organ dysfunction appear as a **consequence of generalized hypoperfusion** of the organs out of the "vital zone", because only heart, brain, liver and adrenal gland have the proper circulation in the compensated phase of shock.

Renal dysfunction. Several mechanisms have been proposed for the pathogenesis of acute renal failure occurring in shock. Normally, the kidney maintains renal blood flow and glomerular filtration through autoregulation dependent on the tone of the afferent and efferent arterioles. In compensated phase of the shock, there is a vasoconstriction, and the renal perfusion is considerably reduced to the point which will activate RAA system, and diuresis will be maintained, however severely reduced (below 30 ml/hour). **Pre-renal renal insufficiency** may develop. Ischemic damage of proximal tubular cells and cell of the ascending part of the loop of Henle may occur after long-lasting renal hypoperfusion. **Acute tubular necrosis** lead to intrarenal renal insufficiency with considerable reduction of glomerular filtration and inability to maintain homeostasis. Later the kidneys are further damaged by reperfusion, ROS, DIC. The renal function in shock must be carefully monitored and maintained by fluid resuscitation and pharmacological management.

Gastrointestinal system is affected by hypoperfusion too; in fact, vasoconstriction causes very serious changes to the GIT blood supply. The barrier function of the intestinal wall is compromised due to hypoperfusion. After that a **translocation** of intraluminal bacteria or their endotoxin might occur, leading to the worsening the homodynamic parameters. There is a possibility for the development of septic complication in patients with shock based on the mechanisms of translocation of intraluminal bacteria. Hypoperfusion of the GIT mucosa may also lead to the development of gastric mucosa erosions, and lesions in the intestinal mucosa that bleed. Bleeding can be further promoted by the DIC.

Pulmonary dysfunction is common in the patient with shock and manifests as tachypnoea, hypoxemia and respiratory alkalosis. When severe, it may progress to acute lung injury (ALI) and **acute respiratory distress syndrome** (ARDS). The primary pathological process is pulmonary capillary endothelial dysfunction resulting in interstitial and alveolar oedema of protein and phagocytic immune cell rich exudative fluid. Endothelial permeability is increased in response to cytokines and endotoxin from the GIT hypoperfusion. Damage may progress to the alveolar denudation and basement membrane destruction. Another mechanism employed in the ALI is destruction of surfactant with formation of atelectasis in lungs.

Heart dysfunction is a part of the vicious cycle which appear in the progressive stage of the shock. The response to the fall in blood pressure is an increase of cardiac output. Baroreceptors mediate a pronounced **tachycardia and increase of stroke volume.** Independent of the effects of preload and afterload, intrinsic myocardial depression is present within 24 hours of the onset of shock. Tachycardia reduces ventricular filling and also coronary perfusion, therefore tachycardia as a compensatory mechanism has negative influence on the heart. In shock, the tissue hypoperfusion leads to the acidosis, which **reduces heart contractility.** Acidosis and tissue hypoperfusion elevates concentration of the K^+ in the extracellular fluid – **K^+ is the main determinant of the resting membrane potential in the heart. Hyperkalaemia has negative effect on heart electrophysiology.** Tissues are releasing many molecules with **cardio-inhibitory effects, e.g. MDF – myocardial depressant factor** is released **from hypoperfused pancreas.** Endotoxin and pro-inflammatory cytokines have been shown to induce **myocardial depression**. These effects are probably mediated through nitric oxide. Obviously, there are many reasons leading to the myocardial depression which will promote the progression of shock.

Metabolic disturbances appear as a consequences of inappropriate tissue perfusion. They are tissue **hypoxia and lactic acidosis**.

Coagulation problems are often associated with shock hypoperfusion and endothelial damage. Disseminated intravascular coagulation (DIC) produces both bleeding and microvascular thrombi which have been proposed as mechanisms of multiple organ dysfunction. **The cytokine-mediated and endothelial damage mediated** activation of coagulation occurs via the tissue factor dependent extrinsic pathway. Tissue factor is the activator and cofactor for factor VIIa-mediated activation of factors IX and X of the extrinsic pathway. Attenuation of the anticoagulant systems worsens the procoagulant state. Antithrombin III is an inhibitor of the serine proteases responsible for inhibition of clotting factors IXa, Xa, XIa and XIIa and thrombin. Thrombomodulin is an endothelial cell derived inhibitor of clotting and activator of fibrinolysis. It acts as a thrombin binding protein, reducing the effects of thrombin. The thrombin-thrombomodulin complex has further anti-coagulant properties as an activator of protein C which, with cofactor protein S, inactivates factors V and VIII. In shock, the production of thrombomodulin by endothelial cells is downregulated by pro-inflammatory cytokines and circulating free levels of protein S are reduced.

CASE REPORTS

Case report 1

35-years-old motorcycle driver has had an accident, in which he crashed heads on into the car, after the crash he flew for approx. 10m. EMTs were called and they came quickly. Patient was lying on the sidewalk, did not react to stimuli; breathing was agonal, pulse weak, blood pressure was unmeasurable. Patient was immobilized, oxygen was administered, breathing was supported by BV (bag-valve) mask and patient was transported to the trauma centre.

Based on **initial assessment** the airways were patent, but spontaneous breathing was not present, weak pulse on femoral artery 56/min, patient was hypotensive with unmeasurable BP; skin was cold, dry and pale, GCS 3, anisocoric pupils. He was immediately intubated, breathing sounds were weakened and despite intubation the ventilation of the patient was not appropriate. Catheter was inserted into femoral vein and another two peripheral catheters were procured for saline administration; however, the patient remained hypotensive and bradycardic. Patient suffered head trauma with occipital bone fracture, chest x-ray revealed tense pneumothorax. Abdomen showed numerous contusions and weakened peristaltic

sounds, pelvis was unstable and sphincter tone was diminished. Extremities were cold with unpalpable peripheral pulsation and lowered capillary return. Foley catheter was inserted.

Laboratory results: pH: 7.01; pCO_2 9.06 kPa; pO_2: 5.06 kPa; BE -13; HCO_3^- 11.7; $SatO_2$: 59% (100% O_2, 15l/min).

Patient was still hypotensive, pulse was within the range of 32/min (bradycardia) to 120/min (tachycardia). After i.v. administration of crystalloids, erythrocytes, fresh frozen plasma the systolic blood pressure was stabilized on 102 mmHg and pulse 98/min. CT revealed closed craniortauma with contusion of parenchyma, fractures of cervical and thoracic spine, open book fracture of pelvis with injury of vessels and multiple fractures of lower extremities.

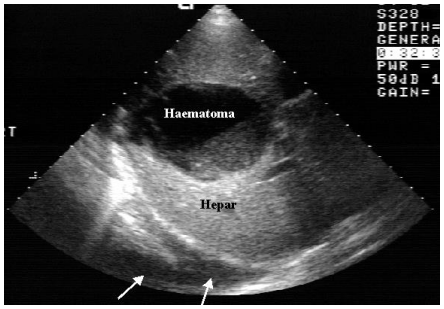
Questions & Tasks

1) What type of shock is present in this patient? Can individual types of shock combine in our patient?
2) What signs and symptoms of shock were present in this patient?
3) How does organism react to decrease of arterial blood pressure?
4) Based on laboratory results determine the acid-base balance disturbance in our patient.
5) If urinary catheter was inserted, what volume of urine would you expect and what would be the concentrations of sodium and potassium in urine? Explain.

Case report 2

45-years-old woman after planned laparoscopic cholecystectomy. Patient was stable, had only minor pains which were treated by i.m. administration of pain killers. BP 120/80 mmHg, HR 75/min, BR 14/min, hourly diuresis 100 ml/h. Drainage drains coloured fluid. In the afternoon, she wakes up from sleep and complains about dull pain in abdominal region, drainage does not drain liquids since noon (drainage was clogged).

Physical examination: Patient is pale, scared; abdomen is distended, tender with signs of peritoneal irritation. Her vitals were checked: BP 90/55 mmHg, HR 110/min, BR 14/min, hourly diuresis decreased to 50 ml/L despite slow i.v. administration of saline. Urgent abdominal USG revealed presence of haematoma in gall bladder bed and fluid in peritoneal cavity. Patient was immediately transported to operating theatre for laparotomy and revision of peritoneal cavity.



Questions & Tasks

1) What type of shock is present in this patient? Which signs and symptoms of shock are present in this patient?

2) Explain the decrease of hourly diuresis in this patient.

3) Estimate the levels of haemoglobin, haematocrit and red blood cells in this patient. Estimate the levels immediately after haemorrhage. How would the levels change if the losses were corrected only by administration of crystalloids or plasma without administration of red blood cells?

4) Why was the skin of this patient cold?

5) Explain the importance of vital functions monitoring in relation to possible development and progression of shock.

Case report 3

40-years-old man, firefighter was admitted on specialized burn unit, who suffered severe burns affecting almost 50% of body surface while on duty. During transport, the patient was haemodynamically stable with BP 110/75 mmHg, HR 78/min, intubated and ventilated due to airway injury, when he was not able to maintain O_2 saturation. Hourly diuresis 100ml/h, laboratory parameters within normal values.

On the second day, the nurse noticed that the patient is not urinating. His laboratory parameters were: Na 130 mmol/L; K 6 mmol/L; Cl 90 mmol/L; AST, ALT normal, GMT, ALP normal; creatinine180 μmol/L; urea 8 mmol/L; HCO_3^- 16mmol/L; pH 7.2, values of oxygen and carbon dioxide normal (artificial ventilation).

Questions & Tasks

1) What type of shock is present in this patient and what is its main cause?

2) After oligoanuria is present, it is obvious that kidneys are not functioning. What is the cause of this condition?

3) How can we determine, whether the acute renal failure is of prerenal or already intrarenal origin by laboratory analysis of urine?

4) Which homeostatic parameters suggest disturbance of homeostasis due to renal failure?

5) Why were the examinations of AST, ALT, GMT, ALP ordered? What could this examination reveal?

6) What kind of acid-base balance is present? Calculate the anion gap. Which anions accumulate in organism?

Chapter 13

PATHOPHYSIOLOGY OF PAIN

Pain is one of the most common symptoms in medicine and it is a consequence of physiological activation of nociceptive part of sensory system, or a consequence of dysfunction of this system. It is often associated with unpleasant sensations. Pain is a complex phenomenon which is difficult to define, quantify and sometimes also identify. Every individual may perceive pain differently, so it is original and unique. This important symptom is modified by many factors, giving the final complexity of symptom. It usually brings important information about the tissue damage or organ dysfunctions; therefore, proper attention to this symptom should be given.

Definition of pain

International Association for Study of Pain defines pain as **an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.**

Dimensions of pain

Definition of pain points to the complexity of this phenomenon, which is further characterized by three dimensions.

1) sensory-discriminative – it is based on **nociception and perception**. **Nociception** means ability of nociceptor to create burst of action potential after its stimulation by appropriate stimulus. This information is transmitted from the site of onset to the CNS where it is processed. The result is the ability of human being to localize the place of induction of pain, its intensity, quality and spatial/temporal aspects of pain. Another result of processing of primary nociceptive signal in CNS is the **ability of organism to identify this signal as painful – perception.**

2) affective-motivational – it is characterized by approach-avoidance behaviour. It is manifested by phenomena as suffering, depression, anxiety or frustration.

3) cognitive-evaluative – it expresses the fact that patient evaluates the significance of pain for him/her, possible cause(s), and what are the possible consequences for him/her and his relatives.

Terms characterizing pain

Pain threshold is the lowest intensity of stimulus identified as painful.

Pain tolerance describes the ability of an individual to tolerate the pain with certain intensity without onset of considerable emotional or somatic manifestations. Pain tolerance is influenced by many factors and there are important inter-individual differences. The pain threshold does not differ significantly among people but pain tolerance may differ significantly.

Classification of pain

There are different criteria for classification of pain, because clinicians and pathophysiologists focus on different aspects of pain. These aspects are:

Duration of pain

Pain according to its duration can be **acute, subacute or chronic.**

Acute pain (duration less than 3 weeks) can be interpreted as **physiologic, protective and defensive mechanism**, because it indicates real or potential damage of the tissues and it will also influence the response of the patients' actions in a way to reduce or prevent further damage and/or progression of tissue damage.

Subacute pain (duration usually between 3-6 weeks) can be present when damage of tissue is larger, more intense and/or healing process is slower.

Chronic pain (duration more than 6 weeks) should be considered as **pathological phenomenon**, which points to severe damage of tissues and/or dysfunction of **CNS neuromatrix of pain** which is responsible for generation of pain. While acute pain has mainly a defensive role, **chronic pain is considered as disease of its own.**

Site of the pain onset

Pain may arise from **somatic structures**, either superficial (skin, subcutaneous tissue, mucosa) or deep (muscles, joints, tendons, bones). Pain can also arise from **visceral structures** (chest organs, abdominal or retroperitoneal organs). **Neuromatrix of pain in CNS** can also generate the pain under specific conditions even without any participation of somatic and visceral structures.

Mechanisms of somatic and visceral pain

This aspect considers the pathomechanisms leading to pain onset and progression; therefore, it describes **pathophysiology of pain**. These mechanisms are the key factors in

understanding of pain and they provide a background for effective treatment of pain/pain syndromes.

Based on the mechanisms leading to the pain onset and progression we recognize different types of pain: **nociceptive pain, neuropathic pain, psychogenic pain and idiopathic pain.**

Nociceptive pain is a pain caused by activation of nociceptive nerve endings (afferents) distributed all over the body. These afferents are not usually damaged and they respond by a discharge of action potential in case of appropriate stimulation by chemical or mechanical stimuli. **Nociceptors are nerve endings of Aδ (myelinated) and C (non-myelinated) nerve fibres.**

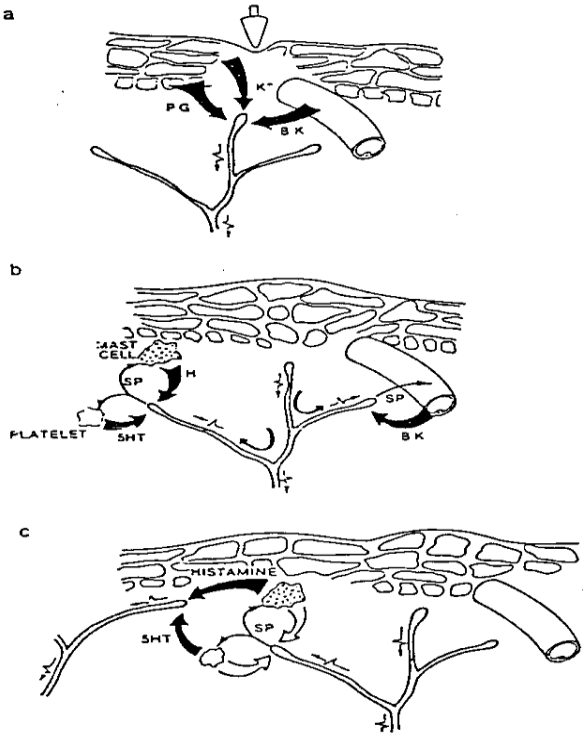


Figure 13.1: Mechanisms of nociceptive pain development

Neuropathic pain is pain caused by **functional and/or structural damage of the nociceptive system** (sensory nerves) and the tissue surrounding this nerve is not necessarily damaged. **This type of pain is pathological**, it does not provide neither protective nor defensive role, considerably reduces quality of life by its intensity and duration. Mechanisms causing the damage of the nociceptive systems are e.g. compression, inflammation, infiltration by tumour, mechanical damage after surgery, radiotherapy, chemotherapy etc. Damage is usually associated with reduction or lack of proper sensory functions in affected region. Affected nerve or its new branches (they appear as a form of regeneration) are

extremely sensitive to nociceptive signalling, what is called **hyperalgesia**, but also to the stimuli that do not normally produce pain, what is called **allodynia** (fig. 2). Increased sensitivity to nociceptive stimuli is caused not only by the changes in the peripheral part of the nociceptive system (**peripheral sensitization**) but also by increased sensitivity of CNS (**central sensitization**).

The most common types of neuropathic pain are pain in the sacral region, pain in diabetic neuropathy, post-herpetic neuralgia, pain in different types of cancer, pain after the lesion of spinal cord, neuralgia of trigeminal nerve, and phantom pain after amputation.

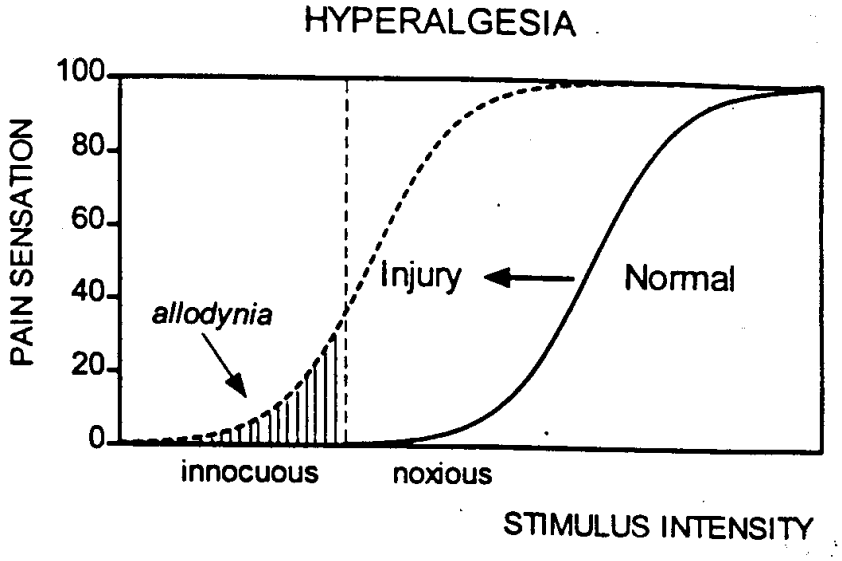


Figure 13.2: Diagram explaining terms allodynia and hyperalgesia

Psychogenic pain is not caused by primary tissue damage or damage of the nociceptive system, but it is a **disorder related to the processing of innocuous afferent information** in the network of neurons in the central nervous system, which are normally responsible for processing of sensory and pain afferent inputs (neuromatrix of pain in CNS). Innocent afferent information is perceived and identified as pain. This is usually a part of psychological (psychiatric) diseases and it is frequently induced by psychogenic factors.

Regulation of pain

Nociceptive information comes from the damaged tissue to the central nervous system in a form of electrical impulse/signal via 1st afferent neuron, body of which is located in the dorsal root ganglia, and it is branching in the periphery. This information is transported to the 2nd order neuron, which is located in the dorsal horn of the spinal cord. It sands this information to the thalamus and subcortical structures (spinothalamic tract). The body of last

afferent neuron - the 3rd neuron-of this pathway is located in the thalamus and projects to the cerebral cortex (thalamo-cortical tract).

The information carried via nociceptive afferent system is modulated along its whole way from the periphery to the cortex. **Modulation of primary nociceptive information may be either augmentation of pain signal or its decrement.** Increase of the pain intensity is mediated by **nociceptive system itself** (e.g. by increase of nociceptive afferentation or decreased activity of antinociceptive mechanisms), while reduction of pain intensity is mediated by activation of **antinociceptive system (endogenous analgesic system)**. It consists of several structures located at different levels of spinal cord and brain:

1) Antinociceptive system in spinal cord – is located in the dorsal horn, and it is a complex of cells called **substantia gelatinosa (SG).** This part of the dorsal horn receives information from certain part of the body via nociceptive and other than nociceptive sensory fibres and it works as a **gate** which determines how much of the "pain" signals will ascend to the higher parts of the central nervous system. Basic principle of this regulation is related to the character of afferent information entering the SG. By simplification, impulses carried by A□ and A□ fibres (non- nociceptive signals) to the SG **close the gate** for the transmission of impulses carried by A□ and C fibres (nociceptive fibres). Intensity of perceived pain is in this condition reduced. However, if the magnitude of impulses carried by A□ and C fibres is considerably higher (e.g. in case of severe tissue damage), it will keep the **gate open**, and the pain signal will much more easily ascend to the higher structures – thus potentiating the intensity of perceived pain.

2) Antinociceptive system in the brainstem – a network which modulates the pain perception located at the level of brainstem. **It creates descending antinociceptive system**, because efferent neurons located in the brainstem project to the dorsal horn (they descend), where their activity modulates transmission of the pain signals. There are more such neuronal structures, but of special importance are neurons of the **nucleus ruber** and neurons located in, so called, **periaqueductal grey.** These structures contain neurons which receive information from ascending medullar nociceptive pathways as well as signals from cortical and subcortical structures of the brain. Activation of these neurons by ascending nociceptive signals lead to the efferent drive directed downwards to the dorsal horns of spinal cord where these axons release neurotransmitters with inhibitory effect on the nociceptive tract. Their synaptic connections to the 1st nociceptive neuron and ability to release endogenous opiates

inhibit the transduction of pain signals. Endogenous opiates binds to the presynaptic membrane in the synapse between 1st and 2nd order neurons of the nociceptive tract, and they inhibit transduction through this synapse. 1st neuron will release less of excitatory mediators, thus the 2nd neuron is less excited. This lead to the inhibition of pain signalling.

3) Antinociceptive system in the cortex and subcortical structures – this system works mainly by the **release of endogenous opiates.** E.g. amygdala – the structure strongly activated by fear lead to the initiation of stress response, which in turn increases production of opiates (they are end products of POMC molecule, which cleaves to ACTH – substantially important in stress, □MSH and endorphins) (Fig, 3.).

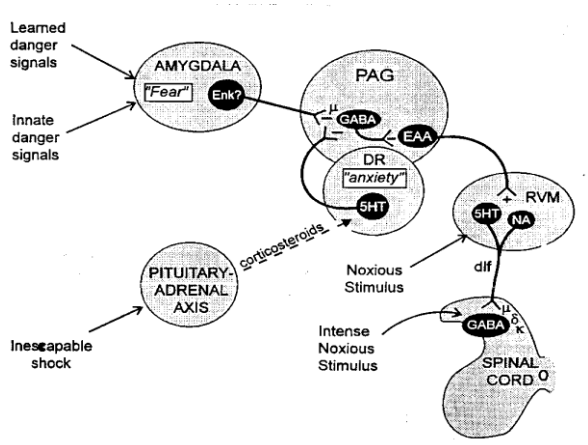


Figure 13.3: Structures of endogenous analgesic system

Increased perception of pain is a consequence of modulation in opposite direction. Augmentation of pain signalling is a result of **peripheral and central sensitization** of nociceptive system.

Peripheral sensitisation is a condition of increased sensitivity and reactivity of nociceptors localized in variety of tissues caused by the presence of mediators released from damaged cells. They **decrease the threshold for activation**, and the nociceptors become **responsive to less intense stimuli**. These fibres may also **express more "receptors**" or "ion channels" which are responsible for the discharge of action potentials. These neurons can also change the type of receptors they express and also **can stimulate growth and branching of these fibres** due to increased concentration of **neurotrophic factors** from inflammatory cells. These processes may lead to increased pain signalling and increased intensity of perceived pain.

Central sensitisation describes increased sensitivity and reactivity of 2nd and 3rd order neurons in the nociceptive tract and/or decreased performance of endogenous analgesic system. For example, 2nd order neuron can increase the expression of NMDA and AMPA receptors (receptors normally activated by glutamate) as a consequence of "long-lasting bombardment" of these neurons by pain signals coming from peripheral tissues. These neurons have adapted to the load of pain signals by increased availability of receptors what will **change the properties of this neural pathway** (neural plasticity). Other mechanisms participating on central neuroplasticity are e.g. sprouting – growth of new branches of the nerve from the central terminal after previous damage to the nerve, onset of new synapses etc. These processes lead to the condition which is characterized by **increased sensitivity and reactivity of central part of nociceptive system.** This condition will manifest by presence of unpleasant sensory sensations (dysesthesia), pain perception even if the stimulus is innocuous (allodynia) and considerable increase of the intensity of perceived pain (hyperalgesia).

Radiation of pain, referred pain

Pain may be perceived in and localized to other region than the primary site of the pain stimulus. **Referred pain** is pain felt at a site different from the injured or diseased organ or body part. Radiation is related to spinal segmentation. The term **radiation pain** is more commonly used in connection with **pain perceived in somatic nerve and spinal nerve root distributions** (e.g. the dermatomes that all physicians learn early in their training). Merskey and Bogduk (2011) specify that "referred pain is **pain perceived in a region that has a nerve supply different from that of the source of pain".** Typically, the pain is referred to other structures that have the same embryonic origin. Usually, pain in ischemic heart disease appears in the middle of the chest, and it spreads to the neck, jaw or left arm. **Mechanism leading to this phenomenon is based on convergence** of afferent (sensitive) nerve fibres innervating both heart and mentioned somatic areas, and these fibres are entering the same spinal cord segment (Fig. 4). These fibres connect onto the 2nd order neurons in the same segment, therefore the "brain" after the processing of this signal identifies it as a pain in the heart and related somatic structures. There must be an origin of pain pathology before referred pain can be perceived.

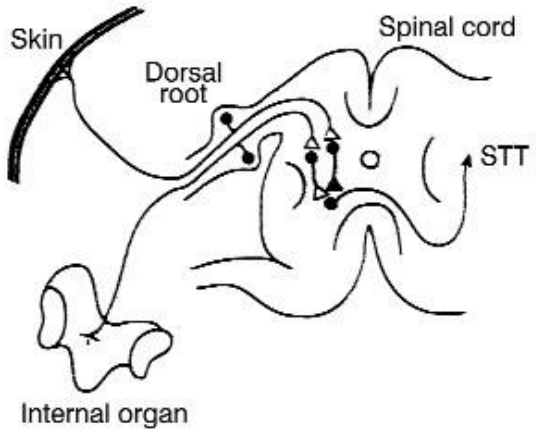


Figure 13.4: Convergence theory of referred pain.

Note that the pain pathways from the skin surface and from internal organs pass very close to each other at the dorsal horn. Via ephatic transmission (analogous to an electrical short circuit) causes the brain to misinterpret the pain from internal organ as pain from the skin (Smith, 2000).

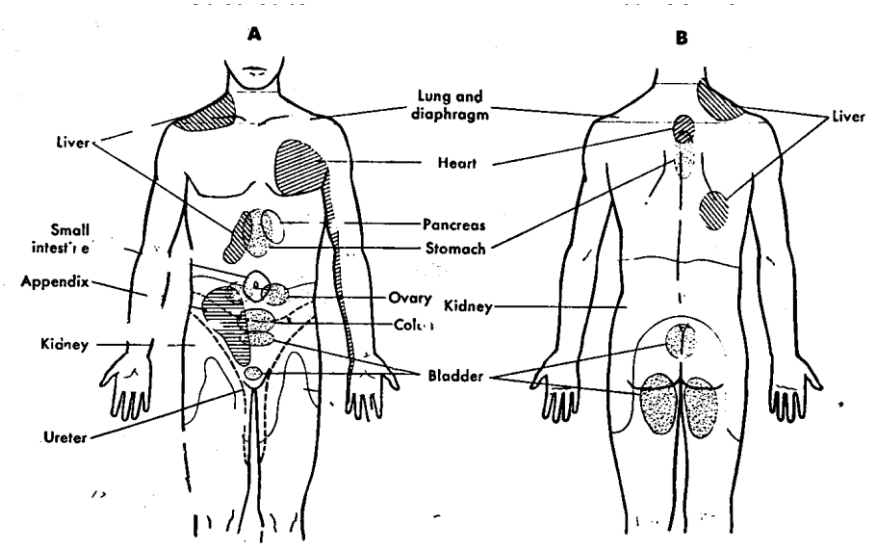


Figure 13.5: Scheme shows typical localities of referred pain from visceral organs

Example of classic referred pain

Phantom pain

Phantom sensations and pain merely mean that the brain perceives the existence of a body part from which no nerve impulses could possibly be emanating, such as from an amputated limb. In a sense, phantom pain is the ultimate “referred pain”. Perception of the

pain is obviously not where the pain is originating, since there cannot be peripheral pain nerve stimulation.

Note that, as with all types of pain with central components, non-existence of the perceived origin of pain pathology makes no difference in the pain perception, which is certainly true for all types of referred pain. However, it does not necessarily follow that every type of referred pain has a central dysfunctional component. Further, stump and neuroma pains post-amputation are not referred pains, and therefore, should not be mistaken for phantom pain. There seems to be surprising confusion about these pains versus phantom pain.

Repeating the above meaning, it may be possible to have phantom pain of a body part that is not missing as evidenced by abdominal pain in patients with spinal cord injury. However, there is also the possibility that this pain may be "real" and actual pain from the perceived site of pain, where pain nerve impulses pass through some other continuous pathways to the central nervous system, such as through the sympathetic chains.

CASE REPORTS

Case report 1

At the end of December 2008, 57-years-old man visited his GP with his problems lasting for couple of last days. He mentioned that he woke up at 3 AM with intense feeling of full stomach and experienced sensation of poor digestion. Immediately afterwards, he experienced strong sensation of the pressure in his chest as somebody sat on his chest or compressed his chest by hands. All this lasted for approximately 20 min. Simultaneously he had a sensation of cramps in his hands and fingers; therefore, he sat on his hands to stop the cramps. Described symptoms and signs lasted for couple of hours. Patient described also some additional symptoms, such as sensation of stiffness and insensitivity in whole body similar to the feeling one has after administration of local anaesthetic. Sensation of stiffness and insensitivity lasted up to 2 hours from the start of the heart attack.

Questions & Tasks

1) Identify symptoms and signs in this patient.

2) Describe the mechanisms responsible for onset of the symptoms and signs.

3) Explain what type of pain this patient has experienced.

Case report 2

55-years-old woman admitted to the ER due to severe facial pain. The primary diagnosis was that this woman has a dysfunction of temporomandibular joint, so she was sent to a dentist to find out. Dentist confirmed the dysfunction of temporomandibular joint, no other dental problems, but he also proposed another explanation of pain, because the pain was related to physical exercise. Cardiology examination which was performed brought some important information – the pain itself starts on the chest, it radiates to the neck and left side of the face and temporal region. Detailed history revealed that this patient has already had surgery of coronary arteries due to ischemic heart disease. Cardiologist suggested increasing the dosage of medication for ischemic heart disease, which in turn stabilized the function of the heart and the symptoms she described before vanished.

Questions & Tasks

1) Identify main symptoms and signs reported by the patient.

2) Discuss some other causes of severe pain on the left side of the face in this woman.

3) Explain the phenomenon of pain radiation pain and referred pain.

4) What is the relationship between facial pain and previous coronary intervention?

Case report 3

66-years-old woman suffers from pain located in the 6th intercostal space at the right side of the chest for 5 years. 5 years ago she had *herpes zoster* infection treated by her GP by some local medication to reduce pain and itch. Despite the medication, the pain remained the same even after the herpetic blisters were already healed. She took ibuprofen to ease the pain, later also tramadol (opiate), but without much success. The pain is constant, present at rest; its character is described as burning. This pain also causes insomnia and even little contact with clothes or gentle touch to this area causes severe pain. The examination showed pain after non-nociceptive contact with the skin in the 6th intercostal space at the site of former herpetic infection. Patient also has psychological consequences of this condition; she suffers from depression and anxiety.

Questions & Tasks

1) Identify all important symptoms in this patient

2) What type of the pain she suffered from?

3) Explain the mechanism of this type of pain.

4) What is the name for pain induced by non-nociceptive stimulus?

Case report 4

49-years-old patient suffers from scoliosis since childhood. Now, she suffers from pain in the lower back lasting for more than 27 years, provoked very likely by complicated childbirth she had. This condition was treated by physical methods – massages, non-steroid analgesics (ibuprofen, diclofenac and others without much success). Her documentation and also personal communication with the patient revealed that she never had complex orthopaedic or neurological examination, was never educated about appropriate and dangerous movement pattern and physical activity and exercise to strengthen muscles of the back. Analgesic medication was not systematic and also it was not selected appropriately. After the complex examination in the centre for chronic pain, she was diagnosed with severe dysfunction of the spine with scoliosis and narrowing of the spinal canal with other multiple dysfunctions and spasms of the muscles in the thoracic and lumbar segments.

Questions & Tasks

1) Identify all important symptoms in this patient.

2) What type of pain does she suffer from?

3) Why did the presented medication fail?

Chapter 14

PATOPHYSIOLOGY OF CEREBRAL ISCHEMIA

Cerebral ischemia and ischemic heart disease, common entities nowadays, are important manifestation of disorders in cardiovascular system. Cardiovascular diseases, followed frequently by brain stroke, represent the leading cause of morbidity and disability. Brain can only survive for approximately 5-7 minutes when deprived from oxygen and glucose, therefore its blood supply should be very well controlled, it should be very sophisticated, reliable and stable. There is rich anastomotic system among extracerebral and intracerebral arteries represented by collaterals to prevent oxygen and substrate deprivation in case of isolated cerebral artery occlusion.

The blood supply to the brain consists of four main arteries – **left and right carotid arteries and left and right vertebral arteries.**

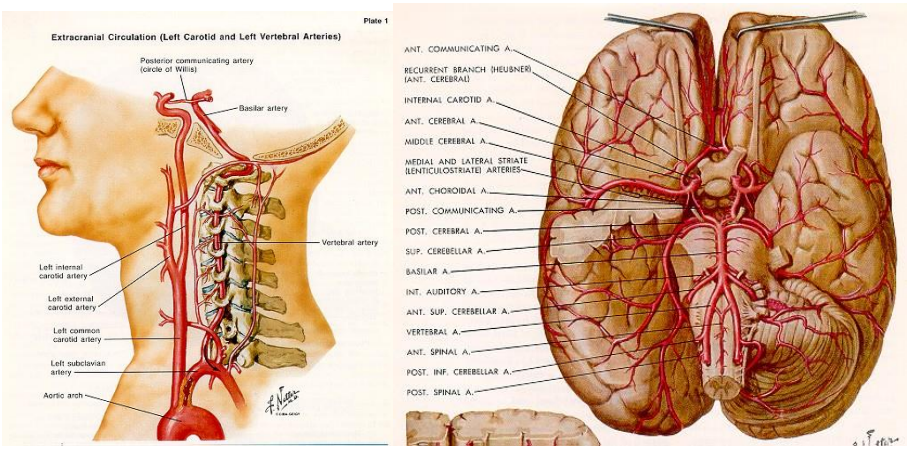


Figure 14.1: Anatomy of brain blood supply, forming the circle of Willis at the bottom of brain.

Extracranial and intracranial collateral system provides the blood supply to the entire brain even if one or two of the main brain arteries are occluded (however, the blood flow in the remaining arteries must be unobstructed and systemic blood pressure is not decreased). Functional collateral system plays an important role in the brain blood supply under physiological conditions, but its importance is critical in case of pathology, when the oxygen and substrates are carried to the ischemic part of brain mainly by mentioned system. The main cerebral arteries are branching into arteries with smaller diameter and they are entering

the brain tissue as **penetrating arteries**. They bring substrates and oxygen directly to neurons. There are also collaterals at this level of blood supply but their function has some limitations.

The brain blood supply can be negatively influenced in general by many factors, not only by arterial occlusion, but also e.g. inadequate venous outflow from the brain or significant decrease of systemic blood pressure.

Cerebral vascular events/brain strokes - sudden damage of brain induced by decreasing or suspending delivery of oxygen and glucose to the brain due to disturbances of brain vessels and heart.

According to the mechanisms stroke can be classified as:

1) **Focal cerebral ischemia** (approx. 80%)
2) **Intracerebral bleeding** (approx. 15%)
3) **Subarachnoid bleeding** (approx. 5%)

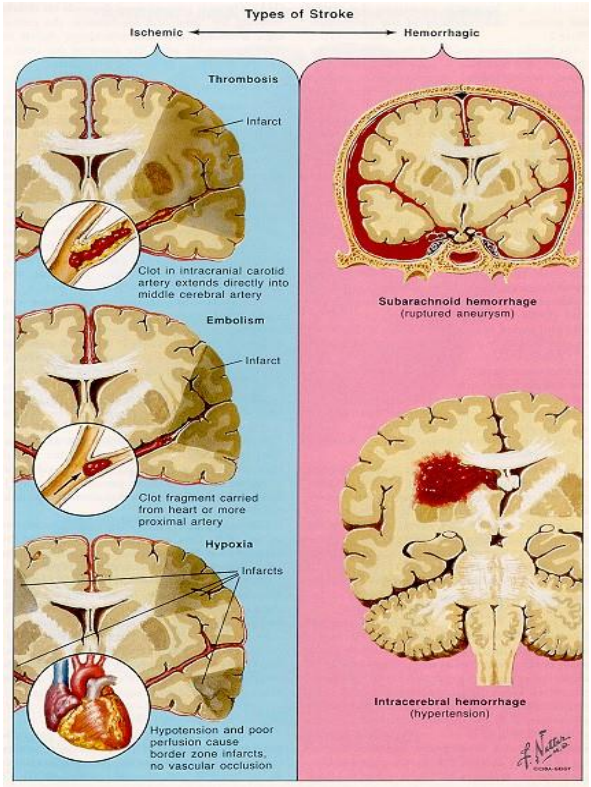


Figure 14.2: Types of strokes

Definition of cerebral ischemia

The term **cerebral ischemia describes potentially reversibly altered state of the brain physiology and biochemistry of affected tissue.** It is caused by **total block or**

considerable reduction of the oxygen and glucose supply to the tissue due to arterial stenosis or occlusion and by decrease of perfusion pressure caused by cardiac conditions (reduced cardiac output, reduced blood pressure).

Pathogenesis of cerebral ischemia

Main pathogenetic mechanisms leading to the cerebral ischemia are:

1) Microembolisation to the cerebral arteries

The sources of the microemboli are mainly displayed on Fig. 3

a) Thrombus in the left atrium in atrial fibrillation releasing small fragments to arterial blood stream

b) Subacute bacterial endocarditis – growing bacterial vegetation on the affected parts of endocardium, potential disrupture of vegetation with their movement along the blood stream

c) Transmural or subendocardial myocardial infarction with subsequent thrombosis inside the left ventricle

d) Aneurysm of left ventricle after previous myocardial infarction – possible multiple embolizations due to big thrombus in the aneurysm which may be a source of many microemboli

2) Stenosis of cerebral artery combined with decrease of systemic arterial pressure – intensity of stenosis itself does not lead to ischemia (subclinical stenosis), but in combination with the decrease of systemic arterial pressure it may lead to the clinically important decrease blood flow to the respective part of brain, which results in ischemia. These two mechanisms potentiate each other, and this is also common reason of ischemia occurring in late-night hours (or early morning hours when blood pressure is at its lowest) in older individuals with some stage of atherosclerosis in cerebral circulation.

3) Thromboembolic damage of main cerebral arteries

This process – narrowing of the cerebral arteries by thrombus, is mainly a result of damage to the vessel wall by atherosclerotic process. Atherosclerotic plaques, mainly after rupture, are massive source of factors promoting coagulation of blood, thus leading to thrombosis. Entire thrombus or its fragments may travel along the blood stream causing embolization of vessels with smaller diameter. Sometimes the content of the plaque (lipids, foam cells, tissue debris) pour out of it after the rupture and occlude the vessel, because this mass is of high viscosity. The result may be **transient ischemic attack** (TIA).

4) Severe reduction of cardiac output

The cause of reduction of cardiac output can be e.g. sudden decrease of myocardial contractility, sudden generalized vasodilation and also considerable reduction of circulating volume. These circumstances lead to severe decrease of systemic arterial pressure and also perfusion pressure in the main cerebral arteries. The result of such a process is **borderline ischemia.**

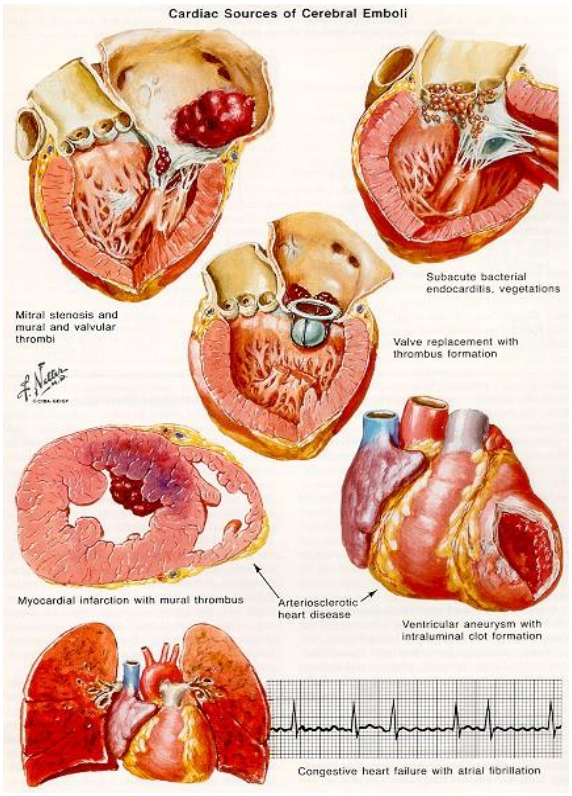


Figure 14.3: Cardiac sources of microemboli to the cerebral arteries

Pathogenetic mechanisms involved in modulation intensity of focal brain ischemia

Decrease of blood flow to brain tissue is the critical first step in development of brain ischemia. Immediately after onset of ischemia, other processes are started as well – **defensive or damaging**, which will form **final intensity, localization and size** of ischemic field of brain. Among these processes we may mention e.g.:

a) **Number, diameter and function of collaterals, rheological properties of blood and conditions in microcirculation, perfusion pressure,**
b) **metabolic changes in ischemic field,**
c) **changed regulation of brain vessels diameter,**
d) **steal phenomenon,**

e) threshold of ischemic injury, ischemic penumbra

f) changes in contents and composition of fluids in ischemic field, ischemic brain oedema.

a) Number, diameter and function of collaterals, rheological factors, perfusion pressure

Higher number of collaterals with optimal diameter, good perfusion pressure and low blood viscosity provide very good conditions for proper function of collateral circulation, what leads to reduction of size and intensity of primary ischemic focus. On the contrary, low number of open collaterals or collaterals with small diameter, together with low perfusion pressure and high blood viscosity increase the extent of ischemic focus/damage. Reperfusion of ischemic focus, spontaneous or induced by therapy, does not always lead to the complete recovery of all cells located in affected focus. Some fields of the ischemic area remain ischemic with irreversible damage to the cells, because the arterioles and capillaries in this focus were seriously damaged and they are not sufficiently opened to allow reperfusion. This disorder is called **no-reflow phenomenon** and it indicates worse prognosis for affected brain tissue and for the patient. So, **disturbances of brain microcirculation accompanied by rheological changes at low blood flow velocity are considered as important pathogenic factor promoting development of cerebral ischemia and cerebral infarction.**

b) Metabolic and electrochemical changes in ischemic field

If ischemia lasts long enough and is intensive enough (the term "intensive enough" is not possible to define exactly, because there is a lot of factors which may influence it), it will cause cellular damage with various intensity. The reason of neuronal dysfunction and later also destruction is **lack of energy in the form of ATP** caused by insufficient oxygen and glucose supply. Neurons do not have enough energy to maintain basal vital processes and to perform their functions. This will lead to many changes, such as:

- **acidosis** – caused by anaerobic metabolism, leading to the production of lactic acid,
- **impaired metabolism of lipids** – manifests by lipolysis and lipid peroxidation what lead to functional and morphological changes mainly of cell membranes,
- **impaired metabolism of proteins** – characterized by phosphorylation of proteins leading to dysfunction of receptors, ion channels, proteolysis with the conversion of enzymes and may inactivate cellular cytoskeleton,
- **accumulation of Ca^{2+} in cytoplasm –** it is the consequence of malfunction of membrane

transport mechanisms (accumulation of calcium supports activation of proteases and lipase in cells),

- **production of oxygen reactive species (radicals) -** they are highly reactive and their interaction with intracellular molecules leads to functional and further morphological damage of neurons,
- **decrease of resting membrane potential, eventually complete depolarization of cell –** this may lead to impaired or completely blocked production and conduction of impulses in the neural tissue,
- **release of excitatory neurotransmitters** from damaged cells (e.g. glutamate) lead to the intensification of cell processes further increasing needs for oxygen and glucose, and by this way increasing intensity of cell hypoxia,
- **onset and progression of cellular oedema –** consequence of increased cell membrane permeability for Na^+ with subsequent Na^+ influx into the cells, which is followed by influx of water.

c) Changed regulation of brain vessels

Regulation of arterial lumen arteries may be changed in the ischemic focus, what may further contribute to the intensity of ischemia and size of ischemic field. In healthy brain, mainly penetrating (nutritional) vessels react to the gain of $PaCO_2$ by vasodilation. In ischemic focus, they react with abnormal or paradoxical responses (their vasodilating reaction is decreased or they do not react to CO_2 at all, or they react by vasoconstriction). Myogenic autoregulation of lumen of brain arteries is also important for blood supply to brain cells. In physiological conditions, increase of blood pressure in cerebral arteries leads to autoregulatory decrease of arterial lumen followed by decrease of blood flow. This decrease of arterial lumen is ascribed mainly to vascular smooth muscle constriction induced by releasing calcium into the cells which is stimulated by stretch of smooth muscles. Contrariwise, when there is decrease of blood pressure in cerebral arteries it will lead to vasodilatation with consequent increase of blood flow. Thank to existence of myogenic autoregulation there is stable blood flow in brain arteries maintained even in large fluctuations of systemic blood pressure (between 60 to 160 mmHg). In ischemic zone of brain tissue, this autoregulatory mechanism is also impaired which may be responsible for insufficient vasodilatory response and decreased blood flow to ischemic tissue. These abnormal responses of brain vessels decrease the efficacy of reperfusion and they initiate

phenomena such as post-ischemic hypoperfusion, luxury perfusion and steal phenomenon. (explanation in the handout from the lecture).

d) Steal phenomenon

The interconnection of ischemic and non-ischemic vascular territories by anastomotic channels may divert blood from one region to the other, depending on the magnitude and the direction of BP gradient across the anastomotic connections. **BP gradient may be in such situation directed from ischemic to non-ischemic territory** which may increase intensity of ischemia in ischemic brain field. If this disturbance is accompanied by clinical symptomatology we call it **steal syndrome (phenomenon).** Such a situation may be present in patients suffering simultaneously from focal brain ischemia and respiratory failure with hypercapnia. Hypercapnia will dilate the collaterals in non-ischemic part of brain leading to vasodilatation and decrease of BP in them. Contrariwise, collaterals in ischemic part will not dilate, so their resistance will be higher than in non-ischemic part collaterals. Result will be pressure direction from ischemic to non-ischemic part of brain – blood will leave ischemic field which will result to amplification of ischemia.

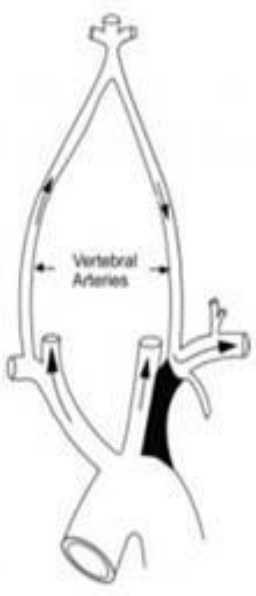


Figure 14.4: Example of extracerebral steal mechanism

The proximal part of left subclavian artery is blocked (black field) so there is no blood flow into left vertebral artery and to left arm. Blood from right vertebral artery enters left vertebral artery and flows back to supply left arm - steals blood from vertebral arteries and

also from brain.

e) Threshold of ischemic injury, ischemic penumbra

Consequences of ischemic injury depend on its **intensity, speed of development and duration.** If there is gradual decrease of oxygen delivery to brain tissue, one can observe two main stages of disturbances:

a) reversible disturbances of coordinating and electrophysiological functions of brain

b) irreversible structural damage of brain tissue occurs

Certain populations of cerebral neurons are selectively vulnerable to ischemia, e.g. hippocampal neurons (Fig. 5). These neurons belong to the limbic system and play important roles in the consolidation of information from short-term memory to long-term memory and spatial navigation. So, consequences of ischemic damage of them lead to problems with long-term memory.

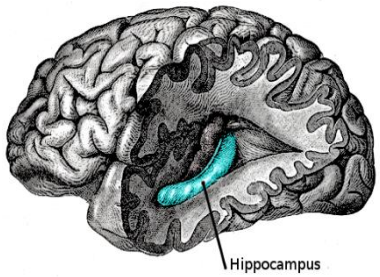


Figure 14.5: Localisation of hippocampus within the brain

Development of reversible and irreversible disturbances has individual dynamics which is influenced by:

- **intensity of ischemia** – more severe ischemia will lead to faster development of these changes,
- **duration of ischemia** – longer ischemia leads to more severe changes than shorter,
- **position of cells in ischemic focus** – ischemia is more severe in the centre of ischemic field and mentioned changes also appear faster; cells located in the periphery of the focus are exposed to less intense ischemia (positive effect of collateral circulation) – therefore, aforementioned changes appear later and they are less intense,
- **temperature in ischemic focus** – higher temperature leads to augmentation of aforementioned pathological processes, cooling of the ischemic tissue slows down the onset and intensity of its pathological consequences,
- **concentration of glucose in ischemic focus –** increased glucose (e.g. in decompensated

diabetes mellitus) increases speed of lactic acid formation which leads to stronger damage of nerve cells.

Position of cells in the ischemic focus is indeed important factor which determines **severity of their damage and a time of their survival.** Neurons located at the periphery of ischemic focus are moderately damaged, but still viable, and their damage can be reversed by optimal reperfusion (early after beginning of ischemic attack, and enough blood perfusion) of this field and to restore their normal function. Their damage was just functional and is fully reversible. This zone of damaged, however still viable cells is called **ischemic penumbra**. These cells located in the penumbra zone can be saved by qualified and optimal therapeutic approach – and of course, this can lead to the restoration of important brain functions.

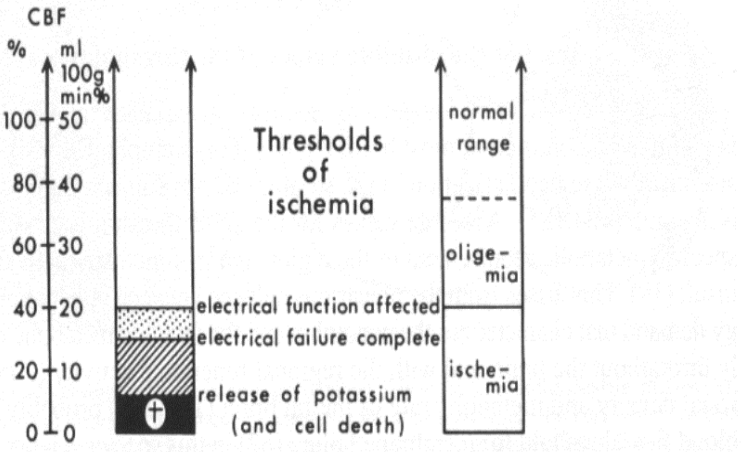


Figure 14.6: Scheme shows relation between brain perfusion (CBF) and development of brain cells damage

f) Changes in volume and composition of fluids in ischemic field, ischemic brain oedema

1) changes in extracellular fluid (ECF) composition:

- decreased concentration of natrium and calcium,
- increased concentration of potassium,

2) Changes in extracellular volume

- decreased volume of ECF

Mechanisms responsible for mentioned changes:

- increase cell membrane permeability due to ischemic damage leads to influx of natrium

and calcium from ECF to intracellular cytosol

- potassium will pass in opposite direction – from cell to ECF

Increase of cytosolic calcium concentration is one of three main factors involved in development ischemic brain injury (other two are acidosis and free radicals).

3) Biochemical changes

Biochemical changes in energy metabolism - first step: shortage of O_2; second step: shortage of glucose. Results are increased NADH, deceased ATP and KP, increased concentration of lactate, lack of energy, acidosis.

Lipid metabolism:

- increased intracellular Ca^{2+} concentration leads to activation of membrane phospholipase A_2 which results in release of poly-unsaturated fatty acids into intracellular compartment
- activation of phospholipase C leads to development of arachidonic acid and PGs, LTs, TBs
- disturbances in neurotransmitters synthesis, degradation, releasing and binding,
- with prolonged or severe ischemia: - decrease of norepinephrine, serotonin, dopamine, increase alanine and GABA (inhibitory neurotransmitters), decrease of aspartate and glutamate (excitatory neurotransmitters).

4) Ischemic brain oedema – it is accumulation of abnormally high amount of fluid in brain tissue. Brain oedema aggravates the pathological process induced by primary ischemia in different ways:

- by interfering with the water and electrolyte homeostasis of the tissue,
- by its adverse effect on myelinated nerve fibres,
- by its volumetric effect causing local compression of the microcirculation, rise intracranial pressure, dislocation some parts of the brain.

Mechanisms involved in development of ischemic brain oedema:

- cytogenic component – due to damage of cell membrane permeability, result: intracellular oedema
- vasogenic component – due to damage of blood-brain barrier, result: extracellular

oedema.

Examples of clinical consequences of focal brain ischemia

1) Neurological deficit

Severity of neurological deficit depends on the intensity, and extent of ischemia, while the character of symptoms depends on location of ischemic focus in the brain. The signs and symptoms are related to the **impaired motor functions** (paresis, paralysis), **sensory dysfunction** (paraesthesia, hypaesthesia, anaesthesia, dysesthesia) affecting different parts of the body.

Figure 14.7

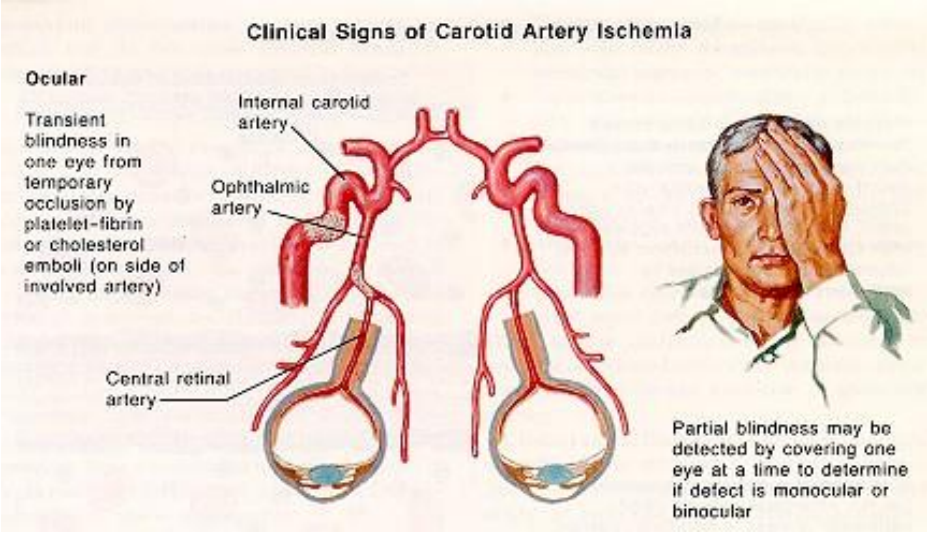
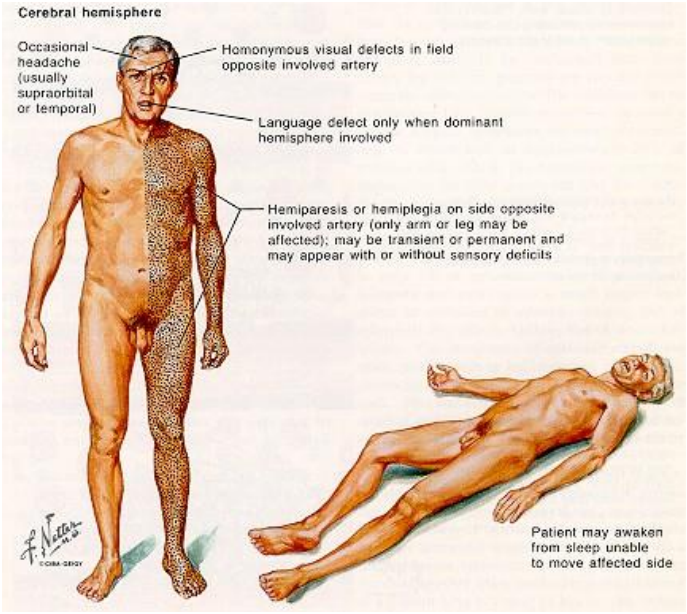


Figure 14.8



CASE REPORTS

Case report 1

54-years-old woman was brought to the emergency department with the history of sudden tonic convulsions (cramps) of left lower and upper extremities and left side of the face. She was not unconscious, and the cramps were followed by muscle weakness at affected side and headache located in the right parietal region. She has never experienced such a situation before, and she has never had any head injury. She is on hormonal substitution therapy – Climonorm.

History: As a child, she was diagnosed with heart murmur, which disappeared spontaneously; she had a goitre and she was treated for hypothyroidism, she has tendency to hypotension; she has 2 children, now menopause since the age of 48 years with Climonorm medication; she has varices, smokes 15 cigarettes daily, she has headache sometimes.

Complaints: At 1 PM the patient started to feel cramps in the left leg and arm, and left side of her face. She sat on the chair, and felt pain at the right side of her head, located to the parietal field. Approximately after 3 minutes, she started to feel her left side becoming weak and she noticed that the left side of her face appears to be melting. She was still conscious, and she called for help. Her condition was slightly improving over time.

Clinical findings: BP: 100/60 mmHg, heart rate 92/min, breathing rate 15/min, Sat O_2: 98%, body temperature was normal. Patient is fully aware of situation, anxious, there are no problems with speech, attenuated movement of eyes to the left side, high probability of quadrant hemianopia at the left side, central paresis of facial nerve, no meningeal symptoms, pulsation of carotid arteries is symmetric, without murmurs, left hemiparesis of second degree, affecting more the arm and hand, patient is able to lift it up and to keep it above horizontal position; mild to moderate left side hemihypesthesia was found as well. There is also ataxia of the upper and lower extremities at the left side present. CT scan does not show haemorrhage. Osmolarity: 305 mOsmol/L.

Questions & Tasks

1) Identify all substantial signs and symptoms present in this patient.

2) What are the mechanisms leading to her problems?

3) What is probable diagnosis?

Case report 2

Patient is 57-years-old man complaining about at least 2 weeks lasting problems with his right hand. Hand is a kind of clumsy, and he cannot use it to perform gentle and exact movements. The onset of the problem was sudden, without progression, so the intensity of his problems is the same as it was in the beginning. There are no problems with the other extremities. He denied having sensory problems, focal weaknesses or headache. He also denied having doubled or blurred vision, problems with swallowing, speech; he also denied cramps or fainting. He however accepts having headaches, which were diagnosed as migraine, but they were never associated with motoric problems with the right hand. He was previously diagnosed with polycythaemia, and his wife is reporting that he used to have red face and hands. Patient is very active, and on the day of admission he already had completed 10 km run. He is non-smoker, does not drink alcohol and does not take any drugs or medication. Family history does not reveal diseases, which can be related to present problems (neurological or haematological diseases).

Clinical examination: patient looks healthy at the first sight**,** afebrile, normotensive, with sinus rhythm on ECG. Neurological tests: mild dysmetria of right hand during the hand-nose test. Testing of the muscle strength showed intact intensity of muscle contraction, there were no signs of focal atrophy or involuntary movements. He cannot push proper buttons of his mobile phone by right hand; however, he can by left – non-dominant hand without any problems. Cranial nerves are intact; speech is fluent, normal, no aphasia or dysarthria, no ataxia during walking. Mental status of the patient was completely intact, his face and hands were plethoric with a mild degree of erythema.

Laboratory findings: Hbg – 213 g/L, Htk – 61.6%, WBC – 6.22 x 10^3/mL with 75% neutrophils, PLT – 345x10^3/mm^3, standard autoimmune markers including antinuclear antibodies were negative. Analysis does not show mutation of factor V Leiden, which would increase coagulation, and mutation of prothrombin gene G20210A (mutation of this gene increases coagulation by increased production of factor II – prothrombin). CT scan showed two foci of decreased density in the left parietal lobe, size of the foci is approx. 11 mm. Heart EF was 55%, vegetation on valves were not present.

Primary treatment: two units of full blood were taken away, and the volume was substituted by 1 l of saline, patient was given Clopidogrel, and haematologist was called for consultation. His primary diagnosis was Polycythaemia vera; later the mutation of gene JAK2 V617F was detected. This mutation is associated with myeloproliferative diseases.

Brain MRI showed 15 - 20 foci with limited diffusion, the size of defects is between 3 and 14 mm, what indicates multiple embolization to the part of left hemisphere supplied by a. cerebri media. MR angiogram does not show critical stenosis of cerebral arteries. Transoesophageal ultrasound of the heart also excluded open foramen ovale, atrial septal defect, atrial thrombus and right-to-left shunt. ECG Holter does not detect arrhythmia, and abdominal ultrasound has detected moderate splenomegaly.

Questions & Tasks

1) Identify all signs and symptoms related to the previous and current patient's health problems.

2) Explain mechanisms responsible for these signs and symptoms.

3) Can these problems be related to his physical activity?

4) How elevated haematocrit influences subjective feelings and objective findings in this case?

Case report 3

Middle-aged man was admitted to the ER unresponsive. He was accompanied by a nurse – she saw him by accident while he was sitting in the hospital corridor when he had suddenly fallen off the chair to the floor and this was immediately followed by generalized convulsions. She called for help immediately; there is no other history or no other information about the patient.

Clinical findings: patient is now responsive, but confused**,** does not reply properly to the doctor's commands, breathing is regular, and he is on oxygen. Vital functions are: temperature 38 °C, BP – 170/90mmHg, heart rate – 105/min, breathing rate – 18/min, Sat O_2 – 99% on 2 l/min oxygen.

Neurological examination: pupils react to light on both sides, symmetric response, vomiting reflex is intact, reduced mobility of the left side of the body, Babinski reflex positive on both sides, other findings are normal.

Questions & Tasks

1) What may be the cause of patients' fall off the chair?

2) What may be the cause of unconsciousness?

3) What may the cause of convulsions in this case?

4) How would you explain the muscle weakness on the left side of the body?

Case report 4

72-years-old man was admitted to the hospital with muscle weakness affecting the right side of the body. It happened during the breakfast when he suddenly experienced the weakness and he was not able to move his right hand and leg. He also lost sensory function at the right side of the body and he experienced problems with speech. His wife had called an ambulance.

History: long history of arterial hypertension**,** hypercholesterolemia, and lately he was diagnosed with coronary artery disease.

Vital signs: normal, except BP - 190/100mmHg.

Neurological examination: melting of the right side of the face, right sided hemiparesis, positive Babinski reflex on the right side, CT scan excluded bleeding.

Questions & Tasks

1) Identify the main signs and symptoms and explain the mechanisms of their onset.

2) What causes may lead to the patient's condition?

Chapter 15

ARTERIAL HYPERTENSION

Arterial hypertension is the main risk factor for coronary, cerebral and renal vascular diseases, and the risk rises progressively with increasing systolic and diastolic pressure. The number of patients with hypertension increases and according to latest epidemiologic data, 20% of all adults have hypertension, in population of 60+ it is 50% of subjects who have hypertension. Only in half of them the hypertension is recognised and treated, and only half of these cases are treated properly. This leads to the unfolding rise of cardiovascular complications of hypertension. Hypertension is called a "silent killer" because its development is progressive and clinically silent. Presence of complication indicate already advanced stages of hypertension with severe vascular damage. Heart failure, cerebral ischemia and chronic renal insufficiency are frequent consequences of developed hypertension. According the Guidelines of European Society of Hypertension the blood pressure values should be interpreted as follows - this classification is based on the values of seated blood pressure measured in the office or hospital by a healthcare professional.

Class	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Optimal	< 120	**AND**	< 80
Normal	120-129	**AND/OR**	80-84
High normal	130-139	**AND/OR**	85-89
Grade 1 hypertension	140-159	**AND/OR**	90-99
Grade 2 hypertension	160-179	**AND/OR**	100-109
Grade 3 hypertension	≥ 180	**AND/OR**	≥ 110
Isolated systolic hypertension	≥ 140	**AND**	< 90

Long-term regulation of arterial pressure

Nervous system has abilities for rapid, short-term control of blood pressure, however, when arterial pressure changes over many hours or days the nervous mechanisms gradually lose their ability to oppose the changes. Therefore, it is important to understand, that regulation of blood pressure over a long period of time is controlled by the kidneys via regulation of sodium balance (extracellular fluid volume).

The renal regulation of arterial pressure is very simple. When the body contains too much fluid, the blood pressure rises and the rising pressure in turn has a direct effect on

kidneys, which will excrete the excess of fluids returning blood pressure to the normal. The relationship between blood pressure and urinary volume output is described by renal output curve (fig.1- denervated kidneys in anaesthetized dog). At an arterial pressure about 50 mmHg, the urinary output is essentially zero. At 100 mmHg, it is normal and at 200 mmHg, about six to eight times normal. Over a long period of time the water and salt output must equal the intake. The only point on the graph where intake equals output is the intersection of the two curves called **equilibrium point**. What will happen if the blood pressure rises to let's say 150 mmHg? At this level, the renal output of water and salt is about three times as great as the intake, therefore the body loses fluids, the blood volume decreases so does the arterial pressure. Furthermore, this negative balance of fluid will not cease until the pressure drops back to the equilibrium point. If the arterial pressure decreases below the equilibrium point, the intake of water and salt is greater than output, therefore the body fluid volume increases, the blood volume increases so does the arterial pressure until it once again returns to the equilibrium point.

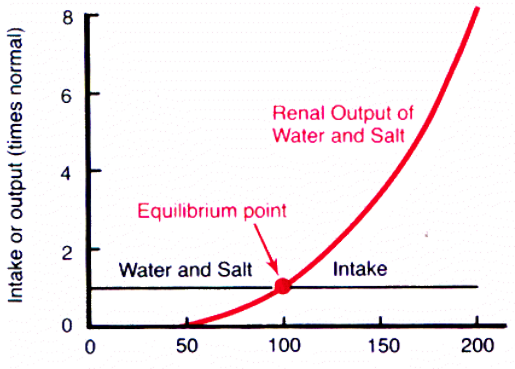


Figure 15.1

There are two main determinants of the long-term regulation of the arterial pressure – the degree of shift of the renal output curve for water and salt to the right side along the arterial pressure axis, and the level of water and salt intake line. Fig 2A demonstrates some abnormality of the kidney which caused the renal output curve to shift 50 mmHg in the high-pressure direction (to the right). The equilibrium point is also shifted 50 mmHg higher than normal. Therefore, one can state that if the intake of water and salt remains constant, but the renal curve shifts to a new pressure level, so will the arterial pressure follow to this new pressure level within a few days. Fig 2B illustrates how a change in the level of salt and water intake can change the arterial pressure when the renal output curve remains the same - in this

case the salt and water intake increased fourfold and the equilibrium point has shifted to the pressure level of 160 mmHg.

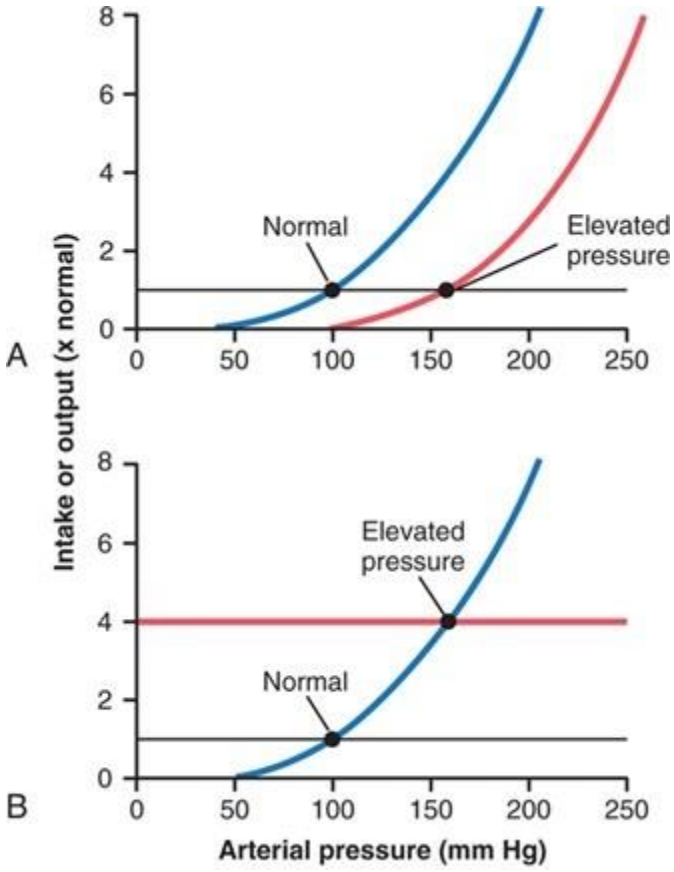


Figure 15.2.

Therefore, it is impossible to change the long-term mean arterial pressure to a new level without changing one or both of the two main determinants – either the level of salt and water intake or the degree of the shift of the renal curve to the right side. The arterial pressure is afterwards regulated at the new point – point where these two curves intersect.

Arterial pressure equals cardiac output times total peripheral resistance, it is clear that an increase in total peripheral resistance should elevate the arterial pressure. Many times, when the total peripheral resistance increases, this increases also the intrarenal vascular resistance at the same time, which alters the renal function and can cause hypertension by shifting the renal functional curve to the higher pressure in a way illustrated at the fig. 2A.

The role of increased volume in elevation of arterial pressure

Increased volume of extracellular fluid increases the blood volume, and this further increases the venous return and finally cardiac output. Increased cardiac output is one of the determinants of increased arterial blood pressure. Increased cardiac output can have either direct effect on blood pressure or also indirect effect resulting from tissue autoregulation of the blood flow. Whenever an excess of blood flows through a tissue, its vessels react by vasoconstriction to decrease the flow back towards normal. When increased volume of extracellular fluid increases the cardiac output – the blood flow increases in all tissues, so the autoregulation mechanisms will lead to vasoconstriction all over the body and in turn, it will also increase the total peripheral resistance. It is important to note that the main determinant of the extracellular fluid volume is sodium.

Arterial blood pressure is the pressure of blood on the lateral wall of a particular segment of the artery. The pressure in particular section of artery depends on volume of inflowing and outflowing blood (to and from this section) and peripheral vascular resistance determined by lumen of arteries. Blood pressure will increase if cardiac stroke volume increases in unaltered arteriolar lumen or in case of arteriolar vasoconstriction in unaltered cardiac output. Hypertension will develop faster if these two determinants will combine. Since the cardiac stroke volume and peripheral vascular resistance are regulated by numerous factors, diagnosis of the causes of hypertension is not easy and requires a sophisticated approach.

Primary (essential) hypertension

In 90-95% of patients with hypertension is not possible to recognize single or specific cause of hypertension, so it is referred as essential. Since persistent hypertension can develop only in response to an **increase in cardiac output or a rise in peripheral resistance,** defects may be present in one or multiple factors affecting these two parameters. Looking for a single defect in all patients with primary hypertension may be a mistake. At the other side, there are multiple mechanisms participating in the regulation of the blood pressure, and the essential hypertension is a hemodynamic consequence of disturbed hormonal, neural and renal regulation of blood pressure developed on multifactorial background.

One factor should be kept in mind. The pathogenesis of the disease is slow and progressive process, by the time blood pressure becomes elevated, the initiating factors may no longer be apparent, since they may have been “normalised” by the compensatory interactions already involved in the process. When group of untreated young hypertensive

patients were studied, cardiac output was normal or slightly increased and peripheral resistance was normal. Over the next 20 years, cardiac output fell down, while peripheral resistance rose. It is supposed in general, that in the initial phase there are involved mechanisms increasing the cardiac output, while later, in the advanced disease, there are involved mechanisms increasing the peripheral resistance with nearly normal cardiac output.

Mechanisms of primary hypertension

In recent years, most scientists agree that the basic mechanisms regulating blood pressure - cardiac stroke volume and peripheral vascular resistance are impaired by **several factors simultaneously,** and there are complicated relationships between them. The idea that essential hypertension is the result of failure of one factor is incorrect.

Dominance of sympathetic nervous centre in the brainstem over parasympathetic can be inherited or acquired due to intense emotional load and long-lasting stress. Increased concentration of catecholamine increases the cardiac output by increased rate and strength of myocardial contractions. It also increases peripheral resistance by contraction of arterial/arteriolar smooth muscles.

Also increased activity of system **renin-angiotensin-aldosterone (RAA)** may contribute to the primary hypertension. Angiotensin II as the strongest endogenous pressor increases the peripheral resistance and via aldosterone it causes reabsorption of sodium and water in the renal tubuli thus increasing volume of circulating fluids. Increased venous return to the heart increases the cardiac output. System RAA is also a growth promoter – long lasting hyperactivity of RAA system lead to the hypertrophy of vascular smooth muscles, and this participate in sustaining of the hypertension.

Circumstantial evidence supports a causal role for sodium in the pathogenesis of the hypertension, mainly its accumulation in the cytoplasm of the cells. This condition is very likely a consequence of **defects in the membrane transport in the vascular smooth muscle cells**. Concentration of the sodium in the cell is controlled by the plasma membrane Na^+ pump, which operates in parallel with the Na^+- Ca^{++} exchanger. Accumulation of sodium in the cytoplasm is potentially toxic for the cell, therefore, it is eliminated out of the cell by its exchange with Ca^{++}. Increased concentration of Ca^{++} in the muscle cells increases the strength of contraction as a response to pressor stimuli e.g. catecholamine or angiotensin II, which is several times higher than normal physiological response of the vessel. Arteries become hypersensitive to pressor signals.

Hypertension is more common among obese people and ads to their increased risk of developing cardiovascular complications e.g. ischemic heart disease. Combination of hypertension with android type of obesity, dyslipoproteinemia, and hypolipoproteinaemia and insulin resistance is called **metabolic syndrome**. Insulin influences multiple processes contributing to the hypertension. It has been postulated that **insulin resistance** and the concomitant **compensatory hyperinsulinemia** contribute to the pathogenesis of hypertension. Insulin is a potent trophic hormone which promotes hypertrophy of vascular smooth muscles. In addition, insulin promotes sodium retention in the kidneys through a direct mechanism and hyperinsulinemia increases sympathetic nervous activity.

As it was described already, **increased peripheral vascular resistance** is important mechanism participating in pathogenesis of hypertension. At the beginning of the process, the resistance is caused mainly by functional changes – vasoconstriction. Although functional constriction of vascular smooth muscles is portrayed as a possible mechanism, it appears that high peripheral resistance in hypertension is determined also by structural hypertrophy. Vascular wall hypertrophy causes permanent narrowing of the arterial lumen and also more intense vasoconstrictor response to normal concentration of vasoconstrictors. Slowly developing vascular hypertrophy is attributed to growth factors, which in case of essential hypertension are norepinephrine, angiotensin II and insulin.

Important role in essential hypertension is played by kidneys and their ability to excrete the sodium. As long as kidneys maintain the balance between sodium intake and excretion, the volume of extracellular fluid remains normal. If the amount of excreted sodium does not equal the sodium intake, this lead to the positive sodium balance and expansion of extracellular fluid. The recent data indicate that patients with essential hypertension could have **inherited or acquired defects in the kidneys characterized by inability to quickly excrete sodium and water.** This functional defect is not related to any clinically manifested disease or condition.

The **role of genetic factors** is also discussed. Every single component participating in the regulation of blood pressure can be affected by genetic alteration, which in combination with epigenetic factors may lead to the manifestation of hypertension. Number of such alteration have been suggested, e.g. alteration of Na^+ transport mechanisms across the cell membranes, defects in renal excretion etc. This concept was confirmed by studies of the twins and family members of patients with hypertension, which confirmed genetic contribution ranging from 30-60%. Essential hypertension is not a monofactorial disease, it is a consequence of combination of multiple factors.

Genetic predisposition is one them, and it has considerable **prophylactic outcome**. Although some of the mechanisms participating in the regulation of blood pressure are altered (on genetic basis) it does not necessarily lead to the onset of hypertension, or eventually development of hypertension may be slow, if the subject with genetic predisposition avoids exposure to external epigenetic factors knows as "civilisation factors". E.g. smoking cessation or reduction of stressors will reduce activity of sympathetic system in case of inherited "over activity" of sympathetic system. Reduced salt intake in the situation that kidneys are not able to eliminate it due to inherited defects may also prevent onset of hypertension. However, it is important to note that not every smoker or every person with high salt intake will develop hypertension. If the mechanisms counterbalancing these negative external factors are enough effective, negative effect of external factors will not manifest and patient will not develop hypertension.

It is critically important to educate the population to eliminate or reduce the **exposure to the risk factors** in general, because it is not known how severe the genetic predisposition in every individual is. Populations known to have very high salt intake have much higher blood pressure values. Healthy lifestyle e.g. coping strategies to manage stress, not smoking, low alcohol and salt intake, regular physical exercise and caloric intake equal to the metabolic demands is important preventive measure against hypertension.

Secondary hypertension

5 – 10% of patients with hypertension have **secondary hypertension**, a condition in which the ethiopathogenesis of dysregulation of blood pressure is known. When this cause is treated, then the blood pressure returns to normal values. The most common conditions leading to the secondary hypertension are **narrowing of the renal arteries, damage of the renal parenchyma, medication, hormonal contraceptives, pathologies in pregnancy and certain endocrine diseases**. Recently, **sleep apnoea** is frequently associated with hypertension. The reason is that desaturations following apnoea during the night repeatedly activates sympathetic nervous system. This imbalance may lead to dysregulation of blood pressure.

Renal hypertensions

These are consequences of exactly specified renal diseases in comparison to essential hypertension where renal dysfunction remain at "subclinical" level and does not manifest by signs and symptoms.

a) **Acute renal diseases** may lead to the hypertension. It may appear with any sudden, severe insult to the kidneys (glomeruli) that either markedly impairs the excretion of salt and water, which leads to the ***volume expansion***, or reduces renal blood flow, which activates the ***renin-angiotensin-aldosterone*** mechanisms. Typically, hypertension accompanies the oliguria and fluid retention after acute renal injury.
b) **Chronic renal diseases with renal insufficiency** is predominantly caused by volume overload resulting from the inability of the reduced functioning renal mass to handle sodium and water intake. This may involve increases in pressor sensitivity to sodium and redistribution of more fluid into the intravascular space. Some degree of renin-mediated vasoconstriction is probably also involved in many patients.
c) **Renovascular hypertension** is the most common form of secondary hypertension. It is caused by narrowing of the renal vasculature which diminishes the perfusion pressure in the afferent arterioles. Then, increased amount of renin is released, which influences peripheral arterial resistance via angiotensin II and volume of extracellular fluids via aldosterone. Both mechanisms combine thus increasing the blood pressure.

Endocrine diseases

Excess of certain hormones produced by adrenal gland may also lead to the hypertension. They are **catecholamine** – produced in pulses by a tumour called pheochromocytoma, then **aldosterone** – produced by an adenoma (primary hyperaldosteronism), and **cortisol**, also produced by an adenoma. Even the primary target of the cortisol is metabolism of glucose, lipids and proteins, it also has mineralocorticoid effects similar, however weaker than the effect of aldosterone. Exogenous sources of cortisol (medication) may also lead to the hypertension. Tumours, located in the kidneys may produce **renin.** This condition may lead to the hypertension. **Hyperparathyroidism may also lead to the hypertension -** if the glands secrete too much parathyroid hormone, the amount of calcium in the blood rises — which triggers a rise in blood pressure. From the endocrine causes it is also important to note **per oral contraceptive pills**, in which both oestrogen and progestogens cause sodium retention.

Complications of hypertension

Even moderate elevation of the arterial pressure leads to the shortened life expectancy, at very high pressures – mean arterial pressures 50% or more above normal – a

person can expect to live no more than a few more years at most. The lethal effects of hypertension are caused mainly in three ways.

Arterial hypertension represents the most common reason for **pressure overload of the left ventricle,** its cardiac manifestation refers to the involvement of both **myocardium and coronary arteries.** Heart muscle itself develops hypertrophy, a decrease in myocardial contractility, cardiac dilatation and, in the end stages, global cardiac insufficiency and pump failure. In the coronary vascular bed, hypertension leads to coronary macro and microangiopathy and in general, **hypertension accelerates the process of atherosclerosis**. Consequently, the coronary resistance is increased, the oxygen availability to the myocardium is impaired, coronary insufficiency and angina pectoris occur, and on the basis of regional contraction disturbances due to myocardial infarction cardiac failure develops.

Another regional circulation frequently affected by hypertension is cerebral vascular network. The vessels are affected by atherosclerosis with narrow passages and eventually aneurysms of these vessels. The sudden increase of the blood pressure may cause a rupture of a major blood vessel in the brain (usually microaneurysm), followed by clotting of the blood and necrosis of major portions of the brain (intracerebral haemorrhage). Narrowed passages may limit the blood supply to the brain, leading to the necrosis of the cells caused by hypoperfusion and ischemia. Both bleeding and ischemia induced **cerebral infarction clinically manifest as "stroke"**. Depending on what part of the brain is involved, a stroke can cause paralysis, dementia, blindness or multiple other serious brain disorders.

Every single form of hypertension leads to the **kidney damage**. Long lasting hypertension causes a damage to the **renal arterioles and glomeruli** (nephrosclerosis) and it leads finally to the renal ischemia. Therefore, hypertension, primary caused by other than renal causes will turn into the "renal" hypertension thanks to the contribution of developed nephrosclerosis. ***Circulus vitiosus*** develops, in which the renal ischemia and hypertension promotes each other. Progressive loss of functioning nephrons leads to the renal failure, uraemia and death.

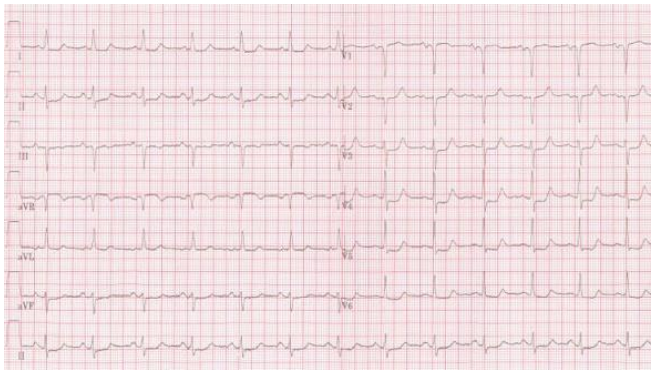
CASE REPORTS

Case report 1

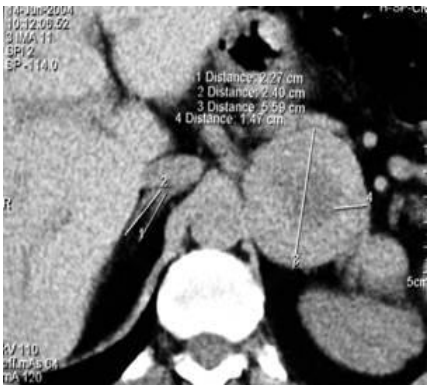
43-years-old patient was admitted to the emergency department with severe headache, nausea, palpitations, fainting and sweating. These symptoms appear repeatedly, they come in a form of attacks and they are gone in like 15 min. There is no obvious trigger for these

attacks, however the patient has noticed they are associated with sudden pallor and anxiety. She never visited her doctor, because she thought this was a manifestation of the menopause. Your patient has never been ill seriously, she does not take any medication, she smokes 5 cigarettes/day, drinks 3 cups of coffee/day, and drinks alcohol occasionally. In ambulance, she received treatment – magnesium, vasodilators and β-blockers. During the examination, the patient is anxious, restless, BP 230/120 mmHg, heart rate 160/min, couple of min later 75/ min, breathing rate 20/min, Na 130 mmol/L, K 3.4 mmol/L, Cl 80 mmol/L, glucose 7.8 mmol/L, urea 2.5 mmol/L, creatinine 80 μmol/L, ALT, AST normal

ECG showed depression of ST segments, mainly in the leads from the left precordium what indicates nonspecific strain of the left ventricle, probably due to the rise of the pressure in arteries. Myocardial markers were negative. Because of episodic presence of the symptoms the doctor suggested the diagnosis of pheochromocytoma, which was later confirmed by CT and laboratory findings.



ECG



CT scan

Questions & Tasks

1) Which laboratory findings can confirm the diagnosis of pheochromocytoma?

2) Explain the mechanisms responsible for symptoms and signs in this patient.

3) Is such elevation of the blood pressure dangerous? What complications may occur?

4) Evaluate the ECG of the patient and analyse, if it matches to the criteria for left ventricular hypertrophy.

5) What effects are expected from the medication used in the ambulance?

Case report 2

45-years-old man with BMI higher than 33 was on regular check-up in his GP. The blood pressure reading showed elevated arterial pressure 160/100 mmHg. Patients does not

have any problems at the moment, however, he has positive family history for hypertension (mother died to heart attack and father died to a stroke). GP recommended 24-hour measurement – Holter test. Blood samples were taken the next morning.

Laboratory examination: Na 146 mmol/L, K 4.5 mmol/L, Cl 97 mmol/L, AST, ALT normal, GMT & ALP slightly elevated, glucose 8.4 mmol/L, creatinine 97 μmol/L, urea 4.8 mmol/L, cholesterol 6.7 mmol/L, TAG 3.2 mmol/L.

Holter 24 hours monitoring of the blood pressure showed that patient has elevated blood pressure all day, with the drop during the sleep. Patient was recommended to make an appointment in DM specialist because of his obesity, high blood pressure, hypercholesterolemia, hypertriglyceridemia and high fasting glucose.

Questions & Tasks

1) Define the syndrome of insulin resistance.

2) Explain how hyperinsulinemia contributes to the hypertension.

3) What are the consequences of combination of hypertension and hyperlipidaemia?

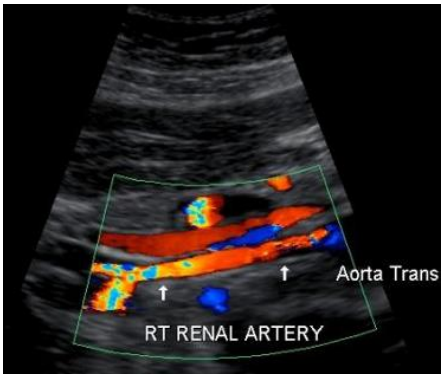
4) Does the fasting glucose concentration indicate diabetes?

5) Define the relationship between the obesity and insulin resistance.

Case report 3

40-years-old patient with BMI 30 was examined because she realized that she is having high blood pressure (repeatedly measured by automatic manometer at home). She is aware of her body weight issue, so she has changed her lifestyle and lost 5kg of body weight. She also started to use low salt diet, however, the blood pressure remained high. On examination: patient is hypersthenic, BMI 30, obesity of the "apple" shape, waist circumference 94 cm. BP 170/100, pulse 72 bpm, breathing rate 13 bpm. Heart action regular, no murmurs, breathing sounds normal, without pathological sounds. Patient also had ultrasound of renal arteries, kidneys, adrenal glands, carotid vessels and ophthalmologic examination.

Waist circumference 94 cm



Ultrasound of renal arteries

ECG: Sinus rhythm, 70 bpm, regular, axis intermediary type, with normal conduction intervals. Heart USG: diastolic and systolic function of the left ventricle normal, EF 75 %, minimal mitral regurgitation, without ventricular hypertrophy.

Questions & Tasks

1) Why the ultrasound of renal arteries and kidneys was performed?

2) Why the waist circumference was measured? What are the negative consequences of android type of obesity?

3) What is the relationship between Na and blood pressure in the body?

4) What type of changes in the heart would you expect in subjects with long lasting hypertension?

5) What would be the trend of the blood pressure if the patient reduced her body weight even further and maintained it?

Chapter 16

ISCHEMIC HEART DISEASE

Definition and notes from physiology

Ischemic heart disease is defined as acute or chronic dysfunction of the heart caused by considerably reduced blood supply to the myocardium, and this condition is a consequence of pathological processes inside the coronary arteries – mainly coronary atherosclerosis.

Cardiomyocytes need continual supply of metabolic substrates – mainly oxygen – for their permanent work. Heart cannot utilize energy resources without **oxygen**, because the metabolic chains in the cardiomyocytes are strictly aerobic. It means that energy in a form of ATP is produced only in case of optimal oxygen supply. During the rest conditions, the heart utilizes approximately 75% of oxygen being delivered by coronary circulation. In case of increased oxygen demands this can be achieved only by increased blood flow and not by increased extraction of oxygen from blood. Therefore, there is a **linear relationship** between the oxygen consumption and blood flow in coronary arteries.

For optimal work of the heart, there must be a balance between two parameters – myocardial demand for oxygen and conditions of coronary circulation to cover it. So, in fact, oxygen consumption and coronary blood flow must be always balanced and precisely regulated. There are several factors, which determine oxygen demands in the heart. They are **the heart rate, contractility and tension of the myocardial walls.** Factors influencing the supply of oxygen via coronary vessels are **perfusion pressure and resistance of coronary circulation**. Perfusion pressure represents the difference (gradient) of hydrostatic pressure at the beginning and at the end of coronary circulation. Since the pressure in systemic circulation is regulated and maintained at a certain value, the change of oxygen supply via coronary vessels will be provided by the change of their resistance (diameter) – by coronary vasodilatation. Coronary blood flow is precisely regulated under physiological conditions to meet the demand of working myocardial cells. One important extravascular factor should be mentioned. Intramyocardial arteries (branches of major coronary arteries) run from the surface of the heart through the musculature towards sub-endocardial layer; therefore, they are compressed by the extravascular pressure generated with every single systole. These mechanisms increase resistance of the circulation mainly during the systole. These changes are most remarkable in the left ventricle due to strong musculature of this heart chamber.

Much better perfusion of the coronary muscle is therefore during the diastole, so increasing heart rate making the diastole shorter really matters.

Coronary blood flow is regulated by multiple mechanisms: **autoregulation** allows to maintain constant perfusion pressure in coronary circulation even when the systemic blood pressure fluctuates. Constant coronary perfusion pressure is maintained within range from 40 to 160 mmHg of systemic pressure. **Metabolic regulation** has the highest priority. Increased metabolic rate in myocardium leads to production and release of substances which act at the local level and their main action is relaxation of vascular smooth muscle – leading to vasodilatation. This will improve the oxygen supply, so the metabolism runs at the higher requested rate. Metabolic products with vasodilating effects on coronary vessels are **adenosine** (conversion of ATP to ADP) in case of energy consumption. This action is further promoted by main vasodilating mediator – NO. Nitric oxide is produced in vessels constantly by the activity of eNOS, and activity of this enzyme is known to be regulated by shear stress. Switch to anaerobic metabolism is a source of other products with vasodilating effects – they are CO_2, lactic acid, H^+ and K^+ ions. Neural regulation via autonomic nervous system is of low importance.

Causes and mechanisms leading to myocardial ischemia

Myocardial ischemia is a consequence of imbalance between oxygen demands and oxygen supply by coronary arteries. This imbalance is caused either by reduction or block of the coronary blood flow or by increased demands of working myocardial cells, which cannot be covered even by proper regulatory mechanisms. Very often, there is a combination of both mechanisms. Coronary lumen can be reduced to 30-20% of normal lumen even without signs and symptoms of myocardial ischemia during rest. However, when the heart starts to beat faster, or work harder (exercise, emotions), oxygen consumption suddenly increases, and this stenosis inside the coronary vessel becomes significant. The vessel cannot provide enough oxygen to match the supply with increased demands, thus the patient develops myocardial ischemia with clinical presentation and eventually consequences and complications. **Severity and extent of ischemic lesion** is influenced by many factors, mainly by the **site of occlusion**, presence and quality of **collateral circulation.** Also the time of progression is important factor – acute ischemic syndromes are usually dramatic, while chronic forms of ischemic heart disease sometimes remain unrecognized. **Size of ischemic lesion varies** from very tiny lesions (microinfarctions) to extensive massive infarctions affecting majority of the left ventricle. Severity of ischemia also depends on the duration of

vascular occlusion, quality of collateral circulation and load of the myocardium when the occlusion appears. Ischemia can be transient, short-lasting, or it may last longer, it can repeat, or it can be permanent. It depends on the character of the pathological processes inside the coronary circulation – e.g. sudden disruption of the plaque with thrombosis or tight narrowing of the artery caused by "stable plaque" will lead to different types of ischemic damage.

Most common type of pathological processes leading to the ischemic heart disease are **atherosclerotic plaques inside the coronary arteries**. Atherosclerotic plaques – lesions of the vessel wall with accumulation of lipids and endothelial dysfunction on their surface – can be roughly divided into two main categories. Plaques with small proportion of lipids and quite strong fibromuscular surface (stable plaques), which are growing progressively in the arteries, leading to the tight narrowing of the artery (75% occlusion of the lumen usually leads to significant stenosis). Fibromuscular surface of these plaques prevents them from complications like disruption; therefore, stable plaques usually lead to the **chronic forms of ischemic heart disease**. If we even simplify this mechanism further, we can say that **stable plaque determines the presence of stable angina pectoris.** Plaques with huge proportion of lipids and very thin surface layer are smaller in size, but they are much more dangerous. They are called "unstable plaques". Combination of high amount of lipids, high activity of macrophages inside the plaque and thin fibromuscular surface lead frequently to complications such as **rupture of the plaque, bleeding to the plaque or embolization of the plaque components to the distal parts of the artery**. Most dangerous complication is **rupture of the plaque with subsequent thrombosis inside the coronary artery.**

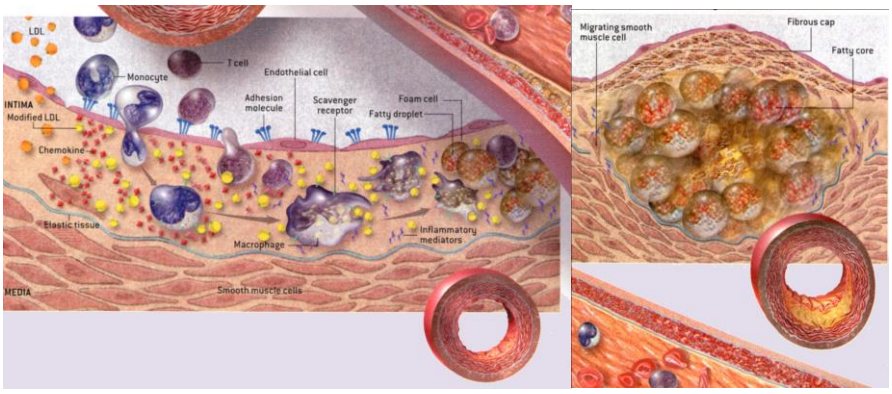


Figure 16.1: Onset and progression of atherosclerotic plaques in coronary arteries

Presence of nonstable plaques (small plaques with big lipid core) represents a risk factor for acute coronary syndromes – nonstable angina pectoris and myocardial infarction. Another important mechanism which may lead to the myocardial ischemia is **spasm of coronary arteries.** It is a consequence of imbalance in production of vasodilating versus vasoconstricting substances. Dominance of vasoconstrictors is typical for endothelial dysfunction which is the hallmark of atherosclerotic process.

The most common cause of acute coronary syndromes is as we said before, **rupture of the plaque with subsequent thrombosis**. Rupture of the plaque is caused by either increased production of proteolytic enzymes by macrophages, which are regular part of atherosclerotic process or by mechanical forces applied to the vessel wall like sever vasoconstriction, very high blood pressure, movement of the arteries with every single systole etc. Rupture of the plaque surface lead to the denudation of endothelial layer and collagen together with tissue factor get contact with the blood. This process initiate formation of the thrombus. Thrombosis if further promoted by **systemic factors** (genetic predisposition for thrombosis, high blood viscosity) or **local factors** (turbulent blood flow, residual thrombus).

Thrombus can be small, causing intermittent occlusion of the artery – this will lead to the **"unstable angina pectoris"** which is defined as sudden presence of ischemic chest pain, with no relation to physical exercise or emotions, lasting more than 15 min, not responding to nitrates or rest). Larger thrombus will cause massive or persistent occlusion, which will turn approx. after 20 min to irreversible damage of the cardiomyocytes – **acute myocardial infarction**. This diagnosis must be confirmed by clinical presentation (ischemic chest pain with some other signs and symptoms), ECG findings, and detection of markers indicating necrosis of cardiomyocytes in the blood. ECG findings are important for further management of the patients. Myocardial infarctions which manifest with elevation of ST segment (so called **STEMI**) need different therapeutic approach then those which manifest without ST elevation (**NONSTEMI**). These findings indicate indirectly severity and extension of ischemic damage of ventricular wall. Presence of ECG abnormalities in certain leads indicate location of ischemic focus (anteroseptal MI, diaphragmatic MI, posterior MI etc.).

Consequences of ischemia

Myocardial cells become ischemic in 10 seconds after occlusion. Early consequences are mainly reduced production of ATP and reduced contractility, exaggerated glycogenolysis, intracellular acidosis, extracellular hyperkalaemia, which will modify distribution of ions in the heart, thus reducing **resting membrane potential of cardiomyocytes**. Resting membrane

potential is determined mainly by uneven distribution of potassium inside vs outside of the cell membrane. This condition potentiated by lack of ATP lead to inability to maintain normal ion transport across the membrane. **It represents risk factor for arrhythmias**. After several minutes, ischemic cardiomyocytes lose their ability to contract and relax, they lack ATP, they produce energy via anaerobic metabolic chains, what lead to production of lactic acid and other end products. Cells are swollen, because sodium cannot be effectively transported out of the cell by ATP pumps, sodium drags water to the cells and first ultrastructural changes may appear. These changes are still reversible.

Cardiomyocytes remain viable approximately 20 min and in case of reperfusion their dysfunction and damage is fully reversible. After this interval, cells are irreversibly damaged, and they become necrotic. **Myocardial infarction is ischemic necrosis of myocardial cells.** This process is dynamic, and necrosis does not appear straight after 20 min. We can observe at least three zones in affected area, which are characterized by different severity of ischemic damage. These zones have also different manifestation on ECG, because cells in these zones have different electrophysiological properties.

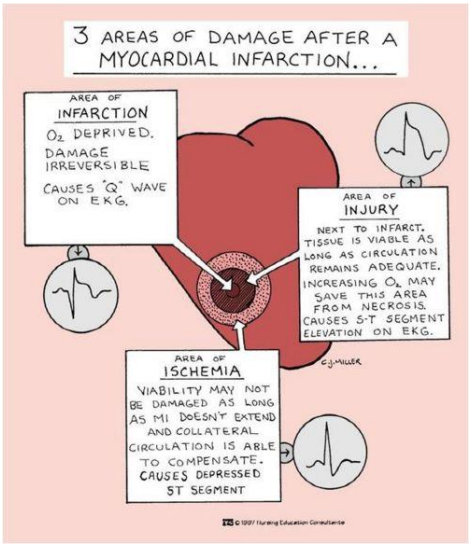


Figure 16.2: Three zones of acute ischemic process

Lack of ATP has negative impact on both functions of the cardiomyocytes – **electrical processes** (electrophysiology dysfunction) and **mechanical force** (contractile dysfunction). Electrophysiological dysfunction is caused by lack of ATP, dysfunction of ion pumps, disturbances of ion balance, accumulation of metabolic end products, release of neurotransmitters from nerve endings and production of reactive oxygen species. Resting membrane potential decreases towards zero because of increased concentration of K^+ in

extracellular compartment. There are also changes of duration of action potential, abnormal automacy, changes of excitability and refractory phase, cell-to-cell uncoupling and decrease of conduction speed. Mentioned changes lead to the onset of arrhythmias Most common are ventricular premature beats, ventricular tachycardia, flutter or fibrillation and conduction disturbances such as bundle branch blocks, or AV blocks. It depends on location of ischemic focus, severity of ischemia and other factors.

Mechanical force of myocardium (contraction and relaxation) are also affected by ongoing ischemia. Contractility of cardiomyocytes decreases considerably after several seconds and this process develops in 3-5 min leading to total contractile dysfunction. This may result to total ischemic contracture after 10-15 min. It is important to note that relaxation is also active process and it depends on ATP, therefore both contraction and relaxation are affected. There are two mechanisms responsible for such situation. Lack of energy (ATP) and accumulation of intracellular H+. Acidosis influences ability of Ca^{++} to bind to myofibrils – what is critical step in contraction-relaxation cycle.

Affected part of myocardial wall can therefore move less than the rest of the heart (hypokinesis), does not move at all (akinesis) or shows paradoxical movement (dyskinesis) under the heart ultrasound. Paradoxical movement of ventricular wall may lead to the formation of an aneurysm of the heart. Contractility of unaffected myocardium is increased by the release of catecholamine – this is a compensation for reduced contractile force of myocardium affected by ischemia. It is also important to note that contractile dysfunction always comes hand in hand with relaxation dysfunction, which leads to reduced ventricular compliance. These changes will influence performance of the heart as a pump, and it will manifest also at the pressure-volume curve of the heart.

Clinical presentation of ischemic heart disease

Ischemic heart disease typically presents with chest pain called **stenocardia** or **angina pectoris.** It is usually characterized as burning pain, chest tightness or a sensation of a pressure above the sternum. Pain typically radiates to the neck, left jaw, left arm (radiation is influenced by location of ischemic focus), pain may also radiate to the epigastrium, or to the back. Patients may display so called Levine´s sign - clenched fist held over the chest. In female, presentation of ischemic heart disease may be "atypical" with chest discomfort, sensation of too tight clothes – this phenomenon is explained by gender differences in nociceptive signalling. Angina is accompanied by vegetative changes – sweating, nausea, pallor etc. If this condition lasts up to 15 min and responds to nitrate and/or rest – it is "stable

angina pectoris". If it does not respond to nitrate and/or rest, lasts more than 15 minutes – it is unstable angina pectoris.

Pain as a signal is produced by nociceptive system, nociceptive fibres in the myocardium are exposed to the mediators produced in the ischemic focus such as potassium, hydrogen ion, adenosine, bradykinin and many more. As it was explained before, pain can be modulated by **age, gender, neuropathy or medication** (e.g. alcohol, NSAID), **diameter of ischemic focus and** also **other signs** like nausea or vomiting, what may indicate acute gastritis, or complications of gastric ulcers rather than acute myocardial ischemia. Myocardial ischemia may not lead to pain sensation – it is called silent ischemia. Silent ischemia is present in e.g. diabetic individuals with neuropathy, or at the beginning of the process in the coronary arteries, which does not manifest at rest. Stress or tread mill exercise may lead to critical ischemia and pain. It is very useful diagnostic tool. At the other hand, every patient complaining about chest pain (does not matter what age, gender or risk factor are present) must be examined to exclude or confirm acute myocardial ischemia. **Clinical presentation, ECG and myocardial markers must be carefully evaluated in each individual with chest pain.**

Nausea and vomiting may be present in subjects with myocardial ischemia affecting diaphragmatic wall of the heart, and they are caused by strong activation of the vagus nerve. **Sweating, pallor, diarrhoea** are also consequences of robust activation of autonomic nervous system. In case of left ventricular inability to pump the blood properly to the systemic circulation, patients develop congestion in the lungs. This may lead to the sensation of **dyspnoea**, eventually **lung oedema** may develop based on the changes of Starling balance across the alveolar-capillary membrane. Extensive damage affecting more than 40% of left ventricular musculature may lead to the **cardiogenic shock.** Clinical presentation is modified by strong emotional response – anxiety and fear of imminent death.

Heart rate can be either **fast or slow** depending on the type of disturbances of pacing, conduction problems or presence of ectopic foci in ischemic myocardium. It is also not possible to predict the value of **blood pressure,** which are determined by cardiac output and peripheral vascular resistance. Stress and anxiety or at the other side activation of the vagus nerve modulate values from case to case. Heart rate and blood pressure must be monitored, because of strict indications and contraindications of certain drugs – e.g. nitrate can be only applied if blood pressure is higher than 90/60 mmHg, otherwise it would lead to circulatory failure.

It is very important to take standard 12 lead ECG in each individual with chest pain, in case of acute coronary syndrome, it points to the subsequent management of the case. ECG in acute coronary syndrome however, has typical pattern when it comes to the onset and progression of changes. Per acute changes appear within 15-20 minutes – it is mainly so called **hyperacute T wave**, which is tall-amplitude, primary T-wave abnormality caused by impaired repolarization of ventricles. Later, as the three zones (ischemia, damage, necrosis) are progressing, the curve will show ST segment elevations in the leads "above the ischemic focus" and their mirror changes (depressions of ST segment) in the leads at the side opposite to the ischemic focus. Movement of ST segment up or downwards is caused by "the wound current" (for more see the textbook Electrocardiography). STEMI myocardial ischemia is treated by immediate recanalization of affected artery, while ischemic syndromes without STE elevations so called NONSTEMI are treated by conservative strategy. Pathological Q deflection, which indicate the presence of necrosis should not be seen on the ECG nowadays, as the early and proper treatment should prevent progression of ischemic process to the necrosis. Necrosis of myocardial cells is confirmed by laboratory findings, when molecules normally present inside the cardiomyocytes leaks through the damaged membranes to the circulation and are detectable in the blood sample.

Reperfusion injury

Primary reperfusion either by thrombolysis or invasive coronary procedures are standardized therapeutic approaches in subjects with acute myocardial ischemia. Immediate reperfusion of ischemic focus and oxygen supply for myocardial cells may considerably reduce the size of ischemic lesion and it also reduces mortality. Paradoxically, reperfusion may also cause myocardial damage and may lead to the reduction of myocardial function known as **reperfusion injury.**

Although ischemia is followed by spontaneous or therapeutic reperfusion, it is very difficult to say exactly what damage has been caused by ischemia and what damage is a consequence of reperfusion. Experimental studies provide an evidence about several molecular mechanisms, which either alone or in combination may lead to serious reperfusion damage of myocardial cells. One of proposed mechanisms is accumulation of **inorganic phosphate** (Pi) caused by degradation of cellular stores of ATP with inability to produce new ATP due to ischemia, another molecular mechanism is production of **reactive oxygen species, intracellular overload of calcium ions and intracellular acidosis**. These processes lead to the damage of **mitochondrial membrane, opening of mitochondrial transport**

pores and activation of mitochondrial apoptotic cascade. Increased production of reactive oxygen species is a consequence of changed biochemical processes, mainly concentration of NADH. Oxygen dose not enter biochemical processes leading to production of ATP, but it is rather utilized in reactions leading to **production of radicals**. They cause peroxidation of lipids, proteins and DNA, but the most important is **damage of membranes of intracellular compartments and membranes of myocardial cells.** Lack of ATP in the cell lead to the cytoplasmic calcium overload, because transport of calcium to the sarcoplasmic reticulum and outside of the cell depends on energy. Lower activity of H^+/Na^+ transporter, which also depends on energy lead to the intracellular acidosis. These processes lead to the opening of PTP pores of mitochondrial membranes and activation of apoptosis.

Example of reperfusion injury is a phenomenon of **stunned myocardium** – this term describes contraction dysfunction of already re-perfused myocardium, even though the oxygen supply and energy production are at normal levels. The reason is that contractile proteins (actin, myosin) have temporary reduced sensitivity to bind calcium ions, therefore to boost contraction strength. Experimental data point to the role of superoxide radical, which together with inorganic phosphate reduce sensitivity of myofilaments to calcium. This situation may last from days to weeks after successful reperfusion. **Hibernating myocardium** is also a phenomenon characterized by reduced contractility, but in this is more often is subjects with chronic myocardial ischemia. Contractile function of myocardium is "downregulated" because of reduced availability of energy resources oxygen). When the blood supply increases, contractility increases as well.

CASE REPORTS

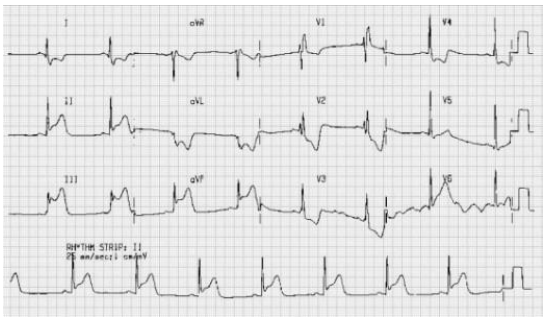
Case report 1

66-years-old man was admitted to emergency with pain in epigastrium, nausea and feeling of imminent fainting, these symptoms aggravated after several hours lasting abdominal discomfort – characterized as dyspeptic problems. He did not vomit, did not faint and based on the history he did not remember eating something "heavy". He was diagnosed with diabetes mellitus and he takes oral antidiabetic drugs for this. He is also overweight, as all his attempts to lose weight were not successful. He has also hypertension on treatment (betablocker + sartan) and he also takes small dose of aspirin based on recommendation by his GP. He does not tolerate physical activity quite well, he gets breathless very quickly and

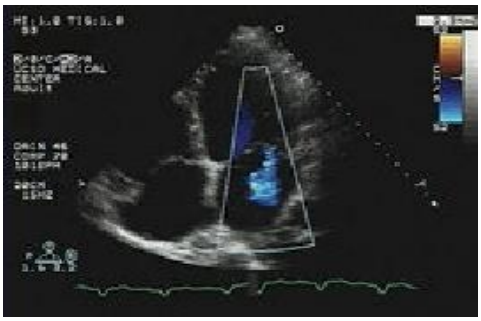
he thinks, this is because of his overweight. Family history is positive for DM type 2, his mother had DM and she died at the age of 77 to stroke. Father was healthy, died in accident.

Examination: Patients communicates, he does not tolerate horizontal positions, so he sits on the hospital bed, sweaty, breathless and pale. He is obese, height 168 cm, weight 109 kg, android type of obesity. Heart rate 44 bpm, RR 20 bpm, breathing is rapid and shallow, diuresis is normal. Heart auscultation revealed systolic murmur at the apex with propagation to the arm pit, and this murmur is new (was not described in the patient's documentation before). Abdomen was not easy to examine because of obesity, but there is no pain during deep palpation and there is also no oedema on lower extremities.

12-lead ECG showed elevation of ST segments in leads II. III, and aVF, depressions of ST in V2 and aVL. Patient was immediately transported to the cardiology unit with attempt to perform invasive recanalization of hi coronary arteries, which cause d MI. **Heart ultrasound** showed only mild dysfunction of the left ventricle, heart chambers were not dilated, and it also showed hypokinesis of diaphragmatic wall of the left ventricle and neighbouring part of the septum. There was also detected regurgitation flow during the systole back the left atrium across the mitral valve and hypokinesis of papillary muscles. Ejection fraction of left ventricle was 55%.



ECG



Heart ultrasound

Laboratory examination: Na 135 mmol/L; K 4.3 mmol/L; Cl 98 mmol/L; creatinine 79 μmol/L; urea 4.2 mmol/L; pH 7.22; BE -6; HCO3 16 mmol/L; pO_2 13.2 kPa; pCO_2 3.9kPa; TnI 0.2 ng/mL; CK-MB 5.0 μg/L; CRP 22 mg/L

Questions & Tasks

1) Typical presentation of acute myocardial ischemia is chest pain. Explain why patient located his pain to the epigastric region? Which factors may modulate perception of ischemic pain?

2) Explain why laboratory findings did not show positive concentrations of myocardial markers?

3) How would you explain the finding of systolic murmur at the apex based on the heart ultrasound findings?

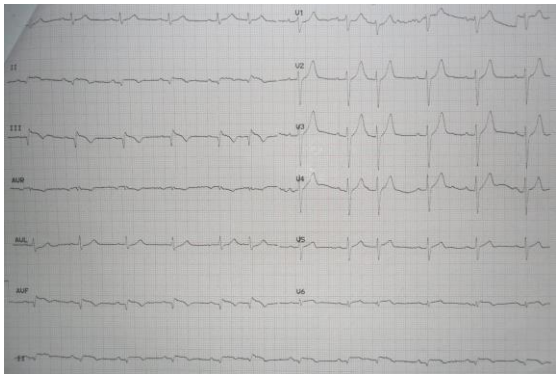
4) What mechanisms are responsible for bradycardia in this patient?

5) What is the relationship between apple shape obesity, insulin resistance and hypertension?

Case report 2

73-years-old man visited his GP after two days lasting pressure pain on the chest, which radiated to the neck and back. He vomited repeatedly, he was not breathless, and he did not have other problems. He has hypertension on treatment, and vertebrogenic algic syndrome (VAS) in the lumbar part of the spine. He never had MI nor stroke before. He smoked 1 pack of cigarettes for more than 40 years, now he is ex-smoker for like a year or such.

Examination: Patient is oriented, communicates normally, normal BMI (175 cm vs 78 kg), hydration status seems to be normal, normal neurological findings, bilateral normal pulsation of carotid vessels, filling of jugular veins is also normal. Breathing eupnoeic, vesicular without pathological phenomena, heart action regular, HR 70 bpm, no murmurs, BP 100/70 mmHg. Abdomen, and other findings physiological.

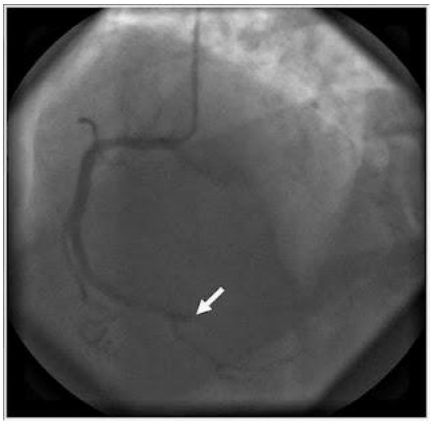


ECG

ECG showed pathological Q wave, elevations of ST segment in II, III and aVF leads, and inverted T wave in the same leads. This finding is indicative for subacute diaphragmatic STEMI. Concentration of cardio-specific markers were positive – troponin I 10 ng/mL.

Heart ultrasound revealed akinesis of diaphragmatic and posterior wall of the heart, hypokinesis of the septum, diastolic dysfunction, dilatation of right ventricle, systolic dysfunction of left ventricle with ejection fraction of left ventricle 40%.

Due to remaining chest pain, even after 2 days on treatment, the patients underwent the re-coronarography via right brachial artery which revealed distal occlusion of right coronary artery with the visible blood flow to the periphery through collaterals, and also up to 50% stenosis of ramus circumflexus of left coronary artery. Specialists recommended to continue in conservative treatment with repeated controls of the heart ultrasound.



Coronarography

Questions & Tasks

1) Identify symptoms and signs typical for ischemic heart disease.

2) Explain mechanisms responsible for onset of ischemic pain and its propagation to distant places.

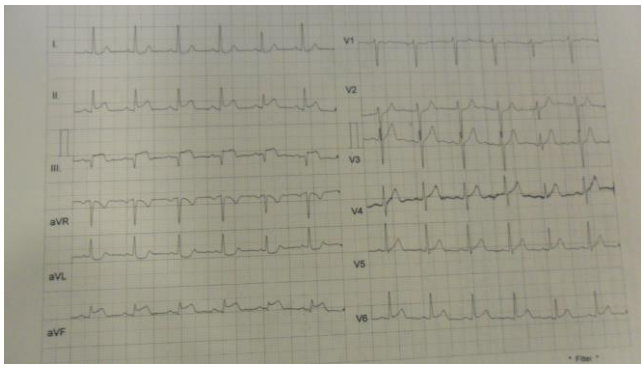
3) What biochemical markers can be used to confirm necrosis of cardiomyocytes and what is the dynamics of their release?

4) What is residual thrombus and what complications may be caused by the presence of residual thrombus in the coronary arteries?

Case report 3

60-years-old woman woke up at midnight with burning pain on her chest radiating to the left side of her back and left arm. She felt nauseated, but she did not vomit. At 8 AM she visited her GP who sent her to the regional hospital, where she was diagnosed with myocardial infarction. The patient´s history revealed arterial hypertension (WHO III), hyper and dyslipidaemia and DM type 2 (since 1987, now she is on PAD and insulin treatment).

Examination pointed to high BMI 157 cm vs 74 kg), patient is oriented, communicates, afebrile, pale, no cyanosis, nor jaundice, no dyspnoea, feeling of jugular veins seems to be normal, BP -110/70 mmHg, HR 80 bpm, heart action is regular, breathing vesicular with no pathological sounds, lower extremities without oedema, Homans sign negative at both legs. ECG showed typical findings indicating diaphragmatic STEMI. Troponin I = 0.45 ng/mL (normal level max 0.04 ng/mL) a CK MB = 0.66 μkat/L (normal level max 0.4 μkat/L).



ECG points to the diaphragmatic STEMI

The heart ultrasound has detected hypokinesis of the diaphragmatic myocardial wall and basal part of the septum. Ejection fraction of left ventricle was 45-50 %. Treatment was initiated with Anopyrin 400 mg, Clopidogrel 6x75 mg, Heparin 10 000 IU i.v. and she was transported to the bigger hospital with special invasive cardiology centre. An urgent selective coronarography was performed, and it revealed occlusion of the right coronary artery (see figure), the thrombus has been removed and the arterial lumen was fixed by implantation of a stent.

Coronarography – total occlusion of right coronary artery (left) and recanalization of the lumen by stenting (right)

Questions & Tasks

1) Identify symptoms and signs typical for ischemic heart disease

2) Explain which of the patient´s diseases/conditions contribute to the progressions of coronary atherosclerosis.

3) Which findings on ECG indicate the diagnosis of acute myocardial infarction? Explain how and why they appear on the ECG trace.

4) What changes of mechanical and electrophysiological properties we may expect in ischemic myocardium?

5) Can you identify some findings on ECG pointing to the disturbances of automacy or conduction problems?

Chapter 17

DISTURBANCES OF THE HEART VALVES

Definitions and terminology

The main function of the heart valves is to maintain one directional (forward) blood flow in the heart chambers and they prevent back leak of the blood. Dysfunction of this system can be caused by disturbance of any part of the valve (anulus fibrosus, or leaflets) or papillary muscles which are responsible for movement of the leaflets.

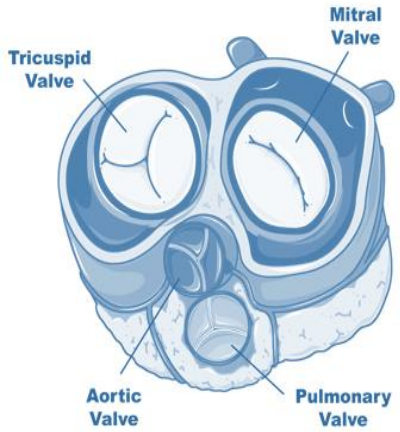


Figure 17.1: The heart valves, function of the heart valves available at https://www.youtube.com/watch?v=M8HYmaDpWpE

There are two main types of disturbances of the valves – stenosis and regurgitation (insufficiency). Stenosis is characterized by narrowed valve orifice, which manifests during the time when the valve is supposed to be wide open, and regurgitation is characterized by inability of the valve to close properly in the time when it is supposed to be closed, and a back leak of the blood disturbs the heamoynamics in the heart. Sometimes the valve dysfunctions combine and we can observe consequences of both stenosis and regurgitation – this is caused by severe structural changes of the valve (fibrotisation, calcification) with inability of the valve to open and close properly during the cardiac cycle.

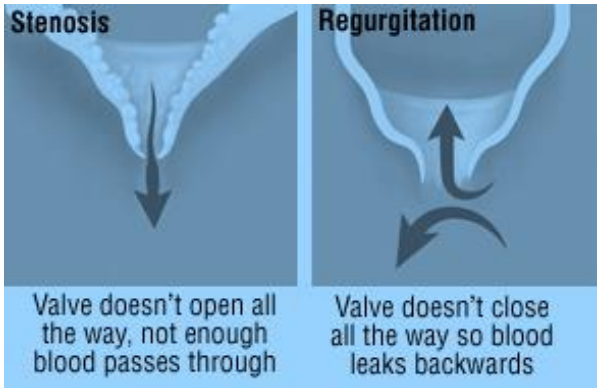


Figure 17.2: Stenosis and regurgitation of the valve

Aetiology and pathogenesis

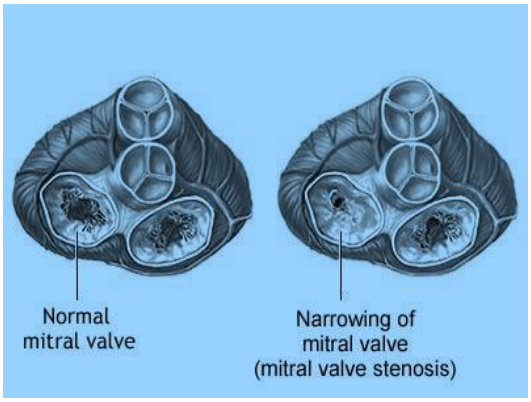
Valvular heart diseases can be congenital or acquired. Just to mention some examples of congenital valvular disorders – stenosis of the pulmonary and aortic valve, either isolated or as a part of complex congenital heart diseases. These disturbances are usually identified very early in infants, mainly in case they cause severe disturbances in the heamodynamics. Some of them, not that severe, affect considerable proportion of otherwise healthy population and they remain unrecognized for long time, e.g. **Barlow's syndrome** – which is congenital prolapse of the mitral valve or **Marfan syndrome** caused by defects in the synthesis of collagen, which also manifests as mitral regurgitation.

Acquired valvular diseases affect mainly the valves of the left heart, which work under higher mechanical forces (pressure, stretch). These factors increase the chance of endothelial damage of the valve, what is predisposing factor for further damage of the valve. Aetiology of acquired valvular diseases has changed substantially. **Rheumatic fever**, which was one of the most common causes of valvular diseases is recently replaced by **degenerative processes such as fibrotisation and calcification** of the valves caused by ageing. Growing population of 70+, 80+ patients results into changes in diseases demographics and requires special approach. Statistically, the most common valve disease in our population nowadays is **aortic stenosis based on degenerative changes of the valve**. Rheumatic inflammation affecting the valve is an example of primary proliferative type of inflammation characterized by excessive fibro-production on the leaflets, leading to the formation of the connection between the leaflets (fibrotic bridges), which limit ability of the valve to open enough and to close completely. **Bacterial endocarditis** can cause the damage of the valves in individuals with immune deficiency. Bacterial vegetation growing on the leaflets produce potentially dangerous enzymes with proteolytic activity (protease, collagenase), which can cause a defect of the leaflets with subsequent valvular regurgitation.

Myocardial ischemia is also pathogenic factor – ischemia of papillary muscles reduces movability of the leaflets in case of hypokinesia or akinesia of papillary muscles with the disturbance of intra-cardiac haemodynamics. **Relative valvular disorders** are caused by dilatation of fibrous annulus of the valve e.g. in case of dilatation of the heart chambers. The surface of the leaflets is therefore reduced relative to the dilatation of the annulus.

Mitral stenosis

Mitral valve directs the forward blood flow from the left atrium to the left ventricle during diastole and prevents the back leak during the systole. Ventricular filling has normally three phases – phase of fast filling during which about 80% of blood from the atrium moves to the ventricle, then diastasis, and finally phase of slow ventricular filling, during which the rest of the blood form the atrium (20%) is forced to the ventricle by atrial systole. Stenotic mitral valve represents an obstruction of the blood flow, and physiological three-phasic filling changes to the monophasic process which takes longer time and the ventricle is filling under higher pressure. Stenotic mitral valve lead to the onset of pressure gradient between the atrium and the ventricle. The most common cause leading to the mitral stenosis is rheumatic fever. Fig 3.



The atrium works against higher afterload what leads to the increase of the tension in the atrial wall. Increased tension in the myocardial wall increases consumption of ATP what may limit performance of cells. Compensation of this condition is achieved by concentric hypertrophy of the atrium. This is haemodynamic adaptation of the atrium to the high afterload and the tension in the wall returns to normal values, so does the consumption of ATP.

End diastolic volume of the left ventricle is usually reduced, what will lead to the reduced cardiac output. Drop of cardiac output will initiate activation of compensatory

mechanisms – mainly disinhibition of the sympathetic nervous system with the rise of peripheral arterial resistance and tachycardia, which leads to undesirable shortening of diastole. Shorter diastole worsens the haemodynamic problem, and the heart does not have enough time to pump the blood from the atrium to the ventricle through stenotic valve. This will lead to the gain of hydrostatic pressure in the atrium, which further influences pulmonary circulation with the onset of postcapilary pulmonary hypertension. Pulmonary circulation is characterized as low pressure, low-resistance circulation, therefore postcapillary hypertension will lead to the change of Starling balance across the capillary membranes. This imbalance may lead to the transudation of fluids from capillaries to the pulmonary interstitium, which is the initial step in formation of cardiogenic lung oedema. Episodic transient elevations of hydrostatic pressure in pulmonary circulation (e.g. during physical exercise) may induce onset of functional and morphological changes – thickening of the alveolocapillary membrane, and hypertrophy of media in pulmonary vessels. These changes are preventive measures against onset and progression of lung oedema in subjects with haemodynamic problems in the left heart. Mentioned morphological changes lead to permanent pulmonary hypertension, which develops as an "adaptation" of pulmonary vasculature to high pressure in the left atrium. Pulmonary hypertension represents high afterload for the right ventricle, therefore, primary problems with the mitral valve influenced haemodynamics in the right heart via pulmonary vasculature.

Symptoms and signs of mitral stenosis

Muscle weakness and fatigue are caused by reduced cardiac output and its redistribution to the central circulation, while periphery (including muscles is hypoperfused). Centralisation of circulating volume is mediated by sympathetic nervous system and other compensatory mechanisms initiated as a response to reduced cardiac output. Hypoperfusion of skeletal muscles is subjectively perceived as a fatigue, weakness and reduced physical performance. **Cyanosis** is typical for mitral stenosis, it is peripheral type of cyanosis, also called stagnation cyanosis. It is caused by slow blood flow in microcirculation of peripheral tissues due to the vasoconstriction which was mentioned above. Slow rate of perfusion is associated with higher extraction of oxygen, thus increasing the amount of reduced haemoglobin to more than 50 g/L, which will manifest by bluish colour of the skin of peripheral parts of the body. Dyspnoea – subjective sensation of lack of the air, or "the air hunger" appears mainly during the physical exercise, because tachycardia worsens the pumping of the blood from the atrium to the ventricle, later, in more advanced mitral stenosis

and high pressure in the atrium the dyspnoea may be present permanently. Dyspnoea is complex sensation caused by activation of multiple nerve endings in the lungs by congestion, presence of the fluid in the neighbourhood of alveoli, small airways oedema and also afferent drive from the chest wall mechanoreceptors and proprioceptor of respiratory muscles, and finally afferent drive from peripheral and central chemoreceptors in case of hypoxia or hypercapnia caused by impaired ventilation and oxygenation. Since this problem was induced by haemodynamic disturbance in the heart, this type of dyspnoea is called "cardiogenic". Haemoptysis – the presence of the blood in the sputum is caused by rupture of anastomoses between functional and nutritional circulation in the lungs caused by higher hydrostatic pressure in pulmonary circulation. Atrial fibrillation is caused by hypertrophy/overload of the left atrium. Both processes lead to the increased consumption of ATP, promoting energy depletion in the cells, which will influence electrophysiological processes in cardiomyocytes. These conditions may lead to the onset of multiple foci of ectopic electrical activity, which as arrhythmogenic substrate initiates atrial fibrillation. Fibrillation is undesirable, because it induces tachycardia (with shorter diastole) what worsens the filling of the left ventricle and haemodynamics in lung circulation. Stagnation or recirculation of blood in the atrium due to the lack of systolic contraction (in fibrillation the atrium does not have synchronized contraction) predispose to the formation of the thrombus in the atria, with the risk of embolization to the GIT, lower extremities or cerebral circulation etc. Auscultation finding depends on the pressure gradient and morphological changes of the valve. Typical is opening mitral click followed by diastolic murmur at the apex, which usually lasts during all diastole and it may have presystolic accent caused by atria pushing the blood through the stenotic valve. First heart sound is usually louder, because the force of ventricular systole closing the valve is high due to increased inotropic stimulation. https://www.youtube.com/watch?v=f4H2CfPnwog

Mitral regurgitation

Mitral regurgitation belongs to the most common valvular disturbances. Minor, haemodynamically insignificant mitral regurgitation is quite common finding in otherwise healthy individuals, and it does not cause any problems. Causes of considerable valve damage leading to the mitral regurgitation are rheumatic fever, endocarditis, ischemia of papillary muscles or dilatation of the annulus of mitral valve. Specific problems are related to the prolapse of mitral valves caused typically by production of abnormal collagen with the structural abnormality of the valve.

Disturbance of the valve causes problems during the systole of the ventricles, when blood is pushed forward to the aorta through the aortic valve. A portion of end diastolic ventricular volume leaks backward to the left atrium through insufficient mitral valve. Regurgitating volume reduces the stroke volume of the left ventricle, so does the cardiac output. Left atrium receives blood from pulmonary veins and also extra volume leaked back from the ventricle. Increased volume from atrium moves to the ventricle, therefore both heart chambers work with higher volume then normally. Increased preload in the left heart initiates eccentric type of hypertrophy as a compensatory mechanism to the extra volume work. It is important to note that instead of increased end-diastolic volume of the left ventricle, the fraction of the blood ejected to the aorta is diminished due to the back leak to the atrium.

Mechanisms, responding to the changes of cardiac haemodynamics forward and backward are similar to those initiated by mitral stenosis, however volume overload is much better compensated. Symptoms and signs of mitral regurgitation depend on the magnitude of regurgitation flow and how quickly insufficiency develops. E.g. rupture of the papillary muscle caused by myocardial infarction lead to the "acute mitral regurgitation" which manifests by acute lung oedema, while progressive development of regurgitation lead to the symptoms similar to the mitral stenosis such as dyspnoea, muscle weakness, fatigue, atrial fibrillation, embolization, cyanosis. There is one more symptom – **palpitation**, which is defined as a subjective sensation of the heartbeat, because the heart works with huge volumes, which gives subjectively unpleasant sensation. Mitral regurgitation typically manifest by systolic murmur at the apex, radiating to the arm pit, accent if patient lies on his left side. First heart sound is silent (valve does not close sufficiently, what normally produces the first heart sound).

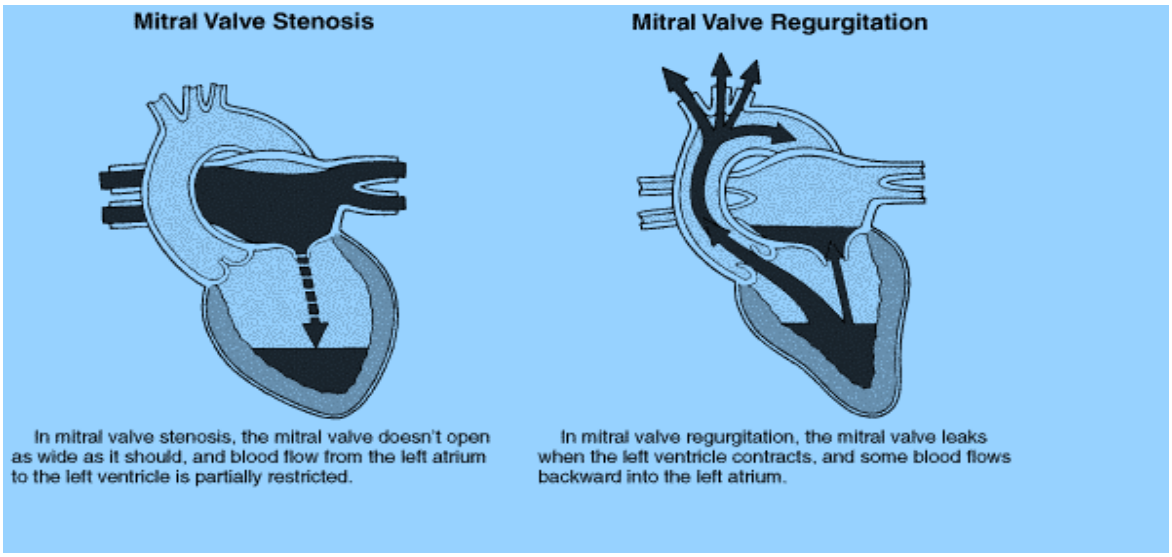


Figure 17.4: Figure represents haemodynamics problems in the heart in case of mitral stenosis and mitral regurgitation, Animation available at: https://www.youtube.com/watch?v=pJtmOkkaDDI

Aortic stenosis

Aortic stenosis if nowadays the most common valvular disturbance. In our population, it is caused mainly by degenerative process of the aortic valve due to ageing. Fibrotisation and calcification lead to the stiffness of the valve with reduced movability and reduction of the aortic orifice. Reduction from normal surface area 3.5 cm^2 to 1 cm^2 is believed to have considerable haemodynamic importance leading to the changes of intra and extra-cardiac haemodynamics.

Figure 17.5: Degenerative and inflammatory changes of aortic valve leading to the stenosis

Obstruction of the aortic orifice limits emptying of the left ventricle and pushing the blood to the aorta, which works against higher afterload. This induces concentric type of hypertrophy of the ventricle. Since the left ventricle is the strongest part of the heart with the most massive musculature, its hypertrophy can compensate aortic stenosis for quite long time. Symptoms and signs appear usually late, after the failure of compensatory mechanisms.

Low cardiac output, which is sufficient during the rest conditions (thanks to the activation of compensatory mechanisms) limits cerebral perfusion during the physical exercise. This manifests by collapse (syncope – fainting during exercise) – short lasting unresponsiveness caused by brain hypoperfusion, while blood is redistributed to the working muscles. Even syncope may have innocent origin (vaso-vagal, orthostatic etc.) the patient must be carefully examined to exclude cardiogenic syncope, which has considerable prognostic value for the patient´s outcome. Another manifestation of aortic stenosis is chest pain – typical angina during the exercise. The cause is ischemia of hypertrophic ventricle. Tachycardia, which typically occurs during the exercise shortens the diastole, which is the only phase allowing sufficient coronary perfusion. Moreover, myocardium is hypertrophic,

while capillaries providing oxygen are not. Coronary arteries have same diameter, as they had before the hypertrophy developed and this lead to the disproportion between oxygen need and ability of coronary circulation to provide it. The pain has typical features of angina pectoris defined for ischemic heart disease. Subjects with aortic stenosis may have completely intact coronary arteries, but since this is a process affecting older people, there for sure is some degree of coronary atherosclerosis, therefore ventricular hypertrophy combines with coronary atherosclerosis leading to a substantial reduction of oxygen availability for cardiomyocytes.

Aortic stenosis may manifest by symptoms and signs of left heart failure (muscle weakness, fatigue, dyspeptic problems, short breath and later oedema). Extreme type of manifestation if sudden cardiac death, where aortic stenosis is recognized ex-post during autopsy. As it was mentioned already, hypertrophic myocardium has increased consumption of ATP and frequently develops relative lack of ATP in certain areas. Lack of ATP lead to the electrical instability of membranes of cardiomyocytes, leading to the formation of ectopic automatic foci, which triggers fatal arrhythmia – ventricular fibrillation. Auscultation is characterized by systolic ejection murmur above the aortic valve (aorta) with propagation of the murmur towards carotid arteries or to the back (inter-scapular region), second heart sound is less intense. Watch the video describing changes of haemodynamics in aortic stenosis and aortic regurgitation.

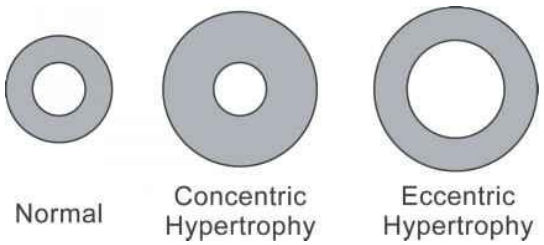
https://www.youtube.com/watch?v=Z9cuXSaiZnw

https://www.youtube.com/watch?v=LS_ZSfgXoqI

Figure 17.6: Scheme of aortic stenosis and chart with signs & symptoms in aortic stenosis caused left heart failure

Aortic regurgitation

The most common cause of aortic regurgitation is degenerative damage of the valve, relative insufficiency due to dilatation of the annulus or aortic dissection. Rheumatic process or syphilis are rare nowadays. The cause can be also congenial malformation of the valve with two leaflets only, which cannot close the orifice completely (aortic valve has normally three leaflets). Haemodynamic problem appears during diastole – a portion of the blood ejected to the aorta moves back to the ventricle. The ventricle is however receiving blood also from the atrium, what lead to the volume overload of the left ventricle. High end-diastolic volume is then during systole ejected to the aorta, and the circle repeats. Volume overload induces adaptation changes of the left ventricle. Hypertrophy of eccentric type re-models the ventricular architectures, ventricular wall thickens, with increased internal diameter of the ventricle. In contrast, in concentric hypertrophy (response to high afterload) the wall is thicken but the internal diameter remains unchanged.



The heart can deal with higher preload much better than afterload, therefore, the ability to compensate aortic regurgitation may last for decades. Symptoms such as the chest pain, left heart failure or sudden cardiac death are present in advanced stages of the disease. Aortic regurgitation is the only valvular disturbance characterized by increased cardiac output, and symptoms and signs are remarkably influenced by this fact. Peripheral circulation responds to the increased cardiac output by **reflex vasodilation.** Skin is warm, well perfused, and patients is sweating more than normally. He/she does not tolerate warm surroundings. Pulse wave spreads through the arterial part of the circulation to the capillaries, due to the peripheral vasodilation, wat can be observed on the nail beds as a rhythmic redness followed by pallor, pulse by pulse (**Quincke's capillary pulsation**)

High volume of the blood ejected to the carotid arteries with its kinetic energy can induce rhythmic movement of the head forward and back pulse by pulse (yes, yes-signs, or Musset´s sign). Palpation of the pulse on the radial artery is characteristic – *pulsus celer at altus* (high volume of the pulse with rapid up-stoke and decline) called also **Corrigan's**

pulse. Blood pressure has typical high systolic/diastolic difference caused by high stroke volume (high systolic pressure) and peripheral vasodilation (low diastolic pressure). Patients are experiencing palpitations, because the heart works with huge volumes of the blood. Physical examination of the patient may reveal visible pulsation of the heart apex, and its position may shift to the 6th intercostal space lateral to the medioclavicular line, there is a diastolic murmur above aorta with radiation of the sound to the Erb's point. Sometimes, we can also hear a murmur at the apex, similar to the murmur in mitral stenosis, so called – **Flint-Austin´s murmur**, which is caused by the collision of normal blood stream filling the ventricle from the atrium with the regurgitating stream. Watch the video demonstrating changes of heamodynamics in aortic valve disturbances.
https://www.youtube.com/watch?v=j40U9WYOXFk

Valvular disturbances of the right heart

Valvular disturbances of the right heart are not that common, because the pressure in the right heart is lower, therefore the leaflets are not mechanically damaged by haemodynamic forces. Typically, right heart valvular disturbances are present in subjects with pulmonary diseases (e.g. COPD) with pulmonary hypertension with consequent hypertrophy and dilatation of the right heart (including the dilatation of the annulus). They can be also present in subjects with a tumour "carcinoid" and its liver metastases. Carcinoid has endocrine activity releasing vasoactive substances such as serotonin, histamine etc. These cause an irritation of the leaflets in the right heart with formation of fibrous plaques on the leaflets of the right heart valves.

Tricuspid stenosis and regurgitation

Tricuspid stenosis (most often post-rheumatic or as a part of carcinoid heart disease) represents higher afterload for the right atrium. Tricuspid regurgitation (most often relative caused by dilatation of the annulus in the right heart) represents higher preload for the right atrium. Possibilities for both concentric and eccentric hypertrophy of the atrium are limited, because the right atrium normally has very thin musculature with limited ability to adapt to haemodynamic load. Symptoms and signs therefore appear quite early, and they are very similar in case of stenosis and regurgitation. These symptoms and signs are **increased filling of jugular veins, hepatomegaly, systolic pulsation of the liver, hepato-jugular reflux, jaundice** (caused by venostatic damage of hepatocytes) **oedema, ascites, dyspeptic problems**. Disturbances of valves in the right heart can also manifest by regression of

dyspnoea in primary left sided heart failure. Auscultation of the heart reveals systolic murmur (in regurgitation) or diastolic murmur (in stenosis) at the margin of the sternum.

Pulmonary stenosis and regurgitation

Stenosis of the pulmonary valve appears often as a congenial malformation of the heart, regurgitation is caused most often by lung pathologies (pulmonary hypertension, COPD etc.) either by dilatation of the right heart (acute cor pulmonale) or by hypertrophy and subsequent dilatation (chronic cor pulmonale). Clinical presentation is characterized by presence of signs and symptoms of the right heart failure.

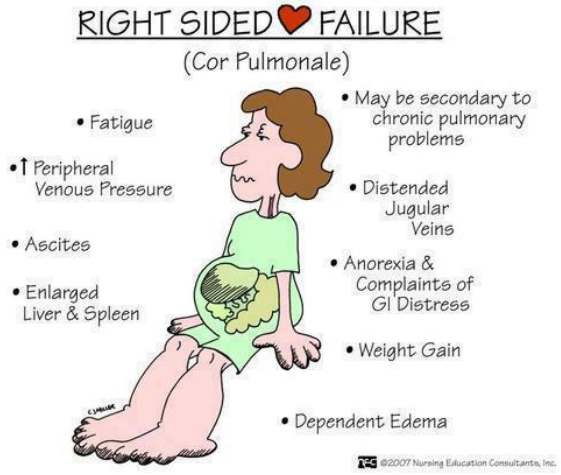


Figure 17.7: Symptoms and signs of right heart failure

CASE REPORTS

Case report 1

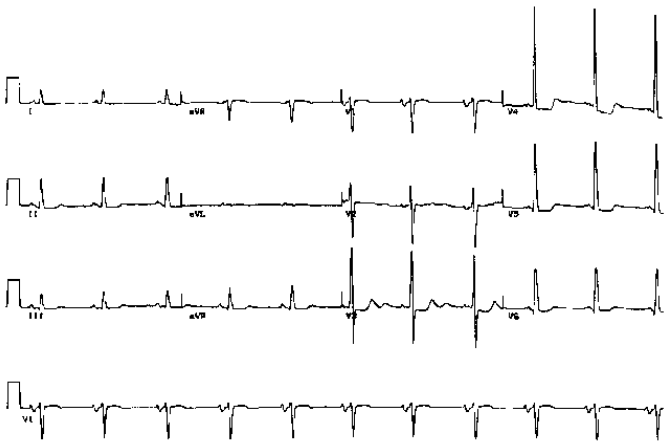
54-years old patient with multiple renal pathologies in the past (inflammation of the urinary tract in 1974, pyelonephritis at left side in 1977, nephrolithiasis with the recidivation of pyelonephritis in 1978, polycystic kidneys in 1989). In 1996 urosepsis caused by pyelonephritis again. These conditions resulted to the chronic renal insufficiency and since the 2000 the patient was enrolled to the dialysis programme. She was diagnosed with normochromic normocytic anaemia in 1993 (treated by iron supplementation and Eprex), hypercholesterolemia in 1993 and secondary hypertension in 1998. Other findings mentioned in the patient´s record – cystic degeneration of the liver, osteoporosis, pan-gastritis and reflux esophagitis. The patient had appointment at cardiology ambulance in 2001 due to progressive breathlessness NYHA III-IV caused by minimal physical exercise. She also reports nocturnal

breathlessness associated with angina-like chest pain. The dyspnoea appeared two years ago, but it was present only during considerable exercise.

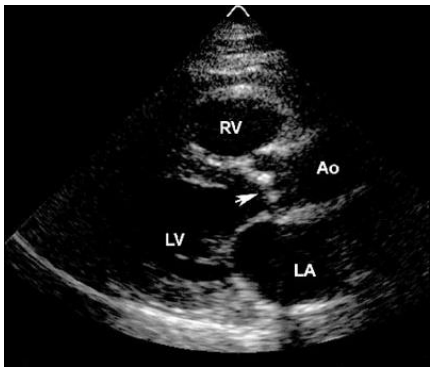
Examination: 157 cm / 64 kg, heart rate 92/min, BP 110/80 mmHg. Normal nutritional status, pale skin, without pathologies, breathing vesicular without pathological sounds, heart action regular, 92 bmp, and coarse systolic murmur at the aorta site with intensity 4/6 and propagation to the carotid arteries. Abdomen – liver is palpable as a resistance below the right costal arch + 3 cm with uneven surface, no other pathologies. Lower extremities without varices and oedema.

Laboratory findings: FW 44/88; RBC 3.2×10^{12}; HBG 98 g/L; WBC $5{,}1\times10^{9}$; PLT 249×10^{9}; fibrinogen 5.1 g/L; urea 23 mmol/L; creatinine 776 μmol/L; cholesterol 6.3 mmol/L; TAG 1.24 mmol/L; Na 139 mmol/L; K 5.1 mmol/L; P 1.77 mmol/L; Ca 2.7 mmol/L.

ECG sinus rhythm, PQ 0.12 s, intermediary axis, depression of ST in V5-V6, indicators of LV hypertrophy.



ECG with left ventricular hypertrophy



Heart ultrasound

The heart ultrasound revealed significant aortic stenosis with reduced systolic function of the left ventricle, diastolic parameters indicate restricted filling of the left ventricle. The patient has follow-up ultrasounds in her documentation allowing to observe a progression of aortic stenosis, which has started in 1997 as a post-rheumatic process. The progression of valve disturbance is caused by haemodynamic and metabolic consequences of chronic renal failure.

Questions & Tasks:

1) What ECG criteria (indexes) indicate hypertrophy of the left ventricle?

2) Which of the patient´s complains indicates the presence of aortic stenosis? Explain mechanisms of their onset.

3) What is the effect of uremic serum on cardiovascular system in subjects with chronic renal failure? How can it lead to the damage of the heart valves?
4) Aortic stenosis is based on degenerative changes of the valve caused by ageing, which factors (other than age) contributed to the onset of aortic stenosis?
5) Why the patient has left ventricular hypertrophy? What are the risks of this condition?

Case report 2

56-years-old man with hypertension, DM type 2 on diet was admitted to emergency department with progressively worsening dyspnoea, chest pain radiating to the left arm, left jaw, the patient was sweating and nauseated, he did not collapse, did not vomit. Based on examinations, ECG and laboratory tests the patient has anterolateral STEMI (myocardial infarction). Patient was transferred to the coronary intensive care unit and he underwent recanalization of occluded coronary artery with good outcomes. He was stabilised, but three days after he started to feel short breath again, does not tolerate horizontal position and he is anxious. Heart auscultation revealed new systolic murmur at the apex with propagation to the arm pit. The heart ultrasound revealed a presence of mitral regurgitation.

Questions & Tasks

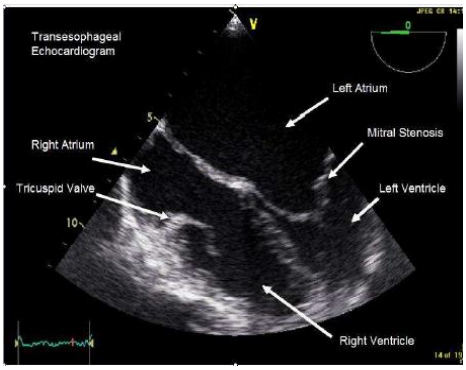
1) Which causes may lead to the acute left heart failure in the patient with myocardial infarction?
2) What mechanisms may lead to the onset of mitral regurgitation in this patient?
3) Explain the effects of acute and progressive (chronic) mitral regurgitation on pulmonary circulation.
4) Explain mechanisms of dyspnoea in this patient on admission and three days after admission, what do you think happened to the patient?

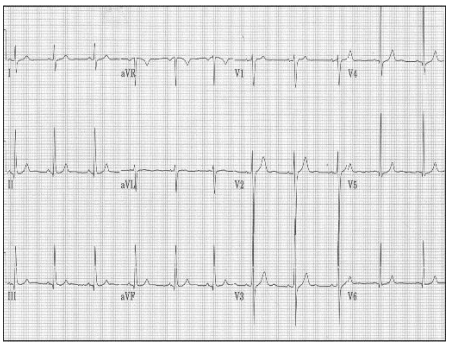
Case report 3

30-years-old man was admitted to the hospital due to decline in his physical performance, intolerance of exercise with breathlessness, and also episodes of nocturnal breathlessness which disturbs his sleep. He had to sit to relieve these difficulties with breathing. The man is living at the moment in bad socio-economic conditions, he admits some drug abuse in the past, and laboratory tests confirmed rheumatic inflammation in the past, he confirms an episode of rheumatic endocarditis in the past, as well.

Examination: Patient is responsive, asthenic, 170 cm, 56 kg, pale skin, anicteric, no cyanosis. Breathing is normal, vesicular sound without additional respiratory auscultation phenomena, the heart action is regular, loud first sound, opening mitral click and diastolic murmur at the apex intensity 4/6, no propagation of the murmur. Abdomen and lower extremities without pathologies. Heart ultrasound confirmed rheumatic mitral stenosis,

haemodynamically important, with pulmonary hypertension, mitral orifice reduced to 0.7-0.9 cm^2.





Heart ultrasound and ECG in a patient with mitral stenosis

Based on the test results and exclusion of bacterial endocarditis and its consequences the diagnosis of post-rheumatic mitral stenosis was established. The patient was treated by percutaneous balloon dilatation of the valve.

Questions & Tasks

1) Evaluate the ECG
2) Explain mechanisms leading to the presence of patient´s complaints
3) Explain the mechanisms of the damage of the valve in case of rheumatic fever
4) What additional signs and symptoms would you expect to appear in case of progression of the disease?
5) Why the patient's history focused on possible drug abuse in the past?

Chapter 18

HEART FAILURE

The heart failure (HF) is a **clinical syndrome rather than a disease unit**. It unites many end-stage cardiovascular conditions; therefore, clinical manifestation of the heart failure is highly variable. Moreover, heterogeneity of diseases which may eventually end up as the heart failure contributes also to **heterogeneity of mechanisms participating on pathogenesis of the heart failure**. The underlying condition of this clinical syndrome is that heart is not able to maintain its functions, as it is described in the definition of the heart failure.

Definition

Heart failure is a clinical syndrome that results when the heart is unable to provide sufficient blood flow to meet metabolic requirements or accommodate systemic venous return despite of normal preload.

Understanding of HF pathophysiology requires understanding of basic mechanisms and principles of regulating optimal cardiac function. These mechanisms are:

1) **Coordinated electrical and mechanical function of the heart (**atria with ventricles**,** left and right ventricles **–** spatio-temporal synchronization of atrial and ventricular activity)
2) **Optimal return of venous blood to the heart** (filling of ventricles) determines optimal **preload** (optimal function of Frank- Starling´s mechanism)
3) **Optimal contractility of myocardium** (inotropic status of myocardium determines the strength of contraction)
4) **Optimal afterload** – total peripheral resistance (TPR) against which the ventricles eject the blood
5) **Optimal number, size and function of cardiomyocytes –** also their normal spatial architecture
6) **normal rhythm and heart rate**

When all of these mechanisms work normally, appropriate amount (volume) of blood is ejected during unite of time (e.g. in one minute) to the circulation – this volume is called **cardiac output (CO)**. CO is determined by **heart rate** and **stroke volume** (how much blood

is ejected in one systole). Heart rate is regulated by **autonomic nervous system** (sympathetic activity increases the heart rate, while parasympathetic decreases it) and **hormones, humoral factors and body temperature**. **Stroke volume** of each ventricle depends on preload, contractility and afterload. Thinking about heart failure, one must understand that disturbance of any of these mechanisms may reduce cardiac output.

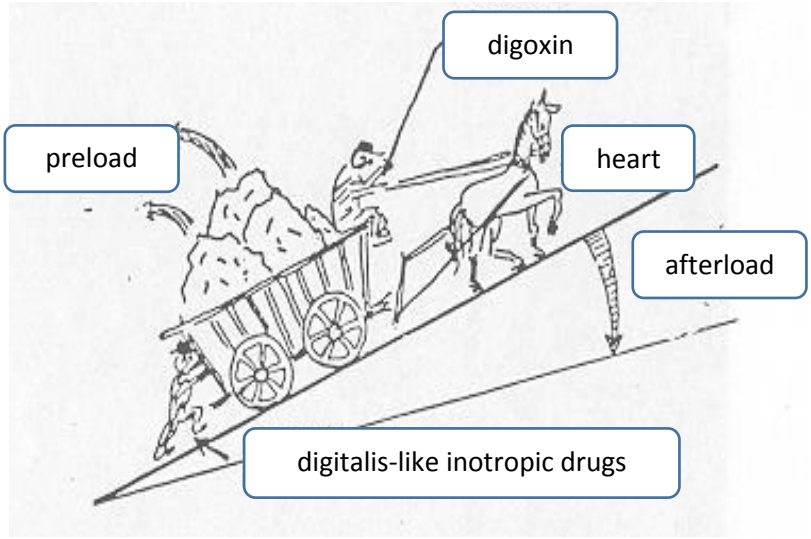


Figure 18.1: Regulation of cardiac output with analogy explaining the effect of preload, contractility and afterload on cardiac output (explanation in text)

Syndrome of heart failure has **different clinical forms**, which are described by **specific terms**. Failure can be related to the **systolic function (**impaired contraction and ejection**)** of the ventricles or **diastolic function (**impaired relaxation and filling**) of** the ventricles.

a) Failure of systolic function of the ventricles (systolic heart failure) clinically manifests as so called **forward failure**, because the main signs and symptoms are related to ejection of lower volume of blood to the organs and tissues of the body than is necessary. **Backward heart failure** is a concept of heart failure emphasizing the resultant passive engorgement of the pulmonary and systemic venous system due to failing left or right ventricles.
Failure of the right ventricle (systolic or diastolic or combined) typically manifest as **backward failure** with congestion of the blood in venous system

b) If the heart cannot maintain its function due to the problems with diastole (disturbance in relaxation, increase stiffness), it is classified as **diastolic heart failure**

c) Both ventricles can fail at the same time – **biventricular heart failure**

d) the term congestive heart failure describes a situation when cardiac output of left and/or right ventricle is reduced, and it lead to the impairment of oxygenation of blood in lungs, decreased delivery of oxygen and substrates to organs and systems with reduced perfusion of kidneys which react to hypoperfusion by intense reabsorption of sodium and water (RAA) thus expanding intravascular volume. Ventricles and atria become dilated progressively, and the fluid accumulates in tissues (anasarca).

e) Considering the **time course** of the process we can distinguish **acute and chronic heart failure**. However, there is not only a difference in the time characteristics, but also **mechanisms participating in their onset and progression**. **Acute heart failure** develops within hours or days (max 2-3 weeks), while **chronic heart failure** is process which develops progressively within weeks, months eventually years. Logically, slow progression of cardiac pathology allows full development of compensatory mechanisms, which unfortunately does not stop or reverse the process, but rather lake it worse supporting progression of pathological process towards end-stage.

f) Heart failure with increased cardiac output may sound paradoxically, since the definition says basically that heart failure represents a condition when heart cannot maintain optimal cardiac output. This is however possible, and this term describes real clinical situation – this situation relates to the condition when the heart is fully functioning, but it cannot meet metabolic requirements of tissues, because these requirements are beyond capacity of otherwise healthy heart. This may happen in case of severe anaemia, thyrotoxicosis, septic shock or a-v shunts.

g) compensated heart failure is a term which describes a situation when the heart itself cannot cover metabolic demands of tissues, however compensatory mechanisms initiated by this process (or therapy) supports heart function enough to cover those metabolic needs at rest, common daily activity and mild degree of physical exercise (e.g. patient with aortic stenosis), **compensation can be complete or partial**

h) Term **decompensated heart failure** means that heart is not able to cover metabolic

demands of peripheral tissues despite fully activated compensatory mechanisms and their maximal capacity.

Main causes of heart failure

A. Myocardial damage caused by different pathological processes

a) **Ischemia and hypoxia** – ischemia is typically caused by narrowing of coronary arteries (ischemic heart disease), hypoxia is a result of many conditions e.g. severe anaemia, respiratory diseases, problems with haemoglobin etc.

b) **Inflammation –** of myocardium (myocarditis) causes damage of cardiomyocytes thus reducing their contractility

c) **Toxins -** e.g. alcohol, bacterial toxins, acid (acidosis) and some drugs

d) **Endocrine problems –** e.g. hypo- or hyper-function of thyroid gland, overproduction of catecholamine (pheochromocytoma – tumour of adrenal gland), over activity of RAA caused by hypoperfusion of kidneys

e) **Mechanical over-load** caused e.g. by increased preload or afterload due to the valve diseases, or systemic arterial hypertension, which leads to the dilatation or hypertrophy of myocardium

How these processes damage myocardium?

- By impaired production and utilisation of ATP
- By damage of contractile proteins which decreases their function
- By uncoupling between electrical excitation and contraction of cardiomyocytes
- By necrosis and therefore loss of certain percentage of cardiomyocytes
- By changes in relaxation of cardiomyocytes leading to decreased compliance (relaxation) of ventricles
- By changes of intracellular homeostasis of calcium (mainly increased concentration)
- By permanent increase of the sympathetic tone and increased concentration of catecholamine in the blood and heart of patients with heart failure, β_1, β_2, α_1 sympathetic receptors in the heart are overstimulated what leads to toxic damage of cardiomyocytes with reduction of contractility, and ejection force of ventricles with arrhythmia and tachycardia, activation of β_1 and α_1 adrenergic receptors in peripheral tissues initiates strong activation of system RAA – this causes vasoconstriction and retention of fluids.

Hyperactivity of RAA participates on remodelling of heart architecture, which decreases its performance. Remodelling of myocardium promotes progression of heart failure.

It was confirmed in numerous studies that **RAA plays important role in pathogenesis of chronic heart failure.** Angiotensin II – a part of this system has plenty of functions which are primarily important in regulation of fluid balance and circulation under physiological conditions, however, chronically elevated levels of angiotensin II have adverse effects on heart, vessels and other tissues in the body e.g.:

- strong vasoconstriction effect on resistance vessels – increase TPR
- retention of Na and water
- release of vasopressin with further effects on vessels and water retention
- facilitation of norepinephrine release form sympathetic nerve endings
- increased sensitivity of vessel wall to norepinephrine
- mitogenic effect on cardiomyocytes and other cells in the heart including fibrocytes
- causes contraction of mesangial cells in the glomeruli leading to reduction of filtration surface and glomerular filtration
- effect on hypothalamus causes the perception of thirst; therefore, subject drinks more
- increases production of aldosterone in adrenal cortex

B. Disturbances of heart rhythm

Mild disturbances of the heart rhythm and heart rate do not have considerable impact on heart function, e.g. a-v block 1st degree, tachycardia around 100 – 110 bpm.

Moderate and severe disturbances have adverse (negative effect) on function of the heart, e.g. ventricular tachycardia (heart rate more than 150 bpm), ventricular flutter and fibrillation, ventricular rhythm with bradycardia (heart rate around 45-40 bpm) – not applicable for trained sportsmen, a-v blocks of 2nd or 3rd degree, WPW syndrome (syndrome of ventricular preexcitation) and other.

C. Mechanical limitation of heart function

Limitation can relate to the **filling of heart chambers with blood, or their emptying to** the aorta and pulmonary artery. **Filling of heart chambers** can be limited e.g. in constrictive pericarditis, heart tamponade, mitral or tricuspid stenosis, thrombosis of veins carrying the blood to the right or left atria. This is the reason why heart does not have optimal preload to be ejected to great vessels, therefore its work is not effective. **Emptying of heart**

chambers with normal /increased preload can be limited in case of volume expansion e.g. caused by renal failure, sudden increase of arterial resistance (pulmonary embolism, malignant hypertension).

D. Reduction of venous return

Heart cannot maintain optimal cardiac output in case of reduced preload caused by reduced venous return to the heart. This can happen e.g. after loss of considerable proportion of body fluids (severe bleeding, diarrhoea, vomiting), failure of cardiovascular regulatory mechanisms e.g. anaphylactic shock, failure of central regulation of vascular tone.

Compensatory mechanisms

These mechanisms attempt to maintain sufficient blood pressure to perfuse vital organs by compensating for the decrease in cardiac output that occurs in heart failure.

Systolic failure leads to decrease SV and CO due to decrease of contractile strength. This will result in global hypoperfusion of body tissues. Mean arterial pressure (MAP = SBP + 2xDBP) will decrease.

This is an important stimulus for activation of compensatory mechanisms: – **Frank-Starling mechanism, neurohumoral activation, and ventricular remodelling.**

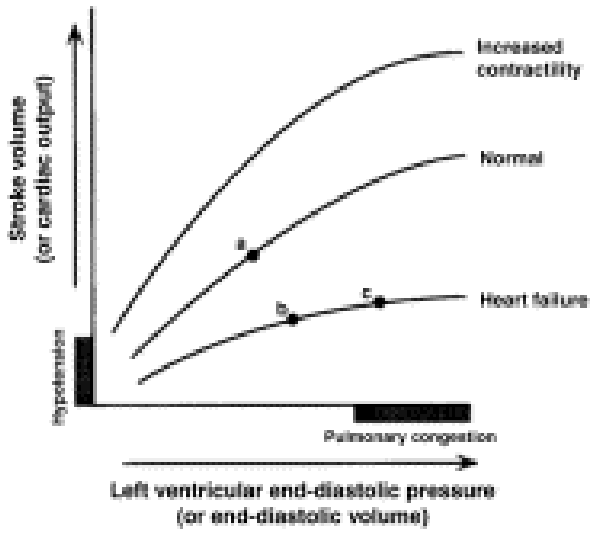


Figure 18.2: Relation of end-diastolic volume and stroke volume of heart ventricles – Frank-Starling mechanism

First of them is **Frank – Starling mechanism** which plays important compensatory

role in the early stages of HF (Fig.2). Scheme explains this mechanism: ventricular stroke volume increases with increase of ventricular end-diastolic volume (to limited extent). From this is clear that when you move with point **a** up at the middle curve which means increase left ventricular end-diastolic volume (increase preload –on axis x) is increasing also its stroke volume (and also cardiac output –on axis y). Middle curve represents a healthy person. The resultant increase of CO is limited as a curve flattens out (right parts of curves). Points **b** and **c** are on another curve which represents patient with **systolic dysfunction**. This curve is below that of normal heart because contracting ability of LV is decreased. So, stroke volume (SV) will decrease, left ventricle end-diastolic volume will increase (increase preload – marked by point **c**) and rather only small increase of SV with compensatory increase CO. Compensatory increase of CO is under such conditions insufficient, so symptoms and signs of LV failure will manifest. At advanced stage of LV failure, the end part of this curve will descend, it means that Frank-Starling compensatory mechanism lost its effect. Result is another decrease of LVSV and pulmonary congestion and pulmonary oedema will develop (black blocks in axis x and axis y).

Neurohumoral activation plays important role in the maintenance of MAP under physiological conditions and is activated as compensatory mechanism in HF at very early stages. Neurohumoral activation (NHA) **serves to augment MAP** by **increase total peripheral resistance** (TPR), and by **releasing of some necrohormones** (system renin-angiotensin-aldosterone) which promote sodium (by aldosterone) and water (by ADH) retention. The preload of ventricle is than increased. Decrease of MAP following HF leads to stimulation of central sympathetic nerve system (SNS) mediated by decrease afferentation from carotid baroreceptors (decreased MAP leads to decreased activity of baroreceptors and this will lead to decrease inhibitory influence of afferentation to central SNS and ADH production). Result is increase releasing of catecholamines with direct effect on the heart (positive chrono-, dromo-, bathmotropic effects), increase contractility and effect on peripheral vasculature (vasoconstriction mainly in skin, visceral organs and kidney). These mechanisms increase SV and TPR with improvement of MAP. Overproduction of catecholamines through stimulation of adrenergic receptors (beta 1, 2, alfa 1) can lead to myocardial toxicity manifested by decrease contractility and ejection fraction (EF), dysrhythmias, and tachycardias. In renal circulation stimulation of beta1 and alfa1 adrenergic receptors will lead to activation of RAAS resulting in vasoconstriction, sodium retention and thirst with increase intake of fluids. Overproduction of renin from kidney is supported also by decrease of renal blood flow from a decrease of MAP. **The end results of stimulation of this**

part of neurohumoral system are: to facilitate release of norepinephrine, aldosterone (sodium retention)**, increase production of ADH and increase myocardial contractility.**

Activation of neurohumoral system in HF, especially during early stage of this disorder, has important compensatory effects; however, **its long-term activation leads in ventricular remodelling which accelerates myocardial dysfunction and progression of HF.**

Ventricular remodelling means **alteration of size, shape, structure, and function of** the ventricle. This is a result of chronic noxious hemodynamic stimuli. It is logic that form, intensity and results of ventricular remodelling depends on the type of primary noxious stimulus, on duration of abnormal stimulation/stage of disease, on intensity of influence to myocardium and on some others factors, as well. Result may be increase or decrease of ventricular mass, change of shape (e.g. from oval to spherical). These changes have initially compensatory effect; later on they will have more and more hemodynamic negative effects supporting the process of HF.

The remodelling process in HF is progressive and eventually becomes detrimental. As the ventricle continues to enlarge and the myocardium hypertrophies, this leads to increased tension in wall which limits the blood flow in intramuscular arterioles and supply of oxygen and substrate to myocardium. The result may be fibrosis which eventually impairs contractility and relaxation of ventricles. The long-term process of remodelling also leads to an increase in myocardial apoptosis. In addition, there is significant contractile desynchrony in the dilated and remodelled ventricle leading to less effective pumping (Kemp and Conte, 2012).

There are also other necrohormones involved in the process of HF development. Among them are **natriuretic peptides** (atrial, brain, and c- neuropeptide) which are released from atria and ventricles when stretched. The have opposite effects as previous necrohormones – the increase salt and water excretion, vasodilatation, decrease renin, aldosterone and ADH secretion. Brain natriuretic peptide (BNP) is thought to be one of the first signs of HF and is used to follow the progression of disease (Kem and Conte, 2012). **Endothelial cells activation** is also present in people with HF. It is manifested by release of set **vasodilatory factors** (NO, bradykinin, prostacyclin) and **vasoconstrictive factor** endothelin. Their cumulative effect on vessels is miscellaneous – vasoconstriction or vasodilatation. Due to damage of tissues by hypoxia are released some **inflammatory cytokines** – tumour necrosis factor alpha, interleukins and interferon. They are able to decrease myocardial contractility.

Symptoms and signs of heart failure

Symptoms and signs of heart failure are very variable, they differ according to the **underlying condition** leading to the heart failure, also in case of **acute versus chronic heart failure** and finally depending of **right versus left side heart failure**. In general, signs and symptoms of heart failure are:

- **Increased body weight** caused mainly by accumulation of fluids in the body (via RAAS)
- **Dyspnoea (breathlessness)** – subjective felling of air hunger or difficulties with breathing caused by congestion in lungs, eventually lung oedema and disturbances of gas exchange
- **Presence of pathological lung auscultation findings** caused by accumulation of fluids in lung interstitial space and alveoli
- **Tachypnoea** – rapid shallow breathing, which is very likely caused by activation of lung J- receptors by increased interstitial hydrostatic pressure due to fluid accumulation in case of left heart failure
- **Orthopnoea** – breathlessness present in supine position, because it enhances venous return from lower extremities to the right heart, which then ejects more blood to the lungs than it would be in sitting or standing position. This mechanism determines onset and progression of lung congestion, eventually lung oedema.
- **Paroxysmal nocturnal breathlessness,** which interrupts sleep (caused by above mentioned mechanisms)
- **Cyanosis –** grey of blue colour of mucosa and skin (mainly at peripheral parts of the body), which is caused by increased concentration of deoxygenated haemoglobin in capillary blood above 50 g/L. Insufficient oxygenation of blood in lungs caused by mismatch of ventilation and perfusion (e.g. right-to-left shunts) lead to so called **central cyanosis**, which is visible on the tongue, lips and face. Severe reduction of cardiac output caused by heart failure lead to **hypoperfusion of peripheral tissues** and intense deoxygenation of haemoglobin directly in the tissue. This mechanism is responsible for **peripheral cyanosis,** which is best visible at the peripheral parts of the body e.g. fingers.
- **Oedema of lower extremities** – is a consequence of increased hydrostatic pressure in venous system caused by either right heart failure and/or activation of RAAS with retention of Na and water. Expansion of intravascular fluid lead to the shift in balance of Starling forces at the capillary membrane mainly in venous system of lower extremities

(mainly in walking patients), favouring filtration of fluids to the tissue. Despite offered enough blood to right or left ventricles these are unable to send enough blood to lungs and LV (when right ventricle failure) and from LF to systemic arterial circulation which results in **decreased effective arterial volume and MAP** which further stimulates RAAs following accumulation of sodium and water retention. **This mechanism of vicious cycle contributes to progression of oedema.**

- **Hepatosplenomegaly** – caused by congestion of these organs by venous blood in RV failure
- **Positive hepato-jugular reflux** – compression of liver during palpation increases filing of jugular veins typically in case of right heart failure (due to tricuspid regurgitation)
- **Ascites** – presence of fluid in peritoneal cavity caused by complex disturbance of Starling forces in peritoneal capillaries (portal hypertension and hypoalbuminemia due to hepatomegaly, expansion of intravascular compartment, RAAs overactivity)

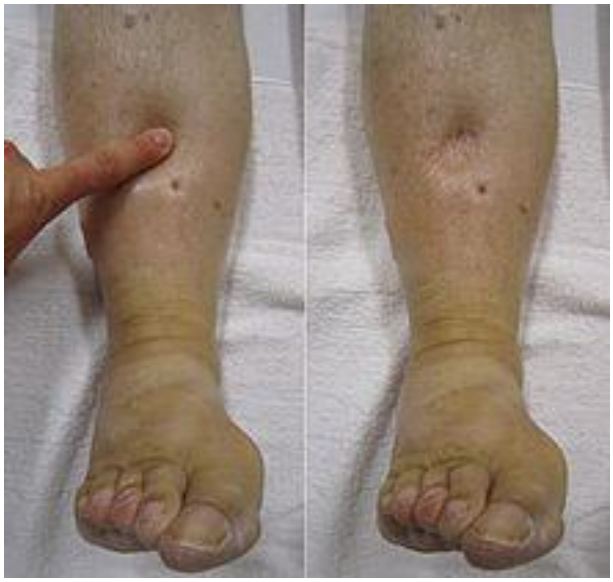


Figure 18.3: Typical symmetrical pitting oedema of lower extremities in subject with heart failure

- **Increased filling of jugular veins -** right heart is not able to accept the blood from vena cava superior what leads to accumulation of blood in upper part of the body – in the neck which is visible in sitting position.

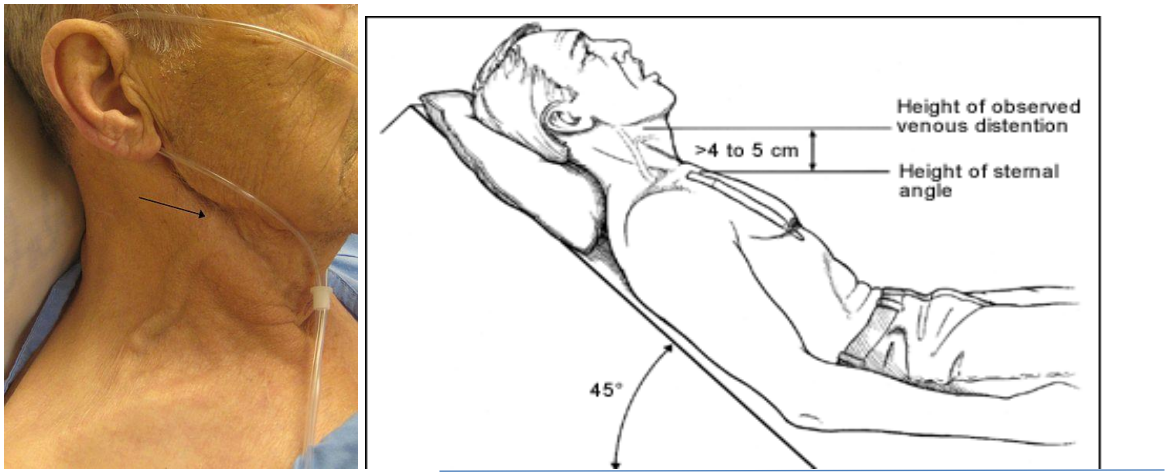


Figure 18.4: Increased filling of jugular veins in subjects with right heart failure

- **Tachycardia** – determined by increased concentration of catecholamine in blood and heart
- **Renal hypoperfusion** – typically present in subjects with left heart failure as a consequence of low CO and drop of pressure in arterial system, with a sequence of compensatory mechanisms and responses initiated by reduced activity of baroreceptors in sinus caroticus with activation of sympathetic nervous system at the end of this cascade. The response is general vasoconstriction and specifically renal vasoconstriction lead to decreased glomerular filtration and production of urine during the day **(oliguria).** At night, sympathetic activity decreases and venous return (so does cardiac output) increases by horizontal position of the body – this lead to better renal perfusion at night (at night when supine, blood flow is redistributed to the kidney, promoting perfusion and diuresis) of course with increased glomerular filtration and increased urine production at night **(nycturia).**

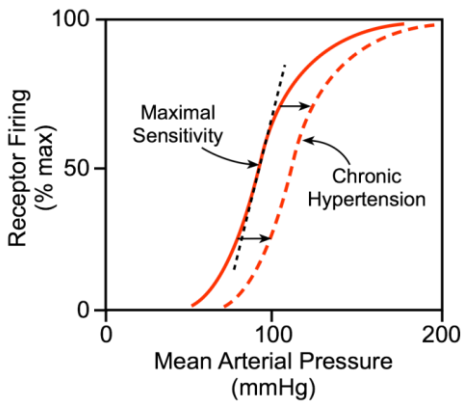


Figure 18.5: Reduction of sensitivity of arterial baroreceptor in chronic systemic

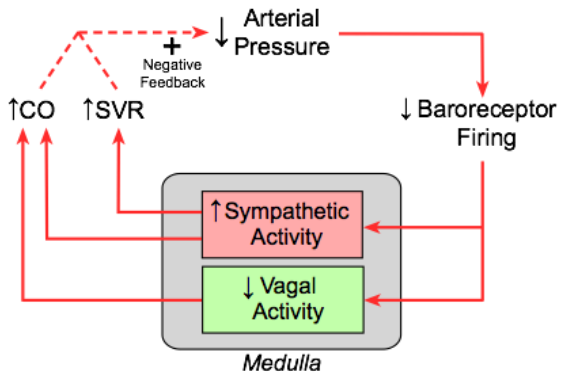


Figure 18.6: Regulation of sympathetic activity via baroreceptors activity

hypertension

- **Fatigue, reduced muscle performance** – caused by reduced oxygen and substrates supply to the muscle (later also to the brain) due to reduced cardiac output and vasoconstriction
- **Reduced appetite and weight loss –** caused by dysfunction of hypothalamic centres regulating food intake and by hypoperfusion of gastrointestinal system which lead to impaired digestion and resorption of nutrients.

CASE REPORTS

Case report 1

66-years-old patient was admitted to the hospital due to progressive worsening of her heart problems.

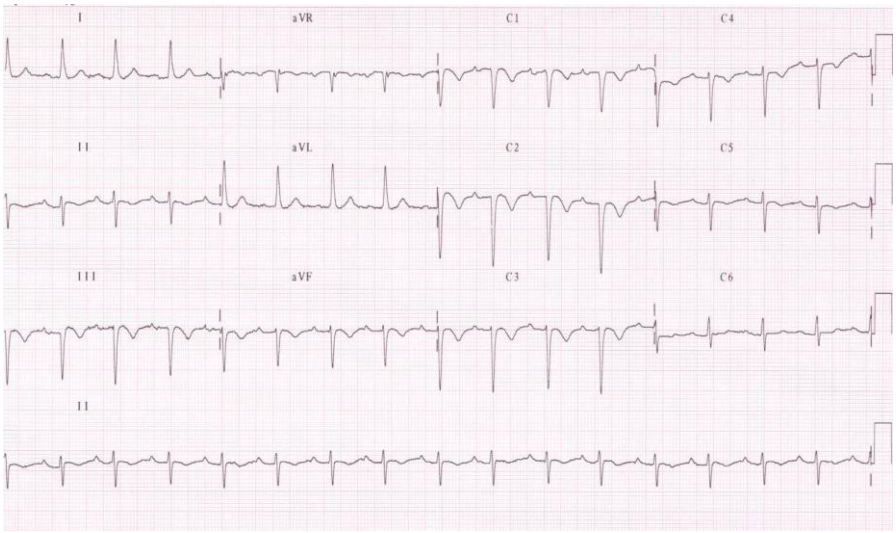
Family history: father died at the age 74 to lung carcinoma, mother died at the age 74 to leukaemia, and she had rheumatoid arthritis (RA), diabetes and she had 2 myocardial infarctions. **Personal history:** the patient was diagnosed at the age 38 with RA, and at the age 59 she had an episode of deep venous thrombosis with bilateral embolization to pulmonary artery. Later, she developed intestinal bleeding due to anticoagulant medication (age 61), and 2 years later she had cerebral ischemia with hemiparesis at right side of the body. A year later she was diagnosed with bilateral alveolitis as a complication of RA. She takes calcium blocker as a medication for hypertension, and she also has chronic gastritis. She also underwent 4 times a surgery of her varices, cholecystectomy (at age 37) and knee joint re-implantation (age 63). She is non-smoker, and she does not drink alcohol.

The patient reports that she feels weak, and fatigued in last 3 years. She started to feel retrosternal chest pain just after the wake up on the admission day. The pain radiated to the back and was accompanied by the air hunger and breathlessness with sweating, and a tendency to fainting. She called ambulance 20 min after the onset of these problems.

Examination on admission: BP - 90/60 mmHg, heart rate – 95 bpm, regular, BT-normal, height -172 cm, weight - 73 kg, patient is dyspnoeic even at rest, sweating, with peripheral cyanosis and visible increased filling of jugular veins, lung auscultation revealed inspiratory crepitation, mainly in basal parts of lungs. Heart auscultation does not reveal any murmurs. Abdominal palpation pointed towards hepatomegaly +2 cm in medioclavicular

line, Lower extremities without oedema with normal arterial pulsation. Right leg seems to be warmer than left. Homans sign is negative, without pain during palpation, plantar sign also negative, circumference of calf at both sides is the same.

ECG: sinus rhythm, heart action regular without premature beats, tachycardia, inverted T waves in V1-V5, dominance of right ventricle



ECG in described patient

Lung auscultation: Low frequency sound phenomenon audible during inspiration – similar to snoring. Very likely caused by secretions present in narrowed airways, after voluntary coughing rhonchi are not present any longer.

Condition of our patient one hour after admission: Patient after admission to ICU underwent heart ultrasound showing normal size and function of left ventricle, enlarged right ventricle with tricuspid regurgitation and paradoxical movement of interventricular septum. Coronarography showed diffuse atherosclerotic plaques without considerable narrowing of coronary arteries, chest X ray showed enlarged lung hilus at both sides. Pulmonary angiography showed subtotal occlusion of pulmonary artery for all three lobes of right lungs and lower left lobe. Blood flow is slow already in upper left lobe and lingula.

Questions & Tasks

1) Identify all important signs and symptoms of the patient

2) Explain mechanisms of onset and progression of all symptoms ad signs described in case report

3) Try to present preliminary diagnosis

(Author: Prof. MUDr. Petr Widimsky, DrSc)

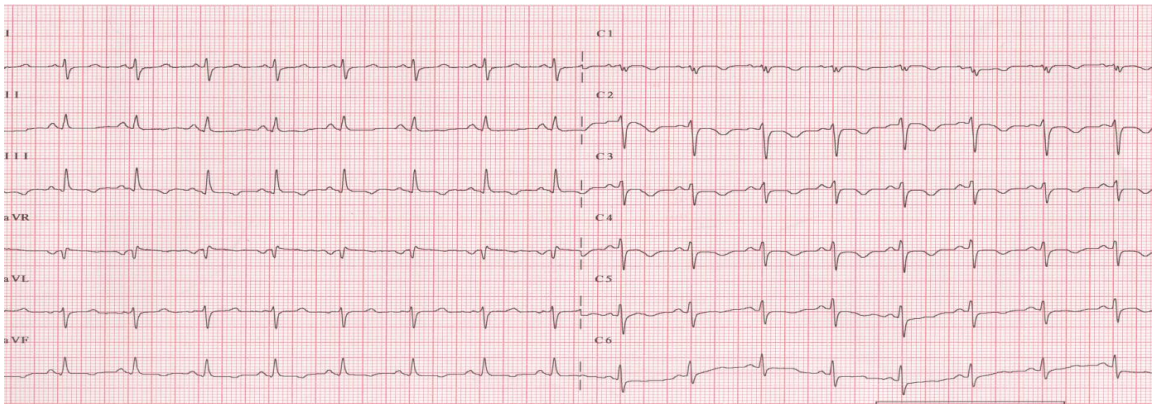
Case report 2

Patient's complaint: 54-years-old woman complains about progressively worsening breathlessness in last three months. Last week, she was not able to get to the first floor by staircase. She was transported to emergency admission ward after the attack of nocturnal dyspnoea. Breathlessness continued even in the hospital and was accompanied by dry cough. The patient felt severe pain in the region of left shoulder and scapula during and immediately after coughing. **Personal history:** appendectomy in 1976, cholecystectomy in 1988, since 1990 – hypertension on treatment, she was never hospitalized because of cardiovascular disease in the past. She also reported weakness and oedema of lower extremities in past 6 months except from symptoms mentioned above. She smokes 10 cigarettes per day in last 10 years, she does not drink alcohol regularly, only occasionally. She is on chronic medication with Gopten 1-0-0, Hydrochlorothiazide 0,5-0-0 – both antihypertensive drugs. **Family history:** father is still alive, mother died to pulmonary embolization at the age of 37, patient is a mother of twins, both suffered from deep venous thrombosis at the age 15 and 17 yrs.

Clinical examination: breathlessness at rest, tachypnoea, intermittent dry coughing, central type of cyanosis with increased filling of jugular veins. Lung auscultation revealed vesicular breathing with rhonchi at the basal parts of lungs, lung percussion is without pathological findings, heart rate 105 bpm, audible 3rd heart sounds, second sound is louder above pulmonary valve, systolic murmur above tricuspid valve, BP 140/80 mmHg, liver +3 cm slightly painful palpation, lower extremities – oedema around ankles, without visible varices.

Laboratory examination: Hbg 14g/L; RBC 4.8 mil/mm³°; WBC 14.3 thousand/mm³; PLT 340 thousand/mm³; ASAT 1.2 μkat/L; ALT 1.8 μkat/L; GMT 6,4 μkat/L; bilirubin 16 μmol/L; troponin I 1.6; CK 2.4 μkat/L; CK-MB 0.12 μkat/L; creatinine 156 μmol/L; urea 9.9 mmol/L; K 4.8 mmol/L; Na 136 mmol/L; CRP 76; ABB and blood gases - pH 7.36; pCO_2 7.6 kPa; pO_2 8.5 kPa; SaO2 86%. Urine tests: albumin +, RBC 0-1; WBC- 4-6.

Heart ultrasound: normal diameter and kinetics of left ventricle, normal diameter and kinetics of left atrium, normal valves, right ventricle enlarged to (38 mm) and atrium to (50 mm) – both dilated, detected paradoxical movement of interventricular septum with tricuspid regurgitation. Pericardial space without fluids.



ECG in described patient – signs of right heart failure

Questions & Tasks

1) Identify most important symptoms and signs of this patient

2) Explain mechanisms of onset and progression of all symptoms ad signs present in the patient

3) Why the heart ultrasound detected paradoxical movement of interventricular septum?

4) What diagnosis this patient has?

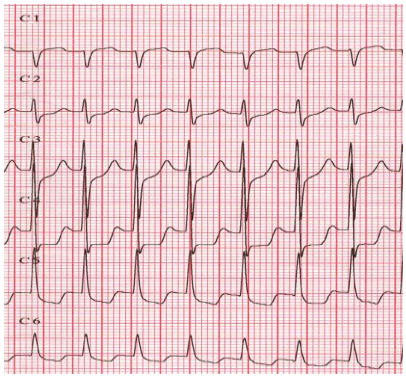
(Author: MUDr. Rudolf Špaček, CSc.)

Case report 3

Patient's complaint: 77-years old woman suddenly experienced breathlessness after his return from afternoon walk, 30 min later she started to feel severe fatigue and nausea, and she was sweating. She took her medication – nitro-glycerine and it relieved her problems for a while. One hour later the symptoms re-appeared again, so she called an ambulance. Paramedics recorded ECG which showed sinus tachycardia, but no ischemic changes, even though they transported the patient to hospital and to cardiology unit. **Personal history**: since 1986 DM, ten years on a diet and antidiabetic drugs, last 7 years on insulin, since 1995 hypertension, no chest pain in the past, tolerance of physical exercise – she must wait a while and catch a breath at approx. 3rd floor if going upstairs, she is non-smoker, occasionally has 1 beer after lunch, and she has one coffee per day. **Medication:** Insulin HMR 12 –0-0 U s.c., Insulin Dep 12-0-16 U s.c., Prestarium 4mg 1-0-0, Plendil 10mg 1-0-0. **Family history:** mother had DM, and she died to MI at the age of 60, father died at the age of 88, patient has no children

Clinical examination: normostenic patient with breathlessness at rest, with increased filling of jugular veins, vesicular breathing with crepitation during inspiration above both

lung bases, heart action is regular, HR 88 bpm, audible heart gallop, loud, rough systolic murmur above Ao with propagation to carotid arteries, BP 160/100 mmHg.



ECG 2 hours after admission: ventricular rhythm, HR – 96/min, depression of ST in $V_3 – V_6$, wide QRS complex.

Laboratory examination: CK 5.6 μkat/L; CK MB 6.4 μkat/L; troponin I 12.4; AST 1.2 μkat/L; ALT 0.80 μkat/L; glucose 21 mmol/L; urea 9.6 mmol/L; creatinine 180 μmol/L; Hbg 13.7; RBC 4.2; WBC 13,4.

Heart ultrasound: normal size of the heart chambers, severe hypokinesis of anterior wall and septum, EF 35%, degenerative changes of Ao valve, turbulent blood flow in the aortic outlet, no pericardial effusion.

Treatment: urgent percutaneous coronary intervention with stenting of stenotic coronary artery

Questions & Tasks

1) Identify most important symptoms and signs of the patient

2) Explain mechanisms of onset and progression of all symptoms ad signs

3) Compare information about ECG immediately after admission and 2 hours after, what is the reason for these differences?

4) How would you interpret and explain information about hypokinesis of anterior heart wall and the septum?

(Author: Rudolf Špaček, MD, PhD.)

Chapter 19

DISTURBANCES OF BLOOD AND LYMPH CIRCULATION IN LOWER EXTREMITIES

From haemodynamic point of view, arterial system of lower extremities belongs to high-pressure system. Blood flow in arteries is determined by pressure gradients in individual parts of the system. Energy of heart systole is converted to ***frontal pressure*** (is responsible for forward motion of blood flow) and ***lateral pressure*** (pressure on arterial wall). Several factors influence blood pressure: cardiac output, peripheral vascular resistance, blood volume in organism or compartment, outer pressure on vascular wall, gravity. Apart from pressure gradients maintained by heart action, elastic properties of vessels during diastole also contribute to continuous blood flow; therefore, the blood flow in arteries is **biphasic or triphasic.** Arterial blood flow is calculated from following equation:

$$\boldsymbol{Q = \frac{\Delta P \pi r^4}{8 l \eta}}$$

where Q – blood flow, P – blood pressure, r – vascular radius, l – vascular length, η - blood viscosity.

The equation shows that blood flow in arteries of lower extremities depends on pressure gradient and arterial radius. Given the fact that blood pressure is relatively stable, the blood flow changes occur mainly due to changes of arterial radius.

Baylis's myogenic regulation (autoregulation) maintains blood flow in regional circulation independently on nervous and humoral influences. Further regulation is **humoral (metabolic)**, which maintains balance between metabolic activity of tissues and blood flow in these tissues. Production of CO_2, acids, adenosine and other metabolic products leads to vasodilation in metabolically active tissue to the degree in which the blood flow is sufficient. Vessels of lower extremities also react to humoral signals, e.g. endothelin, components of RAA system or circulating catecholamine – but the importance of this regulation is lower in comparison with metabolic regulation. **Nervous regulation via lumbar sympathetic fibres** is also of great importance.

Occlusive diseases of peripheral arteries affect 15-20% of population older than 70 years and the prevalence of these diseases can be higher if the occurrence of asymptomatic occlusions is added as well. Measurement of ratio of blood pressure measured on arm and ankle (ABI – ankle brachial index) and its value below 0.9 in elderly patients suggests possible occlusion of arteries on lower extremities. Most common cause is atherosclerosis, but other pathologic processes can lead to arterial occlusion as well, e.g. inflammation, development of aneurysms or vasospastic diseases.

1) Atherosclerosis

Most common cause of occlusive arterial disease of lower extremities is **atherosclerosis.** It affects mostly men, and apart from gender its development and progression is strongly associated with smoking, diabetes mellitus, increased plasmatic concentration of homocysteine, hypertension, dyslipidaemia, obesity and in general in people with unsatisfactory compensation of metabolic response to stress. Atherosclerosis is generalised process affecting vascular wall of large and medium-sized arteries, leading to lesions followed by reparation in form of **atherosclerotic plaques.** Presence of these plaques narrow the lumen of affected artery and can lead to development of hemodynamically significant stenosis or they can lead to development of thrombotic complications – thus limiting supply of oxygen and substrates to tissues.

Presence of plaques decreases the lumen of the artery and this process is asymptomatic at first. Gradual growth of plaques which limits the lumen to 25-20% of its original size leads to ischemia in exercise, because muscles are major recipient of oxygen in working lower extremity. Progression of stenosis leads to development of ischemia even at rest as the pathologic process continues. Acute complications of atherosclerotic plaques are **plaque rupture and development of thrombus in place of disruption, bleeding to plaque and embolization** of these ruptured masses towards periphery – acute and sudden arterial obliteration leads to development of **acute ischemic syndrome of lower extremities.**

2) Inflammatory diseases of arteries

Inflammatory processes can be of different aetiology – from **autoimmune inflammation** (vasculitis and endarteritis) through **bacterial inflammation** (syphilis) to **idiopathic inflammation** with unknown aetiology. Inflammation of arterial wall changes its reactivity to **vasomotor stimuli** and negatively influences the **properties of endothelium.** These changes predispose to development of vasospasms and thrombosis in affected artery.

An example of idiopathic inflammatory vascular disease is **Buerger's disease**, which is non-atherosclerotic vasculitis of small and medium arteries affecting young males (in their forties). Although the aetiopathogenesis of this disease is not precisely known, its development and progression is associated with heavy smoking. Individuals affected by this disease have hypersensitive reaction to intradermal administration of tobacco components, increased cellular sensitivity to collagen type I and III, increased serum concentrations of autoantibodies against endothelium, disturbed peripheral endothelium-mediated vasodilation and increased prevalence in subjects with HLA-A9, HLA-A54, and HLA-B5 suggests to genetic component of disease as well.

Based on aforementioned evidence it is suggested that it is primarily **hypersensitive reaction** to tobacco components or **autoimmune reaction aimed towards structures of arterial wall** primarily damaged by tobacco. Evidence for autoimmune component of this process is indirect in form of positive effect of corticosteroids on disease progression which has three stages: inflammatory – spastic, thrombotic – obliterative and gangrenous. Names of stages correspond to nature of mechanisms contributing to arterial wall damage followed by decreased blood flow in area supplied by affected artery. Patients with Buerger's disease suffer from skin lesions caused by tissue ischemia on periphery of lower extremity (heel, hallux), rarely claudications.

3) Arterial aneurysms

Aneurysm is defined as localized dilation of arterial wall which affects haemodynamics in the artery and thus limiting oxygen and substrates supply to the nourished area. If the dilation consist of all three layers of arterial wall then it is **true aneurysm** and if consists of only one layer (e.g. adventitia) then it is called **false aneurysm.** If an aneurysm had developed in the artery, based on Laplace's law it has tendency to grow. Aneurysms can be congenital or acquired. A cause of congenital aneurysms is inferiority of arterial walls which can pathologically bulge. Causes of **acquired** aneurysms are localized or generalized pathologic processes in arterial wall occurring based on degenerative changes, inflammation or toxins on arterial wall.

An example of **false aneurysm is so-called dissecting aneurysm,** in which tunica intima and tunica media are mechanically damaged and through these damaged layers the blood flows from lumen under tunica adventitia where it accumulates. Haematoma under the tunica adventitia of affected artery develops. Risk of such an aneurysm is its **progressive enlargement, development of ischemia distally from dissection** and the highest is the risk

of **acute rupture** with development of severe haemodynamic consequences. Most common cause of dissecting aneurysms of lower extremity arteries is **trauma.**

Localised aneurysm leads to change of haemodynamic conditions – decreased blood flow and in turn decreased blood flow distally from aneurysm, disturbance of laminar flow with development of recirculation in aneurysm, development of thrombus in aneurysm and its possible complications (embolization).

4) Vasospastic diseases

Damage of vascular wall can influence its reactivity to vasomotor stimuli with tendency to development of inadequately strong and long-lasting vasoconstriction to cold and emotional stimuli. Examples of such diseases are Raynaud's disease and Raynaud's syndrome. Although their clinical manifestation is identical, **Raynaud's syndrome** is secondary vasospastic disease of arteries affected by **inflammation** (collagenoses, vasculitis), **toxins** (ergotism) or **mechanical stimuli** (vibrations). It affects males and females in same proportion and symptoms also occur only unilaterally, typically evoked by cold or emotional stimuli.

Raynaud's disease is idiopathic vasospastic disease, which affects young women without any other cause of vasospasms confirmed. Symptoms are usually symmetrical. Cause of such an increased reactivity is not exactly known, but in patients affected by this disease the hypertrophy of muscle cells in precapillary sphincters, which regulate the blood flow through microcirculation, was observed. Hypertrophy of smooth muscles, as well as increased sensitivity to vasoactive stimuli, are responsible for inadequate reaction to cold or emotional stress. Vasospasm with typical **triphasic skin changes** develops and these changes are based on vascular reactions. First phase is characterized by inadequate vasoconstriction – therefore, the peripheral parts of extremities will be **very pale.** Further, oxygen from haemoglobin, which was present in the tissue during vasoconstriction, is consumed and local concentration of reduced haemoglobin elevates above 50 g/L, what in turn changes the colour of acral parts (fingers) to **cyanotic.** In the third phase, the products of anaerobic metabolism, which have vasodilation effects, accumulate in the tissue. These humoral factors cause passive vasodilation which turns the colour to red (**redness** of acral parts).

Acute ischemic syndrome of lower extremities

Embolization of peripheral artery, trauma, thrombosis and its complications lead to sudden closure of artery, which leads to decrease or cessation of oxygen and substrates supply to given area. **Sources of emboli** are diseases of **left heart** (disorders of mitral valve with development of thrombosis in left arterial auricle, myocardial infarction, dilation cardiomyopathy and pathologic processes influencing intracardial hemodynamics). Rarely, **paradoxical embolization** (in patent foramen ovale) can develop in patients with deep venous thrombosis of lower extremities.

How is it with development of thrombosis in arteries? **Thrombosis never develops in healthy artery!!!** Not even in case of increased concentration of coagulation factors – in that case, thrombosis would develop in veins where the blood flow is slower. Thrombosis develops only in artery, which is primarily damaged by pathologic process and in simultaneous increased readiness to clot formation either on local or systemic level.

Signs and symptoms of acute ischemia develop almost immediately. **Pain is cruel,** occurs via activation of nociceptive nerve endings sensitive to humoral signals – acid, extracellular hyperkalaemia, adenosine. Furthermore, changes of colour of skin develop in affected area – **extremity is pale and cold distally from occlusion; temperature gradient develops** (above and below occlusion); **filling of superficial veins is decreased. Circumference of extremity is decreased.** In physical examination the **pulses on peripheral arteries distally from occlusion are absent.** No trophic changes are present on the extremity.

Chronic ischemic syndrome of lower extremities

Gradual luminal decrease of peripheral arteries on lower extremities via growth of atherosclerotic plaques does not have to manifest from the beginning of pathologic process – so-called **functional occlusion.** In this case, the patient is asymptomatic at rest, but ABI is already decreased and pain occurs only in exercise. If stenosis reaches haemodynamic importance – so-called **critical occlusion –** obliteration of 75-80% of arterial lumen and patient suffers from pain even at rest.

The advantage of gradual narrowing of the artery is slow and continuous increase of pressure before stenosis which creates pressure gradient needed to open **"collateral" circulation.** This circulation can provide oxygen and substrates to given area in case of hemodynamically important stenosis. Presence of collateral circulation decreases the extent of ischemic damage of tissues.

Advantage of gradual growth of atherosclerotic plaques and gradual ischemization of tissues is its adaptation – similar to ischemic preconditioning in myocardium. The result of these changes is decreased sensitivity of muscles to lack of oxygen and substrates in comparison with patient with acute ischemic syndrome without prior adaptation.

In the beginning, the **ischemic pain occurs only in exercise – while walking –** because majority of tissue dependent on oxygen supply are striated muscles. Pain typically occurs in defined workload (is expressed in metres, which patient can walk without pain). Presence of pain dependent on walking is called **intermittent claudication** (from Latin claudicare – to limp). Claudications occur in calf muscles, thigh or gluteal muscles, depending on localization of stenosis.

Later, **pain occurs even at rest** and in case of elevation of extremity, because in this case the blood flow has to overcome not only the increased resistance of stenotic artery, but has to overcome gravity as well. **Postural changes of skin colour** also develop in extremity elevation, which was used as diagnostic method (part of so-called Rashof test). In this test, the extremity with stenotic artery after elevation and repeated plantar flection **turns pale and pain develops;** after lowering of the extremity **reactive hyperaemia** develops. **Paraesthesia** (sensation of tingling or tickling) develops due to hypoxia of nervous system. **Trophic changes** develop based on severity and duration of ischemia – atrophy of muscle, subcutaneous tissue, skin and skin adnexa. The extremity is **cold** and **pulses are not palpable** on obliterated arteries distally from occlusion. Most serious consequence is development of **necrosis** (dry or wet gangrene) of peripheral parts of extremities.

Disturbances of blood circulation in veins of lower extremities

Veins of lower extremities belong to low-pressure and capacitive part of circulation; low blood pressure is maintained by the structure of venous wall which can be distended easily – this allows increasing volume of blood without substantial increase of pressure. Problem for venous return from lower extremities to left hear is the need to overcome hydrostatic pressure of blood column. Venous return from lower extremities is supported by several mechanisms which maintain sufficient level of venous return without increase in blood pressure and disturbances of Starling balance in microcirculation.

Venous system of lower extremities consists of two parts – **deep veins** (in between muscles; on calf, they are doubled), **superficial veins** (in subcutaneous tissue) and **perforating veins** (transfascial connections connecting deep and superficial venous system). **Superficial system is low pressure system** and drains approximately 10-15% of blood from

subcutaneous structures; **deep system is high pressure system** and drains approximately 85-90% of blood. Both systems are equipped by valves which prevent backflow of blood and direct the flow towards heart. Valves are localized in perforating veins as well – in normal conditions they prevent blood flow from deep veins to superficial veins which are not adjusted to high pressure and it can lead to their dilation.

Physiologically blood flows **always from superficial veins to deep veins** (it is "sucked" from perforating veins; another supply is from deep structures from calf and thigh). In muscle contraction, the given level is compressed by muscles and blood is pushed to level higher. The backflow is maintained by **properly functioning valves.** By this mechanism the deep system is drained toward centre, blood pressure decreases and the process repeats itself. It is suction of blood to deep venous system and its push towards higher level.

Diseases of deep venous system of lower extremities – deep venous thrombosis

Deep venous thrombosis (DVT) of lower extremities is pathologic process, in which **intravital blood coagulation develops in veins followed by venous obliteration by blood clot – thrombus** which is not fixed to venous wall and can lead to pulmonary embolism. Apart from this acute complication, there is also a risk of development of postthrombotic syndrome and disturbances of mechanisms maintaining venous return from lower extremities which is a result of recanalization of thrombotic obliteration.

Aetiology and pathogenesis

Most important mechanisms, which contributes to development of DVT is disturbance of balance between three factors physiologically preventing intravital blood clotting and are known as **Virchow's triad.** Triad consists of intact endothelial lining, continuous blood flow and balance in production of coagulation and anticoagulation factors.

DVT is multifactorial disease and to disturbance of Virchow's triad can contribute several etiologic factors which can combine. These factors can be **congenital** or **acquired** and can be divided further as **mechanic, hormonal or haemodynamic.** Clinical studies have shown that DVT develops mainly in activation of coagulation, disturbance of fibrinolysis and in congestion of venous system of lower extremities with decreased blood flow.

Venous congestion, trauma of venous wall, secondary hypercoagulable states	Disorders with increased blood coagulability
Immobilization, quadriplegia Trauma (incl. Surgery) Malignancies (esp. Adenocarcinomas)	Lack of antithrombin III, protein C or protein S Resistance to activated protein C (factor V Leiden)

Thromboembolism in history Chronic venous insufficiency Congestive heart failure Higher age and its comorbidities Dehydration Obesity Pregnancy Contraceptives containing oestrogens After splenectomy	Hyperhomocystinaemia Thrombocythemia Heparin-induced thrombocytopenia Antiphospholipid antibodies Increased activity of plasminogen activator inhibitor (PAI) (presence of HLA-Cw4, DR5,DQw3)

Intravital blood clotting begins in disturbance of Virchow's triad. Process of DVT begins usually around valves, because they protrude to the lumen of vein and they represent optimal place for first deposition of fibrin fibres. **Thrombus gradually forms by deposition of new fibres the fibrin network enlarges together with accumulation of platelets in it.** Thrombus represents occlusion which decreases or prevents venous return via affected deep veins. Given the fact that the vessel wall is not primarily affected by inflammation, the thrombus is not fixed to the vessel wall and there is high risk of embolism to pulmonary circulation. **Acute pulmonary embolism is the most dangerous complication of deep venous thrombosis.**

Blood flow in central direction through affected vein is decreased or completely obliterated by thrombus. Simultaneously with development of thrombosis the fibrinolytic processes are activated as well, which are primarily aimed towards removal of obliteration in the affected area – the process of recanalization begins. On one hand, this process is favourable, because it **restores the lumen** of the vein, but on the other hand locally high concentration of fibrinolytic enzymes and activation of reparation processes has negative effect on venous valves and leads to their damage (destruction or fibrotization of the valves). During and after recanalization the hemodynamics in this area is disturbed, because the muscle pump ejects blood in three directions – towards centre through partially recanalized veins, through anastomoses to neighbouring deep vein (in calf) and through perforating veins which have damaged valves to superficial venous system.

Blood flow from superficial system to deep system is only minuscule in muscle relaxation; therefore, **acute equilibration of pressure in both systems develops.** Blood accumulates in superficial veins which causes permanent hypertension in superficial venous system and recanalized part of deep venous system. If the valves in deep system are damaged as well, blood pushed by muscle pump to higher level regurgitates backwards in muscle

relaxation. The result is permanent increase of pressure in deep and superficial venous system and retrograde venous congestion. Increased pressure transfers to microcirculation which leads to disturbance of Starling forces on capillary membrane with tendency to oedema formation, damage of endothelial lining by stagnation hypoxia and exceeding the capacity of lymphatic system to transport excess of fluids.

Mechanism of development of signs and symptoms of deep venous thrombosis

Clinical course of disease depends on several factors, but the localization and severity of deep venous thrombosis is the most important one. Deep venous thrombosis can sometimes be **asymptomatic,** or with only **mild oedema of calf and pain in calf muscles** (in case it is localized in calf region, where the deep veins are doubled so thrombosis of one of them does not have to leave to severe disturbance of blood flow from this area). If the thrombosis develops above the knee where usually only **one deep vein** is**,** its thrombosis leads to severe disruption of venous drainage and development of severe manifestation. Signs and symptoms are not only local on affected extremity, but signs of systemic inflammatory response indicating severe clinical manifestation.

Oedema of extremity – occurs due to disturbance of Starling balance on capillaries because of increased hydrostatic pressure on venous end of capillaries; this leads to shift of fluids from intravascular to interstitial space and simultaneously the capacity of lymphatic drainage is exceeded.

Feeling of stretched skin and heavy limb – results from activation of mechanosensitive nerve endings in skin and subcutaneous tissue by intensive venous congestion and oedema

Colour changes of extremity – phlegmasia alba dolens (pale extremity), phlegmasia coerulea dolens – (cyanotic extremity) develop due to reflex influence on arterial blood supply, which can decrease in massive venous thrombosis – this leads to pale colour; later as concentration of deoxygenated haemoglobin exceeds 50 g/L the colour changes to cyanotic; **extremity is warm, skin is stretched and extremity circumference is increased; increased filling of superficial vein is present; sometimes arterial pulse is not palpable – due to presence of oedema.**

Systemic manifestation in patients includes anxiety, tachycardia, tachypnoea and fever as manifestation of systemic inflammatory response syndrome. It needs to be mentioned, that **processes as thrombosis cad induce SIRS, because substances released**

from activated platelets possess strong pro-inflammatory potential and also have signalling role in organism.

Pathologic physiology of diseases of superficial venous system

Varicose veins

Varicose veins (varices) are spindly or saccular enlargements of veins in superficial system with **insufficiency of their valves;** this is not only a cosmetic defect, but it represents severe disturbance of mechanisms promoting venous return of blood from lower extremities. This disease is wide-spread in economically developed countries.

According to mechanism of development and causes of varicose veins two forms of disease can be distinguished – **primary and secondary varices. Secondary varices,** as already mentioned, develop as a result of deep venous thrombosis. In recanalization of affected area the valves of perforating veins are also damaged which leads to communication between high-pressure deep venous system and low-pressure superficial system. Superficial veins are not structurally adapted to high pressure and they dilate. Dilation causes relative insufficiency of valve which is supposed to close it.

Primary varices are multifactorial disease – its aetiology and pathogenesis is not exactly known. Based on epidemiologic studies and familiar occurrence the genetic predisposition is assumed (genes encoding synthesis for components of venous wall – loss of elastic properties) and influence of epigenetic factors, which include **obesity, repeated pregnancies, sedentary occupation, occupation where one has to stand for long periods of time without usage of muscle pump, wearing stockings with strong elastic band on thigs and so on.** If the vein is dilated enough for the valve to become insufficient, blood flow through the superficial venous system is disturbed and pressure in these veins rises.

Thrombophlebitis

Thrombophlebitis is an inflammatory disease affecting superficial veins. Inflammation is primary pathologic process and thrombosis develops secondarily as a result of inflammatory damage to the endothelium. Thrombus fairly strongly adheres to endothelial lining and its separation and embolism are practically impossible. Apart from that, anatomical organization of saphenous vein and femoral vein (siphon) prevents larger thrombi from entering deep venous system from superficial system and could cause pulmonary embolism. From this point of view, thrombophlebitis of superficial veins is not a severe disease.

Cause of inflammation of superficial vein is **mechanical or chemical damage** (trauma, syringe), **microbial damage** (catheter infection) or localized cutaneous or

subcutaneous inflammatory processes. Damage of endothelial lining causes activation of coagulation cascade in exposure of subendothelial structures and combined processes – **inflammation and thrombosis** are responsible for signs and symptoms of this disease.

Specific type of thrombophlebitis is so-called migrating thrombophlebitis affecting short segments of superficial veins which alternate with unaffected segments. These migrating inflammations occur as accompanying – secondary findings in other diseases, such as Buerger's disease, malignancies as a manifestation of paraneoplastic syndrome or systemic autoimmune diseases of connective tissue. **Signs and symptoms** are a result of localization and severity; they are manifestation of localized inflammation – calor, dolor, tumor, rubor a functio laesa. Affected vein is reddish as well as its immediate surrounding tissue, oedematous, palpably firm and painful. If the inflammations spreads ascendingly it can propagate into deep venous system via saphenofemoral junction.

Chronic venous insufficiency

Chronic venous insufficiency (CVI) includes every pathologic process which leads to development of **permanent hypertension in superficial venous system in insufficient venous return from lower extremities.**

It occurs in dilation of superficial venous system (varices), insufficiency of perforating veins and damage of valves in deep system (most commonly as a result of recanalization of DVT). Some literary sources classify CVI into primary, in which the deep venous system is not affected and secondary which is also called postthrombotic syndrome – therefore, it is CVI with damaged deep venous system.

Mechanisms, which contribute to development of CVI, are complex. Firstly, it is **pressure increase in superficial system.** Increase of hydrostatic pressure in superficial veins transmits to capillaries in which it causes disturbance of Starling forces and filtration of fluid from intravascular to interstitial space will prevail in case when hydrostatic pressure will be higher than oncotic pressure. Oedema does not have to manifest clinically in the beginning, because excessive fluid will be drained by lymphatic system from tissues. But when the capacity of **lymphatic drainage becomes insufficient,** the oedema develops. Worsening of drainage of venous blood leads to hypoxic damage of endothelium and therefore, to increased permeability of vessel wall, which contributes to development of oedema.

Apart from that, in increased permeability of vessel wall formed blood elements, such as erythrocytes, get into interstitial space. Their lysis in subcutaneous tissue followed by

release of haemoglobin and its biochemical conversion to **hemosiderin** form rust-coloured pigment stains on skin of patients with CVI

Fibrosis is activated in subcutaneous tissue as a reaction of tissue to decrease of pH and accumulation of products of metabolism. These processes lead to thickening of subcutaneous tissue. Trophic changes are also common finding – the most severe manifestation is venous ulcer (ulcus cruris). The cause of these trophic changes is disturbance of oxygen supply – **diffuse hypoxia;** oxygen diffusion is worsened due to oedema and fibrosis.

Venous claudication also contributes to clinical manifestation in patients with CVI. In contrast to disturbances of arterial blood supply they do not develop during physical activity or exercise, but just after it. During walking or other exercise, the venous blood is pushed (at least partially) towards centre by muscle pump. After exercise, the worsened venous return manifests as feeling of heavy limbs, stretched skin or pain due to venous congestion and irritation of nociceptors.

Disturbances of lymphatic circulation

Lymph occurs in tissues as a result of imperfect balance of Starling forces which regulate movement of fluids from/into capillary – filtration always prevails. Fluid which is not reabsorbed is the source for lymph and is drained from given area by lymphatic capillaries. Disturbance of lymphatic drainage leads to accumulation of lymph with development of **lymphedema. It is non-painful oedema** and oedematous fluid contains higher proportion of proteins.

Cause of lymphedema can be congenital or acquired. An example of **congenital** lymphedema is rare genetic disease connected with hypoplasia of lymphatic vessels on lower extremities (e.g. None-Milroy syndrome). Lymphedema is bilateral, progressive and leads to deformities of limbs. Cause of **acquired** lymphedema is obliteration of lymphatic capillaries or lymph nodes by tumour, strictures, parasites or pressure of surrounding tissue. In this case, lymphedema is unilateral based on localization of the cause.

According to mechanism of development it can be **static or dynamic lymphedema.** In static lymphedema is the amount of produced lymph normal in decreased transport capacity of lymphatic system (due to obliteration). Dynamic lymphedema is caused by overproduction of lymph and the transport abilities are not altered. Overproduction of lymph occurs in e.g. inflammation due to increased permeability of endothelium or worsening venous drainage and increasing hydrostatic pressure on venous end of capillary.

Lymphedema is progressively worsening chronic process. Presence of oedematous fluid with proteins leads to reaction of interstitium as **inflammation and fibrosis.** Results of presence of oedematous fluid and interstitial fibrosis are **diffusion hypoxia, further compression of lymphatic capillaries and worsening of lymphatic drainage.**

Accumulation of lymph and fibrotization leads to **deformities of an extremity,** very often to bizarre shapes, skin is affected by **blisters** and in skin and subcutaneous tissue **chronic inflammatory processes with acute exacerbations** take place**.** They are followed by **hyperkeratosis and papillomatosis of skin.**

CASE REPORTS

Case report 1

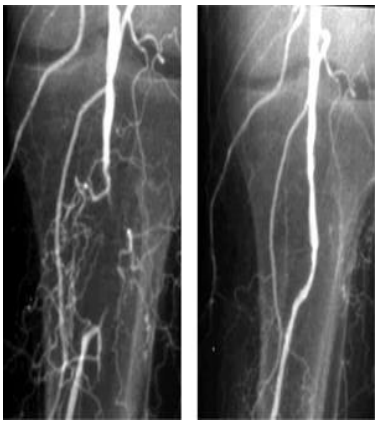
65-years-old patient admitted to Department of internal medicine for planned PTA due to limiting claudications in lower left extremity (IIb Fontain's classification), lower right extremity after PTA on superficial femoral and anterior tibial arteries (2012). Patient is treated for hypertension (since 1963), dyslipidaemia, ischemic heart disease – after MI and PCI (1994); is diabetic (DM type 2) treated with combined insulin therapy and peroral antidiabetics (since 1993). Patient complains about limiting pain in lower left extremity after approx. 300-400m of walking. He negates pain at rest.

Objective findings: Height: 172 cm, Weight: 98 kg, BP: 140/90 mmHg, HR 73/min, BT 36.5°C, RR 16/min. Patient oriented in time and space. Posture active and stance upright. Hyperstenic habitus. Filling of jugular veins not increased, carotid pulsation symmetric. Breathing vesicular, heart action regular. Lower extremities: Acral parts are cold with signs of ischemia – skin atrophy, decreased hair; the symptoms are dominant on left extremity. Pulsations: LLE: palpable only on femoral artery; LRE: palpable on femoral, popliteal, posterior tibial and dorsalis pedis.

Laboratory examinations: GLU 4.6 mmol/L; UREA 11.2 mmol/L; CRE 125 μmol/L; GMT 0.89; Bilirubin total 10.9; ALT 0.43; ALP 1.28; AST 0.39; GGT 0.15; CB 65.5; CRP4.1; Na^+ 141; K^+ 4.6; Cl^- 103; P_APTT 28.8; P_Quick: 0.94.

Ultrasonographical finding (02.05.2013): Right-sided AFS is unobstructed with frequent atherosclerotic plaques. Small aneurysm in Hunter's canal present – 1.2cm without thrombi. Left-sided AFS verified presence of calcified plaques. AFS diffusely affected by numerous haemodynamically important stenoses – most important stenosis in Hunter's canal. Popliteal artery unobstructed, flow velocity 112cm/s.

CT angiography (03.05.2013): Presence of important stenoses in distal part of left AFS in length 6cm and in place of branching of anterior tibial artery. Collaterals only minimally developed.



Obstruction of arteries of LE; LE with collaterals

Questions & Tasks

1) What are risk factors for development of obliterating atherosclerosis of lower extremities in this patient?
2) Which signs and symptoms suggest for insufficient blood supply of lower extremities?
3) What is the mechanism of development of ischemic pain in lower extremities?
4) Is the presence of collaterals in patients with obliterating atherosclerosis of lower extremities advantage or disadvantage? Explain.

Case report 2

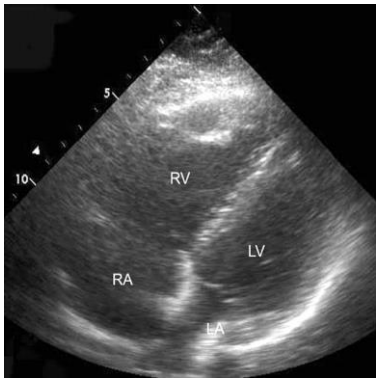
29-years-old woman was admitted to hospital for progressive oedema within last two weeks, acute onset of dyspnoea (1 hr.) and presyncope. Patient has hypothyroidism in history and takes Synthyroid (0.1 mg) daily. One year ago she had miscarriage in 12^{th} week of pregnancy. Otherwise nothing important in history and she was not taking any other medication when admitted to hospital.

Examination showed oedemas and signs of venous congestion on both tibial regions, especially the left one. Weight: 87.6 kg, Height: 167 cm, BP: 110/80 mmHg, HR: 130/min, regular; RR: 24/min

Astrup: pH 7.73; $PaCO_2$ 4.11 kPa; PaO_2 7.53 kPa; HCO_3^- 20.0 mmol/L; $SatO_2$ 90,6%
Coagulation: PTT and APTT, protein C normal; values of fibrin degradation products and D-dimers were 54.6 μg/mL and 6.7 mg/L and concentration of BNP was 354.5 pg/mL. Anticardiolipin antibodies in classes IgG and IgM normal. Antinuclear antibodies and

antibodies against cytoplasm of neutrophils (ANCA) negative. No mutations of factor V Leiden or prothrombin G20210A found. Deficiencies of antithrombin III (18,0 mg/dL) and protein S (33%) activity were found.

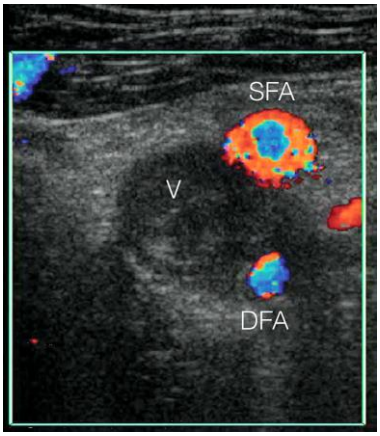
Chest X-ray and echocardiography: Chest X-ray showed mild hilar enlargement. 2D echocardiogram showed normal systolic function of left ventricle, right heart dilated, and systolic function of right ventricle disturbed, estimated pressure in pulmonary artery 55 mmHg.



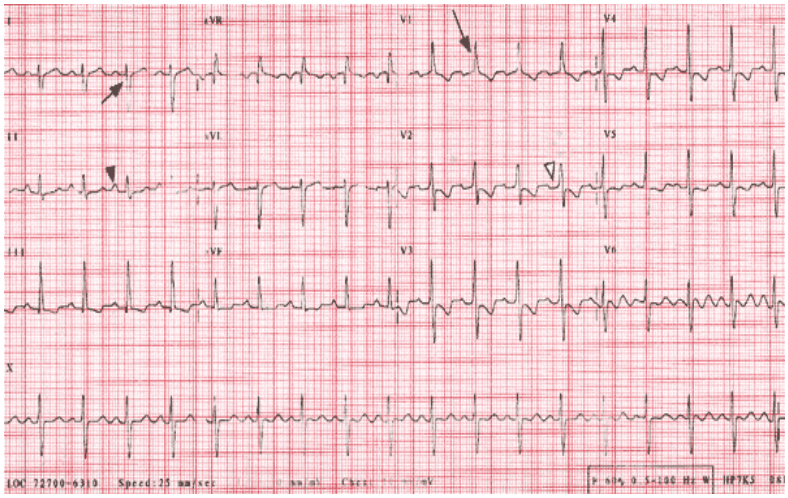
Dilated hypokinetic right ventricle, increased ratio RV/LV caused by bulging of interventricular septum (to LV). Two weeks after thrombolytic therapy significant increase in systolic function of RV and decrease of its size.

Echocardiogram

Ultrasonography of deep venous system of lower extremities: Ultrasonography of venous system showed thrombosis of left calf veins, thrombosis of proximal veins and uncompressible posterior tibial veins V – obstructed vein, SFA – femoral superficial artery, DFA – deep femoral artery



Electrocardiography: Sinus tachycardia with right axis deviation; increased voltage of P wave in lead II, as well as inverted and biphasic T waves in right precordial leads and biphasic P wave in V1-V3 demonstrate acute problems in right ventricle



Questions & Tasks

1) Based on signs and symptoms, laboratory and auxiliary examinations consider what pathologic process is taking place in this patient.

2) Analyse which mechanisms during pregnancy can influence blood circulation in veins of lower extremities.

3) Analyse the results of coagulation tests; which of aforementioned contribute to hypercoagulable state?

4) Explain mechanisms leading to changes of blood gases pressures. Which changes of ventilation to perfusion ratio contribute to their development?

Chapter 20

HYPOXIA

Majority of the oxygen inhaled from the atmosphere is used to produce energy in the form of ATP by oxidation of substrates from nutrition. Oxidation of substrates is biochemical process employing mainly dehydrogenases – enzymes removing hydrogen from molecules. Electrons obtained in the Krebs´s cycle are transported via internal mitochondrial membrane in so called "respiration chain" to the molecule of oxygen, which accepts hydrogen and thus transforms to the molecule of water. A part of the energy released in these oxidation-reduction processes is trapped and conserved in a form of macroergic phosphate groups in ATP (oxidative phosphorylation). Production of ATP and utilisation of the oxygen are closely associated and the oxygen consumption is the indicator of the ATP production. An adult individual in a rest condition needs in average **250 ml of oxygen per minute to produce optimal amount of ATP.** Oxidation of substrates may run even without oxygen – anaerobic metabolism e.g. **anaerobic glycolysis**, where the acceptor of removed electrons is a pyruvate, however this metabolic chain is less effective in production of ATP. Anaerobic metabolism is a source of 2 molecules of ATP from one molecule of glucose, and 2 molecules of lactic acid as the by-products. Aerobic metabolism – oxidation of substrates with additional biochemical processes in the mitochondria lead to the production of 34 molecules of ATP – which makes a difference.

Transport of oxygen

Optimal concentration of the oxygen in the tissue is the result of a balance between oxygen transport from the atmosphere and its consumption. **Tissues have only minimal storage of oxygen**, therefore the mechanisms transporting the oxygen from the atmosphere for oxidation of substrates and production of ATP must be continual. To avoid any possible lack of the oxygen in the tissue, the oxygen delivery must be exactly adjusted to the rate of metabolic processes. If the oxygen transport mechanism fails even for couple of minutes, the tissues will switch to anaerobic metabolism with excessive production of lactic acid and subsequent tissue acidosis.

The lack of the oxygen in tissues is called **hypoxia**. Hypoxia is one of the most common reasons leading to the organ dysfunction. The lack of oxygen in the blood is called **hypoxaemia.** It does not necessarily lead to the hypoxia, because it can be effectively

compensated by other components of the oxygen transport mechanism to avoid or prevent tissue damage. The most common laboratory indicator of hypoxaemia is decrease of partial pressure of oxygen in the blood (PaO_2) or decrease of haemoglobin oxygen saturation (SaO_2) in arterial blood. Decline of PaO_2 below 8 kPa or SaO_2 below 90% indicate clinically relevant (considerable) hypoxaemia. Another term related to the lack of oxygen in the tissue is ischemia, which results from reduced blood flow, tissue usually without hypoxaemia in particular, caused e.g. by occlusion of arteries.

Transport of oxygen from the atmosphere to the mitochondria takes several consecutive steps. It is not only about the transport of oxygen from the atmosphere, but also diffusion of oxygen in extravascular tissue matrix and in cellular compartments towards mitochondria where it is finally utilised. Transport of oxygen to the cells is caused by diffusion, therefore, optimal oxygen supply is maintained by great pressure gradient of oxygen between microcirculation and mitochondria. Optimal **capillary-mitochondrial gradient of PO_2** represents the target function of the oxygen transport mechanism. Essential components of oxygen transport mechanism are:

- transport of oxygen from the atmosphere to the arterial blood in the lungs (oxygenation)
- capacity of the blood for oxygen transport (determined by red blood cells, and haemoglobin)
- transport of oxygen from lungs to tissues (determined by circulation)
- regional distribution of oxygen in tissues
- diffusion of oxygen from capillary to cells
- utilisation of oxygen by cells in mitochondria

Transport of oxygen from the atmosphere to arterial blood in the lungs

PaO_2 depends on the effectiveness of alveolar ventilation and diffusion of O_2 from alveolar air to the lung capillaries. Effective exchange of the gases in lungs requires constant ratio between ventilation and perfusion in particular alveolar units.

Capacity of the blood for oxygen transport

Majority of oxygen is transported via haemoglobin and only small proportion (2-3% of total oxygen transported in the blood) is physically dissolved in the plasma if PaO_2 = 14 kPa. Even though it may be understood that increase of the haemoglobin concentration or red

blood cell (RBC) count can increase oxygen delivery to the tissue, mind that increased haematocrit increases blood viscosity and negatively influences microcirculation.

Transport of oxygen from lungs to tissues

The main role of circulation is to transport oxygen from lungs to the peripheral tissues. Oxygen delivery depends on the cardiac output and amount (concentration) of oxygen in arterial blood (CaO_2). CaO_2 is determined by saturation of haemoglobin (SaO_2), concentration of haemoglobin and coefficient of haemoglobin-oxygen binding capacity. Extraction of oxygen from haemoglobin in microcirculation is about 25% in case of routine daily activity. If the metabolic demands of the tissue increase, or if the delivery of oxygen decreases, extraction of oxygen from haemoglobin will increase to maintain aerobic metabolism. After the maximal extraction of oxygen from haemoglobin was achieved (60-70% in most tissues) further increase of oxygen demands or decrease of oxygen delivery lead to the tissue hypoxia, because the capillary-mitochondrial gradient of PO_2 is considerably decreased.

Regional distribution of oxygen in the tissues

Regional distribution of oxygen is influenced by small diameter resistance vessels – arterioles and precapillary sphincters. Perfusion pressure is important determinant of the regional perfusion, however administration of catecholamine with attempt to maintain systemic hydrostatic pressure may reduce regional distribution, mainly in the renal and splanchnic circulation. Autoregulation of constant blood flow in tissues (or blood flow which exactly fits to the metabolic demands of a tissue) is maintained by two important mechanisms: **a) myogenic mechanism** – a stretch of the smooth muscle cells in the vessel wall (e.g. caused by the rise of blood pressure) will initiate a vasoconstriction in this vessel, **b) metabolic mechanism** which initiates vasodilation in an area with the gain of metabolic end-products e.g. CO_2, lactic acid to restore the aerobic metabolism.

Diffusion of oxygen from capillaries to the cell

Extraction of oxygen from capillary blood is influenced by the velocity of the capillary filling, affinity of haemoglobin to oxygen, capillary-mitochondrial gradient of PO_2, diffusion distance from the capillary to the cell and speed of oxygen consumption in the cell. Relationship between PaO_2 and SaO_2 (dissociation curve) has sigmoidal shape. Shift of the curve to the right side (reduction of affinity) increases oxygen tissue delivery. Low pH in the tissue, increased concentration of 2, 3-diphosphoglycerate in red blood cells and increased tissue temperature reduce affinity of haemoglobin to oxygen. Diffusion of oxygen depends mainly on the density of capillary network.

Utilisation of oxygen in the cell

Intensity of cellular metabolism determines total consumption of oxygen. E.g. increase of the temperature in the tissue about 1°C increases oxygen demands about 10-15%. Toxins released during sepsis (e.g. endotoxin) inhibits metabolism of the cell.

Hypotonic hypoxemic hypoxia

Hypoxaemia is caused by drop of PaO_2, since the tension of oxygen is low, this type of hypoxia was named hypotonic. Alveolar hypoventilation in the considerable proportion of alveolar units results into the decrease of PaO_2 with simultaneous increase of $PaCO_2$. The most common conditions leading to such gas exchange disturbance are **extra-pulmonary disturbances (**e.g. suppression of respiratory centre, disturbances of innervation of respiratory muscles, disturbances of the chest cage, respiratory muscles, pleura or an obstruction of larynx or trachea). Alveolar hypoventilation also follows rapid shallow breathing, which is characterized by undesirable ventilation of the death space instead of ventilation of alveolar spaces.

Ventilation/perfusion mismatch may also lead to the hypoxaemia – specifically if the ventilation/perfusion relationship is low (less than 0.8). Lung regions with low ventilation/perfusion relationship and regions with high proportion of right-to-left shunts considerably contribute to the hypoxaemia. Hypotonic hypoxia is also caused by inhaling air with **low oxygen tension** (e.g. high altitude) and **cyanotic congenital heart malformations with right-to-left** circulation shunts.

Disturbance in oxygen transport mechanisms is compensated by increased cardiac output and in case of long lasting problem by increased concentration of haemoglobin (polyglobulia) and by rise of 2,3-diphosphoglycerate in red blood cells. This type of hypoxia is frequently associated with **pulmonary hypertension**, because hypoxia leads to the vasoconstriction in the lung vasculature. This represents increased afterload for the right heart with all consequences.

Isotonic hypoxemic hypoxia

The total amount of oxygen in the blood is decreased, while the tension of oxygen and saturation of haemoglobin are normal (PaO_2 and SaO_2 are normal). The reason for such condition is either lack of the haemoglobin due to variable types of anaemia or inability of haemoglobin to bind oxygen due to its toxic transformation to carboxyhaemoglobin or

methaemoglobin. Compensation is possible via increased cardiac output and reduction of affinity of haemoglobin to oxygen.

Hypoextraction hypoxia

Arterial blood contains normal amount of oxygen, however, the blood releases less oxygen in tissues due to high affinity of haemoglobin to oxygen. This type of hypoxia is caused by inherited disturbance characterized by presence of abnormal haemoglobins in RBC (e.g. foetal haemoglobin) or in case of enzymatic defects of RBC. Reduced extraction of oxygen from haemoglobin is related also to alkalosis and hypothermia which both shift the dissociation curve to the left side. The consequence of reduced extraction of oxygen is higher saturation of haemoglobin in venous blood. In case of acute hypoextraction hypoxia, the only mechanism which can compensate it is increased cardiac output. Chronic form is considerably compensated by secondary polycythaemia.

Hypocirculation hypoxia

Global hypocirculation hypoxia is caused by reduced cardiac output e.g. in cases of hypotension, circulatory shock or heart failure. Local hypocirculation hypoxia is caused by different types of vascular problems leading to the reduction of the blood flow – thrombosis, embolization, compression of vessels, spasms of arteries, obliterating arterial diseases, traumatic vascular damage, etc. It is possible to recognize two main types of this hypoxia – ischemic and stagnation. **Ischemic hypoxia** is associated with reduced pressure in the circulation, and a problem in "arterial" part of the regional circulation (e.g. thrombosis of the coronary artery, or embolization of mesenteric artery). This disturbance will affect not only delivery of oxygen, but also delivery of substrates and elimination of metabolic waste products. Instead of hypoxic damage of capillaries, there is no tendency for leak of the fluids to the interstitial space. **Stagnation hypoxia** is rather characterized by problem at the "venous" side of regional circulation. It is characterized by pooling of the blood in the tissue due to reduced venous outflow. Hydrostatic pressure in microcirculation increases and together with hypoxic damage of endothelial cells represents preconditions for an oedema.

Diffusion hypoxia

The cause of this type of hypoxia is oedema of the tissue or fibrosis in the tissue which prolongs the distance between the capillary and the cell waiting for oxygen to be delivered. This reduces diffusion capacity of microcirculation for oxygen. The cause can be also a problem with the stagnation of the lymph (lymphedema).

Hyperutilizating hypoxia

It is typically present in the muscle immediately after the start of physical exercise. In pathological conditions this type of hypoxia is present in neurological diseases characterized by muscle convulsions (epileptic attack). Another example is generally increased consumption of oxygen in tissue in subjects with thyrotoxicosis.

Histotoxic hypoxia

This type of hypoxia is characterized by the block of cellular metabolism (block of ATP production) while the amount of oxygen in the tissue is increased. It reduces capillary-mitochondrial gradient therefore the force for extraction of oxygen from capillary blood is diminished. The result is increased concentration of oxygen in venous blood. This disturbance cannot be compensated by any of the components of oxygen transport mechanism. Typical example is poisoning with cyanide. In clinical situation, this type of hypoxia is mediated by the high level of **endotoxin** in tissues.

Manifestation of hypoxia

Detection of initial stages of progressive **generalized hypoxia** is difficult, because the manifestation is highly unspecific. Symptoms and signs include disturbance of mental performance, dyspnoea, cyanosis, tachypnoea, arrhythmia and coma. Hyperventilation as a consequence of activation of carotid chemoreceptors is considerable after the partial pressure of oxygen drops below 5.3 kPa. Central cyanosis is also not valid indicator of tissue hypoxia. It is detected when concentration of reduced haemoglobin in capillary blood reaches 50 $g.l^{-1}$, however it is typically absent in subjects with anaemia, and commonly present in subjects with polyglobulia.

Local hypoxia is caused by reduced blood perfusion in affected organs. Complex of causes and consequences of this type of hypoxia is commonly defined as “ischemic damage”. Reduced availability of ATP in cells lead to the disturbances of ion transport across the cell membrane and permeability of membranes of cellular organs and cell itself increases. Drop of intracellular pH due to accumulation of lactic acid increases and it causes a damage to the intracellular proteins, what in turn inhibits activity of enzymes. These changes results into the suppression of cellular functions and irreversible damage is characterized by the rupture of intracellular organs. The rupture of lysosomes leads to the release of aggressive enzymes – hydrolases, capable to break down the intracellular structures. This is considered to be the

final step leading to the necrosis of the cell. Enzymes released from necrotic cells are used as an indicator of necrosis. Ischemic tissue damage is characterized by severe pain (e.g. angina pectoris, intermittent claudication, or abdominal pain in case of mesenteric infarction). Acute and considerable ischemia lead to the functional changes – supressed function of an organ. Without reperfusion, either spontaneous or therapeutically induced, the prolonged hypoxia could progress towards irreversible damage and complete loss of the organ´s function.

Inappropriate oxygen supply to the body is the most **important factor limiting physical activity.** Physical activity depends on oxidation of carbohydrates and lipids leading to production of ATP, which is essential for the muscle contraction. Ability to maintain physical performance depends on oxidation of glycogen, which might be consumed and it leads to the muscle weakness. Weak muscles with reduced aerobic metabolic capacity lead to perception of an effort related to increased ventilation (breathing) and reduced ventilation capacity. **Dyspnoea** is a symptom of limited physical performance in about one third of patients with heart diseases. Similarly, patients with chronic limitation of the airflow in the airways (e.g. COPD) have reduced aerobic capacity of skeletal muscles. Limitation of expiratory airflow reduces ventilation capacity and therefore it contributes to the perception of breathing effort. Hyperinflation of lungs in COPD causes also reduction of the strength of inspiratory muscles and it further contributes to the perception of dyspnoea during physical activity.

CASE REPORTS

Case report 1

23-years-old woman complains about reduced physical performance, fatigue and weakness of her muscles, she gets extremely quickly breathless during physical activity. She is otherwise healthy, does not take any medication, only contraceptive pills, which were prescribed because of irregular and severe menstrual bleeding. She is surprised by her reduced physical performance, because she recently switched to the vegetarian diet, so she though she will be healthier.

Objective findings: Asthenic patient 173 cm tall, weighing 52 kg, fully responsive, oriented, eupnoeic at rest, cardiovascular and respiratory systems show no pathological findings, BP 110/70 mmHg, pulse 110/bpm, tachycardia at rest, breathing rate 16/bpm. Abdomen below the chest level, painless during deep palpation, no resistance, lower

extremities without pathology. A pallor of skin and conjunctival mucosa was noticed during examination

Laboratory findings: Na 138 mmol/L; K 4.3 mmol/L; Cl 100 mmol/L; ALT, AST normal; urea 3.2 mmol/L; creatinine 90 μmol/L; WBC 5×10^9/L; RBC 2.8×10^{12}/L – microcytes; MCV 45.9 fL; PLT 180×10^9/L, Hbg 98 g/L, Htk 0.28; iron in the plasma is reduced, total transport capacity for iron increased, sideropenia, serum concentrations of folic acid, haptoglobin, transferrin and bilirubin are normal.

Questions & Tasks:

1) Calculate the BMI of the patient and analyse whether her diet change can be related to her current health condition.

2) What type of hypoxia she has and how does the body compensate this type of hypoxia?

3) Based on the laboratory and clinical presentation summarize what type of anaemia our patient suffers from and what are the mechanisms which may lead to it?

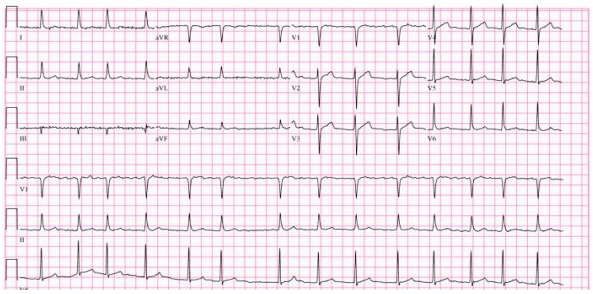
4) Write down an equation characterizing oxygen transport mechanism and point out the component which is limited in this case.

5) Does this type of hypoxia stimulate peripheral chemoreceptors? Explain.

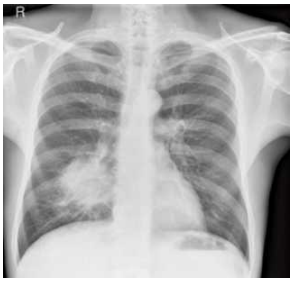
Case report 2

67-years-old man, heavy smoker with COPD was admitted to the pulmonology ward for elective bronchoscopy. He has a history of haemoptysis and an X ray confirmed tumour lesion in the right lungs. Patient complains about breathlessness which limits his physical performance even the daily routine he used to have. He is coughing, mainly in the morning and he claims to have huge expectoration of white sputum. He used to have a headache, now the blood in the sputum is the main complaint.

Objective findings: Patient is fully responsive, 170 cm tall, weighing 78 kg, with mild cyanosis, eupnoeic during examination. Heart action is faster 110/bpm, irregular, with the pulse deficit, BP 150/90 mmHg, breathing rate 17/bpm, breathing sounds indicate limitation of expiratory airflow with wheezes during expiration. Chest is in inspiratory position. Abdomen without pathology, perimaleolar oedema at both lower extremities.



ECG which indicates atrial fibrillation and incomplete right bundle branch block



Chest X ray

Laboratory findings: Na 142 mmol/L; K 3.8 mmol/L; Cl 103 mmol/L; ALT, AST slightly elevated; urea 6.2 mmol/L; creatinine 110 μmol/L; WBC 7.1×10^{9}/L; RBC 5.3×10^{12}/L; Hbg 164 g/L, Htk 0.48. **Astrup:** pH 7.37; PCO_2 7.5 kPa; PO_2 8.3 kPa; HCO_3^- 32 mmol/L.

Questions & Tasks:

1) What type of hypoxia our patient has?

2) Does this type of hypoxia stimulate peripheral chemoreceptors?

3) What compensatory mechanisms have developed in this patient to maintain oxygen tissue delivery?

4) Explain the mechanism leading to cyanosis in this patient.

5) Explain the mechanism leading to dyspnoea in this patient.

6) Explain what disturbance of acid base balance has developed in this patient and why.

Case report 3

30-years-old woman climbed without acclimatisation to the altitude 3500 m above the sea level. She started to experience headache, lost colour vision, became dizzy and felt like fainting. She is also breathless, and complains about dry unproductive cough and problems with articulation. It is was obvious she could not be left without help, so the helicopter with the rescue unit was called.

Objective findings: Patient was transported to the lower altitude and to the hospital, she is fully responsive, oriented, and anxious with visible respiratory effort. Heart action is regular, without pathological murmurs, BP 160/95 mmHg, pulse 120/bpm, RR 24/bpm, breathing sounds are normal, with present silent crepitation at the lung basis at both sides.

Laboratory findings: pH 7.53; PCO_2 3.1 kPa; PO_2 7.8 kPa; HCO_3^- 20 mmol/L; Na 149 mmol/L; K 3.1 mmol/L; Cl 103 mmol/L.

Questions & Tasks

1) Explain signs and symptoms of our patient.

2) What type of hypoxia she suffers from? Are chemoreceptors activated?

3) Explain why she has developed signs and symptoms indicating dysfunction of CNS

4) What type of acid-balance disturbance she has?

5) How does the body compensate the lack of oxygen in high altitude? Is there any difference in case of short lasting stay in high altitude versus living in high altitude?

Chapter 21

DISTURBANCES OF EXTERNAL RESPIRATION

The respiratory system consists of different components of which each plays an important role to fulfil its purpose – **exchange of respiratory gases (oxygen and carbon dioxide)** between organism and the environment. Function of all tissues, organs, and systems is dependent on effectiveness of this exchange. Basic compounds of the respiratory system include:

1) respiratory centres in medulla oblongata and pons Varoli,
2) motor innervation of respiratory muscles and the airways – nn. phrenici, nn. intercostales, autonomic nerves,
3) sensitive (afferent) innervation from whole organism,
4) respiratory muscles – diaphragm, intercostal muscles, auxiliary respiratory muscles,
5) rib cage,
6) pleura (parietal and visceral) and pleural cavity,
7) airways and lung tissue,
8) blood and lymphatic vessels.

We differentiate between **internal and external respiration. Internal respiration** is defined as exchange of oxygen and carbon dioxide in tissues - at the level of cells.
External respiration consists of several integrated processes:

a) **lung ventilation,**
b) **distribution of inhaled air,**
c) **diffusion of gases (O_2, CO_2) across alveolo-capillary membrane,**
d) **lung perfusion,**
e) **distribution of blood perfusion in lungs,**
f) **ventilation-perfusion ratio at the level of alveolar units.**

External respiration changes according to requirements of an organism – its needs of oxygen and elimination of CO_2. Air enter the lung by the **airways** divided into **upper** (nose, pharynx, larynx) and **lower airways** (trachea, main bronchi, segmental bronchi, subsegmental bronchi, terminal and respiratory bronchioli). Lung parenchyma is composed of **alveolar units (acinus) =** alveolar ducts along with alveolar sacs. Each of aforementioned

parts of external respiration can be disturbed separately but its disturbance influences other sections as well (there is integration of all compounds of external respiration).

Lung ventilation and its disturbances

The term lung ventilation describes **process of inhalation of air into the lungs and its elimination to the atmosphere repeating in cycles.** It is characterized by parameter such as:

- total lung ventilation
- dead space ventilation
- alveolar ventilation

For the exchange of respiratory gases only the volume of air reaching the alveolar units (and partly the respiratory bronchioles) getting in contact with blood in alveolar capillaries is important, thus allowing gaseous exchange between alveolar air and blood gases. Dead space represents the volume of air which does not take part in gas exchange. Size of dead space – **anatomic** (upper and lower airways to the level of respiratory bronchioli) and **physiological** (alveolar + anatomic) influences the percentage from tidal volume (VT) reaching the alveolar units during inhalation. The greater dead volume – the smaller percentage of air inhaled reaching the alveoli. Increasing of dead volume decreases efficacy of lung ventilation.

With constant dead space volume, ventilation of alveolar units can be altered significantly by **changing frequency (f) and amplitude of breathing while total lung ventilation will not change** (examples in Tab. 1). Increasing the frequency and proportionally lowering the amplitude doesn't necessarily need to change total lung ventilation compared to normal, but can lead to alveolar ventilation drop which can result in **alveolar hypoventilation**. Vice versa, decreasing the frequency and increasing the amplitude (increasing VT) also doesn't change total ventilation, but increases alveolar ventilation which possibly leads to **alveolar hyperventilation**. Modifying patient's breathing pattern with a help of a doctor or a physiotherapist may improve oxygenation of haemoglobin and CO_2 elimination.

Frequency (f)	V_T (ml)	Total ventilation (ml)	Alveolar ventilation (ml)	$V_{tot} = f \times V_T$ $V_A = f \times (V_T - V_D)$ (V_D = 150 – 230 ml)
12	500	6000	4200	
24	250	6000	2400	
6	1000	6000	5100	

Tab.1 Influence of changes in frequency and amplitude on total and alveolar ventilation

Intensity of alveolar ventilation in healthy individual changes according to metabolic rate. In state of increased metabolism, alveolar ventilation rises as well; by activating regulatory mechanisms to insure the need of higher oxygen supply and CO_2 elimination. When alveolar ventilation equals metabolic rate, we call this **normoventilation** (euventilation); O_2 and CO_2 in blood are within normal ranges. There are two main types of disturbances in this process:

1. alveolar ventilation is lower than the metabolic needs of the organism – **hypoventilation** with tendency to **arterial hypoxaemia** and **hypercapnia,**
2. alveolar ventilation is greater than the metabolic rate of the organism - **hyperventilation** which may lead to **minimal rise of blood oxygen level**, but **significant decrease in partial pressure of CO_2** in arterial blood – **hypocapnia.**

In clinical practice both conditions occur, but the first type, alveolar hypoventilation, is more common.

Basic causes and mechanisms involved in pathogenesis of alveolar hypoventilation

Alveolar hypoventilation may be **partial** (first type - only some percentage of alveolar units are hypoventilated) or **general** (second type - all alveolar units are hypoventilated). Different mechanisms are responsible for development each of them. First type is accompanied by hypoxemia and normo/hypocapnia. Second type is characterized by hypoxemia and hypercapnia. Main causes leading to second type may be **extrapulmonary and intrapulmonary** according the localisation of cause leading to hypoventilation.

a) decreased activity of respiratory centre (extrapulmonary) – functional or structural damage, mainly affecting the inspiratory part; e.g. tumours, inflammation processes, hypoxia, ischemia, extreme hypercapnia, metabolic alkalosis. Specific type of inherited disorder of bulbospinal neurons leading to hypercapnia. It represents diminishing or absence activity of

bulbospinal inspiratory neurons characterised by decreased intensity up to the cessation of breathing in sleep (Ondine's curse).

b) lesion of motor innervation of respiratory muscles – phrenic nerves, intercostal nerves

c) neuromuscular junction disorders (myasthenia gravis) – weakness of respiratory muscles

d) pathologic processes damaging function of respiratory muscles - when the damage is diffuse (e.g. hypoxia)

e) changes in rib cage skeleton leading to stiffness of chest accompanied by decreased its mobility

f) changes of pleura and pleural cavity in inflammation processes, presence of air (pneumothorax) or fluid (haemo-, pyo-, hydro-, chylothorax) in both sides which significantly limit breathing movements of lung along with the limitation of size and function of alveolar units

g) pathologic processes leading to excessive narrowing of the small airways (e.g. status asthmaticus) or **total/subtotal obstruction of larynx or trachea**

Basic causes and mechanisms involved in pathogenesis of alveolar hyperventilation

This kind of disorder may lead to hypocapnia (respiratory alkalosis) which can be accompanied by increased neuromuscular excitability manifesting as increased muscle tone or spasms, and other signs and symptoms (tetany). The main causes may be **functional or organic.** Some examples are:

a) physiologic factors – e.g. high progesterone levels in the second half of menstrual cycle, prolonged speaking or singing (without proper breathing), higher altitude (without acclimatisation in 4000 – 5000 m), fever,

b) psychogenic mechanism – pain anticipation (fear of pain), anxiety, anger suppression, psychological stress, panic disorder, neurosis, hysteria, sense of shortness of breath with no apparent reason (dyspnoea),

c) organic changes within respiratory or other systems – mild grade bronchial asthma (exacerbation of mild grade asthma leading to asthmatic attack), early stage of fibrosing alveolitis, microembolisations to pulmonary artery, pulmonary hypertension, salicylates overdose, stimulation of respiratory centre by adjacent pathologic processes, liver failure.

Summary of disturbances in lung ventilation

For effective gas exchange in lungs, adequate alveolar ventilation is necessary - **depending on total lung ventilation, ratio between frequency and tidal volume, as well as the size of alveolar space and alveolar ventilation.** These parameters influence partial pressures of oxygen and carbon dioxide in alveoli (P_AO_2, P_ACO_2). Partial pressures of gases in alveoli directly affect arterial gases' partial pressures (PaO_2, $PaCO_2$) flowing to the left heart and systemic circulation. Blood gas values are also influenced by metabolic rate and function of regulatory mechanisms which adjust intensity of alveolar ventilation to current metabolic status. Result of process mentioned above is sufficient oxygen supply for cells' function and effective elimination of carbon dioxide to the atmosphere.

Disturbances in distribution of inhaled air

The air inhaled air into central airways is not evenly distributed between all parts of lungs. Therefore, areas where alveolar ventilation is more intense and others with lower intensity of ventilation, do exist. This inequality may be physiological, and is caused for example by gravity. Effective exchange of gases in lungs is determined **not only by total ventilation**, but **mainly by adequate ventilation of each alveolar unit.** Intensity of disturbances in distribution of air in the lungs may be far more strong under pathological conditions. Clinically significant differences in distribution of air into the lung occur as a result of pathological processes affecting separate components of external respiration (changes in tissue properties) and in different parts of the lung. These processes are often spatially and by their intensity differently distributed which creates morphological (and biophysical) basis of unequal distribution of local alveolar ventilation. Unequal distribution of inhaled air in the lung is caused by two main mechanisms:

a) **regional differences in airway resistance** (different intensity of airway narrowing),
b) **regional differences in lung tissue compliance** (different intensity of structural changes in lung parenchyma).

In the first situation, **alveolar ventilation is decreased in those units localized below narrowed airway** because the narrowing increases flow resistance, resulting in smaller amount of air delivered in a time unit. **The ventilation of such units happens with latency and more slowly**. Severity of this kind of disorder can be alleviated when patient will breathe more slowly with a greater tidal volume. Lower frequency of breathing reduces rapidity of airflow in the airway (also at the site of narrowing), thus decreasing the resistance to airflow,

and slower breathing also prolongs the time of inhalation which contributes to greater amount of air passing through the narrowed airway.

In the second case, **alveolar ventilation is decreased in those alveolar units which are in lung tissue with lower compliance**. With each inhalation, these areas of parenchyma distend less than healthy lung tissue resulting in reduced air volume delivered. Apart from that, **filling of such units happens earlier** (stiff tissue reaches maximal distension sooner) than in healthy tissue (e.g. in focal fibrosis). Severity of this kind of disorder can patient lessen by breathing more shallow and faster – reducing respiratory muscles' effort needed to inflate areas of lungs with reduced compliance (reducing dyspnoea).

Summary of disturbances in air distribution in the lung

Regional differences in alveolar ventilation exist in healthy lungs but it has not negative clinical consequences. Under pathological conditions can be the intensity of disturbances in distribution of air in the lung far stronger. **Meaningful deterioration in distribution of inhaled air in the lung is caused by two mechanisms – narrowing of airway lumen in some percentage of airways and changes in lung tissue compliance in important percentage of lung.**

Diffusion of gases in lungs and its disturbances

To oxygen supply and carbon dioxide elimination contribute active processes (lung ventilation and blood circulation) and passive processes (gas diffusion through alveolo-capillary membrane, diffusion through capillary membrane in tissues); function of cells is dependent on their capacity.

Even though gas diffusion is a passive act, it is influenced and limited by several factors:

- solubility of gas in bodily fluids (for O_2 lower than for CO_2),
- diffusion surface area (the greater the area, the more gas diffuses at the same pressure gradient),
- pressure gradient on membrane (the higher the gradient, the faster diffusion – more gas/unit of time),
- thickness and quality of membrane (thicker membrane and/or worse biophysical properties – less gas cross the membrane)

Through alveolo-capillary membrane of all functional alveolar units can in defined time (1 minute) and pressure gradient (1 mmHg) diffuse certain volume of gas. This value is called **diffusing lung capacity** or **transfer factor.** Diffusion of gases is dependent on:

- alveolo-capillary membrane itself,
- capacity of blood to transfer gases,
- rapidity of blood flow in alveolar capillaries

Pathological processes affecting oxygen diffusion across alveolo-capillary membrane

Many processes, within lungs or extrapulmonary causes, negatively influence diffusion capacity for oxygen:

a) decreased alveolar ventilation or decreased partial pressure of oxygen in inhaled air – resulting in lower P_AO_2 ensuing decreased pressure gradient between alveolar air and capillary blood – decreased amount of oxygen diffused,

b) reduction of diffuse area – loss of some percentage of functional parenchyma, e.g. due to atelectasis, tumour, localised inflammation with exudate in alveoli, resection, emphysema, and other similar processes,

c) changes of haemoglobin (Hb) – decreased affinity of Hb to oxygen (e.g. in acidosis, increased CO_2 in pulmonary capillaries, increased 2,3-bisphosphoglycerate, rise in other phosphates' levels, higher body temperature), decreased concentration of functional Hb in blood (anaemia, CO poisoning),

d) changes in circulation in lungs – stasis/decreased blood flow in pulmonary capillaries, thrombosis/embolization of pulmonary artery, significantly increased speed of blood flow in pulmonary capillaries,

e) alveolo-capillary membrane thickening – increased amount of interstitial fluid, alveolar oedema, fibrosis or accumulation of other type of material.

All these processes may lead to development hypoxaemia (in thickening of alveolo-capillary membrane only during physical activity).

Pathological processes decreasing carbon dioxide diffusion

Carbon dioxide diffuses through alveolo-capillary membrane much easier than oxygen. Therefore, in damaged lung function disturbances in CO_2 levels occur later and in more severe conditions than it is for O_2 levels. Main mechanisms leading to decreased diffusion include:

a) **generalised alveolar hypoventilation** (mainly of extrapulmonary origin of respiratory distorders)

b) **high percentage** (75 – 90%?) **of alveolar units with low ventilation-perfusion ratio**

All these processes may result in hypercapnia.

Pulmonary circulation and its disorders

Lungs can effectively fulfil their main function only when alveolar units are well ventilated and alveolar capillaries have adequate blood supply with normal concentration of functional haemoglobin. Sufficient blood supply to alveolar capillaries is due to function of the right ventricle. Considering whole lungs, volume of blood supplied to pulmonary circulation (capillaries mainly) in one minute is circa 5 litres (cardiac output of the right ventricle per minute). Alveolar ventilation in whole lungs during the same period of time equals to 4 litres ($V_A = V_T - V_D$); **then the ratio between alveolar ventilation and perfusion equals to 4/5 = 0.8**. For normal gaseous exchange, this ratio should be equal to or as close as possible to 0.8 in most of alveolar units. Since the alveolar ventilation is not the same in all areas of lungs under physiological conditions, then in the identical conditions perfusion cannot be the same, too (e.g. due to gravity upper lung segments are perfused less then middle and inferior segments, the ventilation is changed similarly.

Pathological processes affecting lungs markedly disturb this distribution of circulation and worsen the conditions for gaseous exchange. For instance:

a) left-to-right shunts – blood gets from the left ventricle through defect in interventricular septum or through shunt between aorta and pulmonary artery (opened ductus arteriosus Botalli) to the right ventricle/ pulmonary artery without getting into systemic circulation, leading to increased cardiac output of the right ventricle along with increased intensity of blood flow through pulmonary capillaries,

b) right ventricle failure which leads to decreased blood supply to lungs

c) unevenly distributed damage to pulmonary capillary system caused by pathological processes, e.g. inflammation, degenerative changes in pulmonary arteries, arterial obstruction, tumours, emphysema destructing interalveolar septa also with capillaries resulting in completely uneven lung perfusion,

d) outflow obstruction of pulmonary capillaries, e.g. in increased pressure in left atrium due to mitral stenosis and/or left ventricle failure – increasing filling of pulmonary arteries (as well as pressure in them) slowing the blood flow which leads to loss of normal apical-basal

stratification of blood distribution (capillaries in all lung segments have equal and evenly increased filling).

Ventilation-perfusion ratio and its disturbances

In the lungs as a whole, ventilation-perfusion ratio equals near to 0.8. **However, main and more important determinants of gaseous exchange in the lungs are ratios** between alveolar ventilation and alveolar perfusion **at local level**, more specifically in each alveolar unit.

Disproportions of ventilation distribution in areas of lung exist (e.g. due to gravity, intensity of breathing); intensity of alveolar ventilation changes according to physical activity, nevertheless exchange of gases remains effective. This means that capillary perfusion must adapt to changed ventilation of a given unit. This adaptation happens via change of diameters of vessels (vasoconstriction or vasodilation at the level of pulmonary arterioles), changing the filling of alveolar capillaries by blood. Mechanism of physiological regulation employs as well in various pulmonary and extrapulmonary pathological conditions. **Proper regulation of ventilation-perfusion ratio means when one parameter changes** (e.g. ventilation)**, the second** (perfusion) **changes accordingly in the same direction; in given alveolar unit this modification is equivalent and synchronised in time to sustain normal ventilation-perfusion ratio, i.e. 0.8** (Fig.1 – schemes 1, 6, 11).

On the other hand, changes in mentioned parameters in opposite directions, or not synchronised in time of a given alveolar unit will lead to disturbances in gases exchange. If the change of both mentioned parameters are in the same direction but not adequately proportional in their intensity will lead to the change of the ventilation-perfusion ratio, too (Fig. 1 – schemes 2, 3, 7); resulting in hypoventilation of the unit. In contrast, ratio above 0.8 results in hyperventilation of the unit (Fig. 1 – schemes 5, 9, 10).

When the alveolar unit is only perfused but not ventilated, ventilation-perfusion ratio equals to zero, hence gaseous exchange cannot happen – in this case it is **right-to-left shunt** through which flows unoxygenated blood from the right to the left heart, decreasing partial pressure of oxygen in arterial blood (Fig. 1 – schemes 4, 8, 12). When alveolar unit is ventilated but not perfused, ventilation-perfusion ratio approaches to infinity, thus in such unit exchange of gases cannot happen as well (Fig. 1 – schemes 13, 14, 15). In this case, **dead space is ventilated,** thus useless, ineffective ventilation which does not contribute to oxygenation of blood.

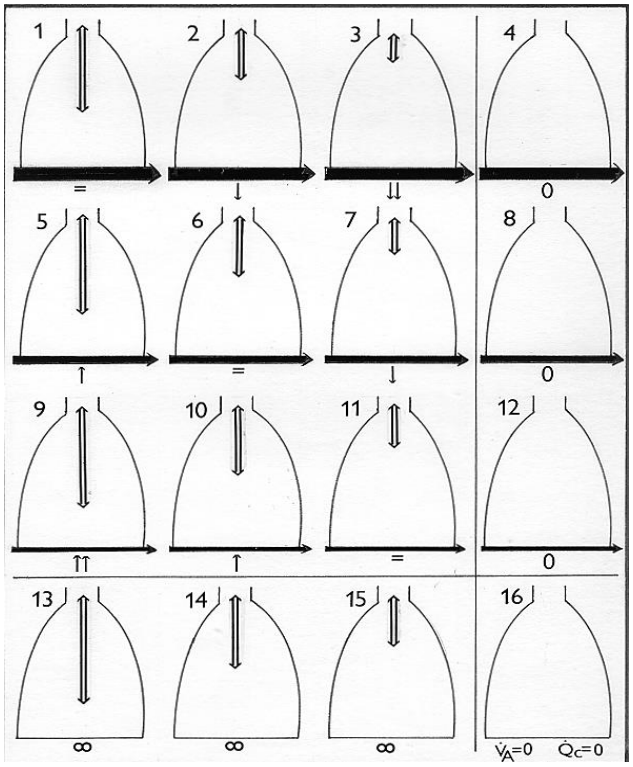


Figure 21.1: Main types of ventilation-perfusion ratios in physiological and pathological conditions (Legend: length of empty arrow - intensity of alveolar ventilation; width of black arrow - intensity of alveolar capillary blood flow; = change of ventilation and perfusion is proportional, so V/Q is 0.8. Note: Scheme 6 represents physiologic conditions.

CASE REPORTS

Case report 1

68-year-old woman was brought to the emergency department with dyspnoea she has been suffering from whole week. Patient haven't coughed, no chest pains or other respiratory signs and symptoms. She doesn't report any weakness in her limbs, blurred vision or difficulties with swallowing. 16 years ago, she was diagnosed with DM, hypertension, and depression; 11 years ago she underwent total thyroidectomy due to papillary carcinoma. Patient regularly takes selective serotonin reuptake inhibitor citalopram, alprazolam and zolpidem for depression and insomnia, levothyroxine and alpha-calcitriol after thyroidectomy, calcium channel blockers for hypertension, and metformin and sulfonylurea for DM.

During **physical examination** patient was not in respiratory distress. Vital signs were: BP 170/90 mmHg, HR 92/min, RR 24/min, T 36°C, BMI 24.2, mental status intact, patient was fully conscious, neurological findings were normal. Pre-tibial pitting oedema was not

present, nor increased filling of jugular veins. In auscultation, mild crackles were audible bilaterally in basal segments.

Laboratory findings: Le 6.580/mm^3, Hb – 12.0 g/dL, Tr – 325.000/mm^3, other parameters within ranges. **Thyroid profile**: T3 – 0.73ng/mL, FT4 – 1.71ng/dL, TSH < 0.003μIU/mL.

ABG and acid-base status: no oxygen administered, pH 7.44, $PaCO_2$ 39.9 mmHg, PaO_2 64.7 mmHg, Saturation 93,2%, $D(A\text{-}a)O_2$ 36 (atelectasis?)

Chest X-ray (admission) – slightly reduced lung volume; CT – no signs of pulmonary embolism, atelectasis bilaterally in basal segments; ECHO – normal systolic and diastolic function

During following 5 days of admission dyspnoea was progressively worsening. On the 6^{th} day patient got into severe respiratory distress with obviously troublesome breathing. Respiration rate was 40 per minute, patient was disoriented. Oxygen through mask (10 l) was ordered; ABG as follows: pH 7.324, $PaCO_2$ 54.9 mmHg, PaO_2 94.4 mmHg, Saturation 96,6%. Chest X-ray showed reduction of lung volume. Patient was transferred to ICU for mechanical ventilation.

In this phase of diagnostic process, it was clear that patient's troubles are of extrapulmonary origin. Guillain-Barre syndrome or Myasthenia gravis should be considered. EMG showed decremented activity in different muscle groups after repetitive stimulation of afferent nerves. In repeated measurements increased levels of antibodies against Ach receptors (8.9 nmol/L and 12.4 nmol/L) were found.

Patient fully recovered in two months thanks to a treatment with Pyridostigmine bromide (parasympathomimetic and a reversible cholinesterase inhibitor), prednisolone, i.v. immunoglobulins, and mechanical ventilation.

Questions & Tasks

1) Summarise all relevant signs and symptoms in described patient.

2) What are the pathomechanisms leading to those signs and symptoms – analyse individually.

3) How Guillain-Barre and Myasthenia gravis change the parameters of ventilation?

4) Explain possible mechanism leading to atelectasis in basal lung segments.

Note: *Myasthenia gravis (MG) is an autoimmune disorder. Respiratory failure is a complication of MG in late phase of the illness known as myasthenic crisis. It occurs in 3-7% of cases, respiratory failure as the first sign of disease was present in 14-18% of cases.*

Case report 2

A young student, 21-year-old woman was sent to a pulmonologist for an examination because of dyspnoea.

Medical history: appendectomy at the age of 7; then diagnosed with decreased thyroid gland function, treated with Letrox (1/2-0-0), now function normalised; non-smoker, no allergy diagnosed; hobbies – playing flute, taking care of dog and cat

Family history: mother treated for repeated bronchitis, father allergic to pollen, 6-year-old brother under treatment for atopic eczema

Present illness: In last few years she suffered from dyspnoea associated with physical activity. Difficulties breathing occurred in all seasons, and limited her sport activities. Now she wakes up at night or early in the morning about 3 times a week with a sense of pressure in chest which alleviates spontaneously or after Berotec administration (asks for medication her mum had prescribed). Sometimes she cannot play flute because of breathing problems. Attacks of dyspnoea are triggered by upper respiratory tract infections mainly occurring in autumn; dyspnoea can be also induced by stress. The patient does not cough, without fever.

Physical examination: BP 110/60; HR 60/min, regular; RR 16/min, T 36.7°C; thyroid gland not palpable; **lungs:** spontaneous normal breathing is vesicular with prolonged exspirium, percussion without pathological findings, during forced expiration rare wheezing can be heard; **heart:** auscultation – heart sounds normal, no murmurs, chest percussion – heart not enlarged; other organs without pathology

Chest X-ray: no pathological findings

Spirometry: VC 3.8 l (87. 9% of reference value – RV), FEV_1 2.44 l (65.4% RV), MEF_{50} – 1.72 l/min (35.4% RV), **Bronchodilatation test** using Salbutamol 400 µg through spacer: FEV_1 increased by 880 ml (i.e. 36%). Wheezing disappeared after administration of Salbutamol.

Questions & Tasks

1) Summarise sign and symptoms from the case report.

2) What pathomechanisms lead to such signs and symptoms?

3) How does the sensation of shortness of breath origin?

4) Interpret spirometric findings.

5) What is the most likely diagnosis in our patient?

Case report 3

65-year-old retired man, formerly a waiter, driven to hospital by an ambulance because of markedly worsened dyspnoea and oedemas on lower limbs.

Medical history: When he was young, he didn't overcome any severe disease, since youth he had smoked 40 cigarettes a day, he stopped smoking 2 years ago, from time to time drinks one beer. He is allergic to penicillin antibiotics. Since 1988 he has been under observation in a centre of respiratory diseases because of benign tumour mimicking chondrohamartoma located in 6^{th} segment of the right lung, its size hasn't changed during the period. Patient had trouble breathing – dyspnoea progressively worsening during past three years. He met the criteria for long-term oxygen therapy (home oxygen therapy), he was given an oxygenator he has been using for past year. He suffers from chronic cough with sputum production, mainly in morning, of white-grey colour, when his condition is worsened, colour changes into yellow-green.

Family history: father died of lung cancer at the age of 50, mother died at the age of 76 of stroke, patient has 3 children, one brother who is healthy

Medication: Spophyllin, Pulmicort, Atrovent, Berodual, Mucosolvan, oxygen 2 litres/min circa 16 hours a day

Present illness: Dyspnoea was worsening during past three weeks, occurred after minimal physical activity, sometimes even at rest. Patient reports that during last week his lower limbs swell, lost his appetite, started to cough out thick, greenish sputum, his body temperature was about 37.5°C. Breathing higher concentration of oxygen did not alleviate his troubles, that is why he called an ambulance. During transport to hospital he was on 90% oxygen.

Physical examination: at the moment patient is not dyspnoeic, skin has normal colour, without signs of jaundice, mildly obese, well hydrated, co-operates well, lips and tongue cyanotic, tongue not coated, lower limbs warm; T 37.4°C, HR 90/min, BP 140/80 mmHg; increased filling of jugular veins; barrel chest, hyperresonant percussion, diffusely diminished breathing; heart not enlarged (percussion), heart sounds normal, no murmurs, regular activity; abdomen above niveau of chest with thick layer of fat, umbilical hernia, liver 4 cm below costal margin, spleen not palpable, tapotement negative; lower limbs are swollen to the knees, dough-like character, peripheral pulses palpable, Homans' sign negative.

Chest X-ray: (AP) chest of hourglass shape, diaphragm descended, diaphragm arches flattened; heart shadow is at upper size limit; mediastinum is not distended, hilar shadow highlighted, increased transparency of lungs bilaterally, mainly upper third, in the right middle segment soft shadow 1 cm in size. In lateral projection barrel-like chest.

Questions & Tasks

1) Identify all important signs and symptoms in this patient.

2) Explain pathomechanisms resulting in those signs in symptoms.

3) What is a "barrel-like chest", what mechanism leads to this condition?

4) How can worsening of patient's condition during last week be explained?

5) In your opinion, what is the most likely diagnosis?

Case report 4

25-year old man visited a general practitioner complaining about worsened breathing, wheezing sounds "arising somewhere from the chest", runny nose, and swollen eyelids.

Medical history: Previously he was not severely ill, smoker – 10 cigarettes a day for past ten years. He doesn't sleep on feather pillows, no animals in his apartment, but he is allergic to cats – presenting with sneezing after each contact with a cat. He is not allergic to any medication, food or insect bite.

Present illness: At present time – from March to April – aforementioned signs and symptoms are more intensive (watery secretion from nose, itching of skin and eyes, conjunctivitis). When lying on back he has trouble breathing, reports audible wheezing in chest and dry cough. During examination patients said that 3 years ago he had been tested for allergic reaction to birch pollen, cat fur, and house dust mites – all positive. He refused recommended therapy.

Physical examination: patient is eutrophic, swollen eyelids, conjunctivitis, watery secretion from nose; lung auscultation – alveolar breathing, wheezing present, HR 68/min, BP 125/80 mmHg

Laboratory findings: all parameters within physiological ranges except from eosinophils in peripheral blood – 14%. **Spirometry:** VC 94.9%; FVC 87.6%; FEV_1 76.1%, PEF 64.3%

Questions & Tasks

1) Summarise all signs and symptoms this patient has.

2) Explain pathomechanisms resulting in those signs in symptoms.

3) The patient most likely suffers from some kind of immune disorder – what kind?

4) What are the typical signs and symptoms for this immune disorder?

5) What pathomechanisms lead to onset of dyspnoea and changes in mucous membrane?

6) What is the diagnosis in the presented patient?

Chapter 22

RESPIRATORY INSUFFICIENCY

Respiratory insufficiency (RI) represents a syndrome characterized by disturbed exchange of O_2 and CO_2 in respiratory system. RI is not a disease, but rather a pathological process caused by serious diseases of respiratory system leading to disturbances of O_2 and CO_2 exchange in lungs, which is potentially dangerous and may cause dysfunction of other organs. Symptoms and signs are caused by the lack of O_2 in tissues, and insufficient elimination of CO_2 from the body.

Definition

RI is a condition in which respiratory system does not maintain optimal oxygenation of arterial blood and optimal elimination of CO_2 produced in metabolism. Levels of PaO_2 and $PaCO_2$ analysed in rest condition breathing atmospheric air at atmospheric pressure close to the sea level are changed: PaO_2 is below 8.0 kPa with or without a $PaCO_2$ increase more than 6.5 kPa in the subject without severe heart disease.

Factors determining ventilation and oxygenation are different and must be considered separately

Exchange of O_2 and CO_2 takes place at the level of alveolar-capillary unit. The $PaCO_2$ must be regarded as a function of the overall ventilation of the entire lungs, without regard to local inequalities of distribution of ventilation and perfusion. The PaO_2 depends not only on the amount of alveolar ventilation, but also on the matching between ventilation and perfusion in particular lung compartments.

Oxygen after its diffusion to the capillary blood binds to the haemoglobin. This chemical reaction is reversible and depends on PaO_2 (S-shaped dissociation curve – see the lecture). CO_2 is transported in the blood in three distinct forms – dissolved in the plasma, attached to the globin part of haemoglobin molecule – carbaminohaemoglobin and majority of CO_2 is transported in a form of bicarbonates. (see the lecture about acid-base disturbances). Dissociation curve describing the relation between the content of CO_2 in the blood and $PaCO_2$ is approximately linear (its shape is different compared to oxygen S-shaped dissociation curve). Since these processes are different, the term **ventilation** is commonly

used to characterize the exchange of CO_2, while the term **oxygenation** is used to characterize exchange of oxygen.

Gas exchange is precisely regulated, and usually normal ventilation of alveolar units is followed by normal oxygenation of arterial blood in case that both lungs and heart functions are physiological. The fact that ventilation and oxygenation are different functions of respiratory system is documented by variable respiratory disturbances, e.g. some of them will manifest only by hypoxemia (O_2 exchange disturbance) without disturbed CO_2 level. Some of respiratory disturbances will manifest by both hypoxia and hypercapnia (both O_2 and CO_2 exchange are affected).

$PaCO_2$ is determined by ventilation of all compartments in lungs (overall ventilation) not considering local mismatches of the distribution of ventilation and perfusion.

PaO_2 depends not only on the intensity of total alveolar ventilation, but also on regional relationships between ventilation and perfusion.

Classification of RI

According to gas exchange disturbance, RI is classified to either **hypoxemic (**PaO_2 < 8.0 kPa, $PaCO_2$ < 6.5 kPa) or **hypercapnic** (PaO_2 < 8.0 kPa, $PaCO_2$ > 6.5 kPa). According to the time of onset and duration we can distinguish **acute** and **chronic** RI. Typical example of acute RI is suffocation (severe occlusion of upper airways or trachea) caused by aspiration of foreign bodies to the hypopharynx or by compression/trauma of larynx or trachea by external pressure. Chronic RI typically develops in patients with chronic respiratory disease such as lung fibrosis or COPD with progressive retention of CO_2 with compensated respiratory acidosis. However, sudden worsening of a patient´s condition (infection, sedatives, etc.) may lead to acute exacerbation of chronic RI, which is a life-threatening condition. RI can be either **latent** (without signs and symptoms at rest) or **manifest**.

Hypoxemic RI

Laboratory analysis of arterial blood shows drop of **PaO_2 below 8.0 kPa, while $PaCO_2$ is normal** (5.0–6.5 kPa) eventually decreased below 5.0 kPa (hypocapnia). PaO_2 = 8.0 kPa represents certain point on the haemoglobin dissociation curve where even small decrease of PaO_2 leads to considerable reduction of Hb saturation. Reduction of PaO_2 from normal values till the 8.0 kPa lead to only mild and insignificant reduction of saturation. Drop of PaO_2 from normal value 13 kPa to 8 kPa corresponds with the drop of saturation SaO_2

from 97 to 89%; drop of PaO_2 from 8 kPa to 5.3 kPa lead to decrease of SaO_2 from 89% to 75 %).

Hypercapnic RI

Analysis of arterial blood shows **severe hypoxaemia (PaO_2 < 8,0 kPa) and hypercapnia ($PaCO_2$ > 6,5 kPa)**. Hypercapnia is caused either by overall alveolar hypoventilation as a consequence of extrapulmonary conditions (hypoxaemia and hypercapnia develop simultaneously) or due to extensive mismatch between ventilation and perfusion of majority of lung compartments. In this case hypercapnia develops after hypoxaemia, due to the failure of compensatory mechanisms which were activated to maintain normocapnia via increased ventilation drive.

Mechanisms responsible for disturbances of the gas exchange

1) Diseases in the lung and airways

- **Diseases of the airways** could lead to disturbances in the distribution of inhaled air into the individual lung compartments by unequal narrowing of peripheral airways in these compartments. Some of them are hypoventilated, while others are receiving enough air for gas exchange. The most common diseases leading to such disturbances of the air distribution are obstructive lung diseases – mainly COPD.
- **Diseases of the lung parenchyma**, which reduce the lung compliance of individual compartments. This pathological process is usually distributed with variable severity over the lungs. Therefore, some of the compartments (alveolar units) expand easily during inspiration, while some of them not, what lead to the uneven distribution of inhaled air into the alveolar units.

Aforementioned disturbances in distribution of ventilation in the lungs which are normally perfused cause severe **ventilation-perfusion mismatch in individual compartments**. The most dangerous are compartments with low ventilation-perfusion ratio ↓ V/Q and compartments with ventilation-perfusion ration equal to zero (venous admixture or right-to-left shunts). Arterial blood leaving these compartments is **hypoxemic and hypercapnic** and ventilator drive is stimulated by chemoreceptors.

Pathology of the alveolo-capillary membrane, which limits diffusion of oxygen, but not much diffusion of CO_2 can also contribute to the RI. While the disturbance of V/Q ratio are common causes of hypoxaemia, pathology of alveolo-capillary membrane causes

hypoxaemia only during physical exercise, when circulation time of blood in lungs becomes shorter – therefore insufficient for correct diffusion process.

Decreased ventilation – perfusion relationship (↓ V/Q)

There are areas in lungs which are less ventilated comparing to their perfusion. Alveolar air in these compartments has reduced PO_2 and increased PCO_2. Blood leaving these compartments is **hypoxemic and hypercapnic**. After this blood is mixed with the blood leaving compartments with normal ventilation and perfusion (with normoxemia and normocapnia), the result is a mixed blood with **mild hypoxaemia and mild hypercapnia** (depending on the severity of pathological process which determines what compartments have ↓V/Q ratio and how seriously hypoventilated they are). However, this is not the end. Change of the levels of oxygen and carbon dioxide in arterial blood stimulates chemoreceptors (peripheral and central). Increased ventilator drive will increase ventilation of those lung compartments, which are not affected by pathological process e.g. airway narrowing and these lung compartments become **"hyperventilated"** – their ventilation-perfusion ratio will be high. This process will increase PO_2 and decrease PCO_2 in alveolar air in compartments, which are currently hyperventilated. Blood leaving compartments with high V/Q ratio will be hypocapnic, but normoxemic (instead of high PO_2 in alveolar air, it is not possible to further increase saturation of haemoglobin, which is fully saturated at 13,3 kPa). Further increase of PO_2 will not influence haemoglobin dissociation curve at its plateau. Mixed blood from all lung compartments will be normo- or hypocapnic, but hypoxemic – increased ventilation drive can compensate only hypercapnia, but not hypoxaemia. Compartments with low ↓ V/Q relationships are a source of hypoxaemia after the compensatory ventilation response.

Right-to-left shunting (true venous admixture)

Lung diseases may lead to complete stop of ventilation of certain compartments, while their perfusion remains normal. This will lead to inequality of V/Q ratio, where V/Q expressed mathematically is zero. Common example of such inequality is the lung oedema (alveolar). Blood leaving these compartments has the same composition of gases as the venous blood. This is the mechanisms which under normal circumstance contributes to the venous admixture. From the functional point of view this situation is characterized as **right-to-left intrapulmonary shunt** (volume of blood, which does not participate in the gas exchange, and remain the same as it came from the right ventricle). Similarly, as in case of ↓

V/Q, increased ventilation drive can compensate hypercapnia, but not hypoxaemia (for more details see the lecture).

2) Extrapulmonary conditions

These conditions typically lead to the total alveolar hypoventilation due to the weak or insufficient extra pulmonary components of respiratory system (nerves, muscles etc.). Consequence of this processes is hypoventilation of all compartments in lungs, therefore compensatory rise of ventilator drive cannot exist to improve the gas exchange. Common mechanisms leading to the RI are:

- **Suppression of respiratory centre** in the brainstem by drugs or pathological process.
- **Damage of motoneurons or efferent nerves** for respiratory muscles. The most common is unilateral damage of the phrenic nerve.
- **Neuromuscular diseases** or **fatigue of respiratory muscles** leading to the failure of the effector of ventilator drive.
- **Deformation of the chest, trauma** or reduced compliance which limit desired expansion of lung parenchyma. Similar effect is seen in chest or abdominal pain, which disables proper expansion of lungs (patient prefers shallow breathing to avid or diminish pain).
- **Expansion of lungs can be limited by fluids** (hydrothorax, pyothorax, haemothorax, chylothorax) or **air** (pneumothorax) in pleural cavity.

Why in lung diseases hypoxemic type of RI could proceed to hypercapnic type, which is more characteristic for advanced and severe clinical manifestation of respiratory disease?

Common, however incorrect assumption claims that this situation is caused by different speed of diffusion of CO_2 and O_2, where diffusion of CO_2 is 20-times faster. This can be disproved by simple physiologic fact – contact of the red blood cells with diffusion membrane during circulation of the blood in lungs at rest is 0.7 – 0.8 sec, while haemoglobin is fully saturated in 0.3 sec, which is a contact time of red blood cell and diffusion membrane during physical exercise. It is therefore clear that even 0.3 sec is enough time for full saturation of haemoglobin.

Explanation of the dynamics of RI in case of intrapulmonary diseases stems in **different shapes of dissociation curves of blood for CO_2 and O_2.** Blood is fully saturated by oxygen (98%) at physiological value of PaO_2 = 13 kPa. However, blood leaving

hypoventilated compartments is considerably desaturated (SaO_2 around 83-85%), because in these compartment alveolar PO_2 is about 6-7 kPa). Compartments with high PO_2 (consequence of ventilatory compensation) are not able to increase saturation, because their localisation on the curve is already at its plateau. Therefore, compartments with ↑ V/Q relationship (hyperventilated by compensatory mechanism) cannot compensate the lack of oxygenation caused primarily by compartments with ↓V/Q. Dissociation curve for CO_2 is linear with mild bend and it allows compensation of hypercapnia caused by compartments with ↓ V/Q (mixed with hypocapnic blood from compartments with ↑ V/Q. (see lecture).

Mechanisms of hypoxaemia

- **Overall alveolar hypoventilation** is important mechanism leading to hypoxaemia in case of extrapulmonary diseases, and it is always associated with hypercapnia. From intrapulmonary causes, the most common mechanism leading to hypoxaemia is the presence of compartments with **↓ V/Q**.
- Very common are **intrapulmonary right-to-left shunts** in compartments with zero ventilation and normal perfusion, which cause true venous admixture.
- As it was already explained, **impairment of diffusion lead to hypoxaemia only during physical exercise,** because even slow diffusion across the diffusion membrane is effective enough to achieve full saturation at the rest condition (here the contact time of RBC is 0.8 sec). The problem may appear during physical exercise, where the circulation becomes faster and diffusion contact time is reduced to approximately 0.3 sec. Combination of shorter contact time and thickness of diffusion membrane can lead to desaturation ~ 80% (see lecture).

Mechanisms of hypercapnia

Extrapulmonary causes typically lead to **hypercapnic type of RI**. In case of intrapulmonary diseases, there must be a critical number of compartments with disturbed V/Q (low, zero or their combination), which means, that even higher ventilatory drive would not bring more oxygen, nor eliminate more CO_2, because of extension and severity of primary pathological process. In this case, increase of compensatory efforts (increase of alveolar ventilation) is limited by following processes:

- increase of ventilatory drive represents **increase of work of respiratory muscles**, which has its limits,

- increase of the respiratory work load lead to the **fatigue of respiratory muscles.**

Symptoms and signs of RI

Symptoms and signs observed in subjects with RI are determined by **hypoxaemia and hypercapnia and also by the involvement of compensatory mechanisms**. Since these signs and symptoms are highly unspecific, it is necessary to monitor partial pressures of both oxygen and CO_2 in arterial blood. It is also important to note that manifestation of primary respiratory disease which caused RI can be considerably covered or even hidden in manifestation of respiratory insufficiency.

Symptoms and signs caused by hypoxaemia

- **Tachycardia, tachypnoea and secondary polycythaemia** represent compensatory mechanisms which are activated to increase oxygen transport to tissues.
- **Dyspnoea –** subjective unpleasant sensation of "air hunger" caused mainly by increased work load of respiratory muscles initiated to maintain oxygenation and ventilation.
- Since the neural tissue is the most sensitive to the lack of oxygen, impairment of **mental performance** (disorientation, lethargy, or excitation) appears.
- **Cyanosis** (blueish or violet colour of the skin and mucosa) caused by rise of concentration of reduced haemoglobin to more than **50 g/L in capillary blood**. In case of RI patients, it is called "central cyanosis". This condition is further promoted by polycythaemia.

Symptoms and signs caused by hypercapnia

- The most common symptom is **morning headache**, hypercapnia dilates cerebral vessels thus increasing intracranial pressure.
- Similar mechanism lead to the **oedema of retina, dilatation of conjunctival arteries and superficial facial arteries**
- Severe hypercapnia has **narcotic effect**, anxiety proceeds to delirium and unresponsiveness.

Respiratory failure

While in **respiratory insufficiency** patient can maintain his/her oxygen and CO_2 levels at defined values for hypoxaemia and hypercapnia, in **respiratory failure** this is not

possible any longer. Level of $PaCO_2$ progressively increases (8-10 kPa) and patient will die **without artificial ventilation support.**

Chapter 23

PULMONARY FUNCTION TESTS

The main function of respiratory system is continuous exchange of O_2 and CO_2 between blood in lung capillaries and air in alveoli – permanent oxygen supply to the lungs and elimination of carbon dioxide. Effective ventilation requires **patent airways, normal elasticity of lung tissue and chest, efficient respiratory muscles, and proper regulation of breathing.** Pulmonary function test objectively shows level of function of airways and lungs, helps to create a picture of respiratory system disease based on medical history and sophisticated examination. The most important condition to obtain valid data using pulmonary function test is trained personnel, well cooperating patient, equipment of acceptable quality, and the use of standardised procedures.

1) Purpose of pulmonary function tests

Pulmonary function test helps doctor/patient to:

a) establish diagnosis, e.g. early diagnosis of incipient respiratory disorder which at the time doesn't cause any subjective trouble to a patient, to identify type and severity of respiratory disorder, to point out the cause of chronic cough, dyspnoea, sense of pressure on chest, and other respiratory signs and symptoms,

b) monitor efficacy of treatment of respiratory diseases, e.g. bronchial asthma, COPD,

c) assess course and prognosis of respiratory diseases, e.g. asthma, COPD, before and after surgical interventions on chest, airway, lungs, and abdomen.

2) Methods of pulmonary function tests

Basic – screening methods

a) examination of forced expiratory vital capacity (FVC, FEV1, FEV1/FVC%)

b) measuring **peak expiratory flow** using peak flow meter

c) pulse oximetry

Basic – extended methods

a) recording flow-volume loop

b) rhinomanometry

c) bronchoprovocation test – dilatation and constriction

d) stress test (6-MWT)

Special methods

These methods include measurements of airway resistance (body plethysmography), obtaining indirectly measurable static parameters (plethysmographically, dilution and washout method), diffuse lung capacity for CO (transfer factor), lung compliance, respiratory muscle function assessment, blood gases and acid-base status, spiroergometry, examination of lung circulation, examination in sleep laboratory, monitoring of NO in exhaled air (FeNO). Methods assessing reactivity of the airway to irritating substances also fit into this category – bronchoprovocation tests (BPT): exercise challenge – running, or pharmacological stimuli – methacholine, acetylcholine, histamine most frequently. They can show **bronchial hypersensitivity** (increased sensitivity of the airway to different kinds of stimuli), and **bronchial hyperreactivity** (inadequately strong response of the airway to different kinds of stimuli). These abnormalities accompany mainly bronchial asthma, acute or chronic inflammation of bronchi, as well as can be seen in patients with allergic rhinitis, temporarily after overcoming a viral or bacterial infection of the airway. Using these methods, the status of airway reactivity in long term, and also efficacy of treatment can be evaluated.

Spirometry

Examining lung volumes and capacities gives us information about lung "size" and about properties of system lungs-chest (Fig. 1). Direct measurements of volumes and capacities are most frequently done using spirometer. Nowadays, sophisticated spirometers with built-in pneumotachograph and automatic data processing are available. All volumes and capacities are expressed in litres under standardised conditions (BTPS). Cooperation between patient and personnel is essential. Patient should follow instructions – have their nose closed with a clip, when obtaining maximal ventilation parameters, patient really should do so with maximal effort and rapidity. Examination is usually performed repeatedly, for evaluation the best results are taken into account. When patient does not cooperate well, along with examination done technically wrong, we acquire false positive/negative results. Static and dynamic spirometric and/or spirographic parameters are evaluated (Fig. 2 and 3).

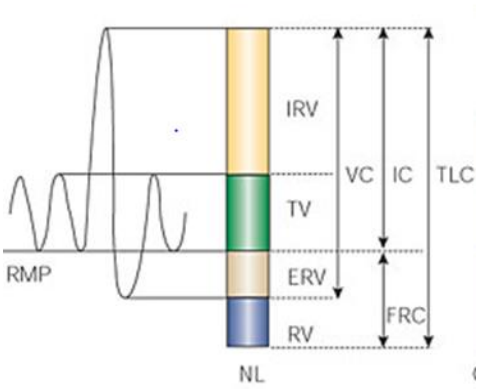


Figure 23. 1: Static lung volumes

IRV – inspiratory reserve volume, **TV** – tidal volume, **ERV** – expiratory reserve volume, **RV** – residual volume, **VC** – vital capacity, **IC** – inspiratory capacity, **FRC** – function residual capacity, **TLC** – total lung capacity

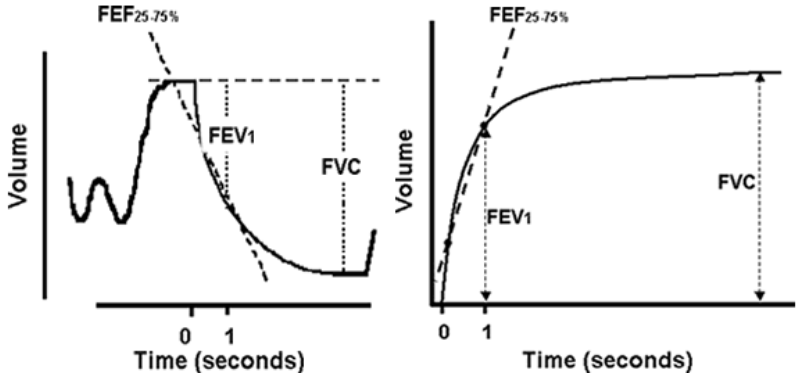
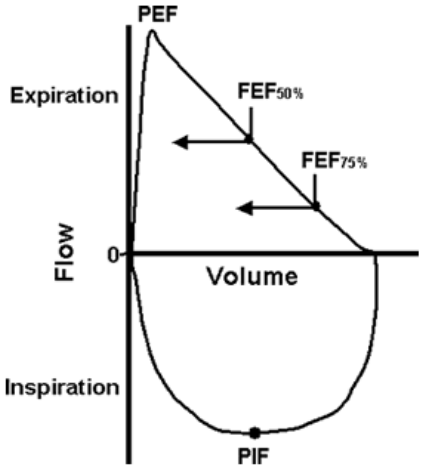


Figure 23.2: Dynamic lung volumes

From recording forced expiratory vital capacity we can obtain these dynamic parameters: FEV_1, FVC, $\mathbf{FVC_{25\text{-}75\%}}$ - average air flow in the airway at FVC at level between 25-75% VC. $\mathbf{FEV_1}$ – volume of air exhaled in the first second during FVC examination, **FVC –** VC exhaled/inhaled with maximal effort, **VC** – slow maximal exhale/inhale, (in healthy individuals VC = FVC), in obstruction of airway VC > FVC. $\mathbf{FEV_1/VC}$ or $\mathbf{FEV_1/FVC}$ **–** proportion between volume of air exhaled in the first second of FVC to total volume of VC (FVC), it represents clinically important and useful index.

Apart from measuring lung volumes, for lung function diagnostic are also important measurement of air flow in the airway gained from flow-volume loop (Fig. 3).



Factors determining shape of the loop:

- expiratory effort
- lung volume and elasticity
- airway clearness
- bronchial elasticity

Figure 23. 3: Flow-volume loop - normal shape during maximal ventilatory effort

This manoeuvre starts from the level of maximal inspiration (TLC) when airway is maximally distended. Continues with maximal expiration along with reaching peak expiratory flow (PEF) which is dependent on expiratory effort (compression of large airways), then followed by continuous air flow that is not dependent on expiratory effort (meaning increasing expiratory pressure doesn't change the flow). Size/rapidity of the air flow in this phase of forced expiration (as well as shape of the loop) are dependent on elasticity of lung tissue, airways, and lung volume. Convex shape is common in young individuals, linear in young adults, slightly concave shape of this part of the loop is characteristic for healthy airways and lungs in elderly. Flow in the terminal phase of exhale depends on elastic properties of chest wall and again is dependent on expiratory effort. Maximal flow is gained during forced inspiration (PIF).

Measuring peak expiratory flow (PEF) expressed in l/s or l/min gives us information about airway patency, power of expiratory muscles, effort needed to exhale, volume and elasticity of lungs and airways. These tests, apart from spirometry, are done with simple device – pocket peak flow meter. During spirometric examination measured values are compered to reference values which depend on age, weight, height, and gender.

Basic ventilatory disorders and their characteristics in pulmonary function tests

Lung function tests are used to diagnose two basic types of ventilatory disorders – **obstructive** and **restrictive ventilatory disorders.** In clinical practice, it is known that ventilatory disorders are usually combined, they have sign of both obstruction and restriction, e.g. in cystic fibrosis or COPD.

Obstructive ventilatory disorder (OVD)

OVD leads to reduced ability to ventilate lungs because narrowing of the airways increases resistance to the air-flow. Time of expiration (FET) increases according to the severity of the process. Diagnosis is based on reduction of FEV_1 and FEV_1/FVC. PEF and $FEF_{25-75\%}$ decrease simultaneously; VC and FVC can be normal or decreased. RV, FRC, and TLC are increased.

Causes of OVD – accumulation of mucus in airway during inflammation, contraction of smooth muscles in airway, oedema and inflammatory infiltration of airway mucous membrane, airway remodelling, outer pressure on the airways as a result of an expansive process, loss of elastic properties of lungs.

Aforementioned disturbances occur in diseases such as **bronchial asthma (bronchoconstriction)** and chronic obstructive pulmonary disease – **COPD (mucus overproduction – chronic bronchitis, loss of lung elasticity – emphysema).** Severity of OVD is determined according to decrease of FEV_1 compared to reference value. According to established classification, there are three grades of ORD:

- **Mild OVD** FEV_1 in range of 60 – 79% of reference value
- **Moderate OVD** FEV_1 in range of 45 – 59% of reference value
- **Severe OVD** FEV_1 less than 45% of reference value

Obstruction of the airways by aforesaid processes causes premature closure of medium and small (peripheral) airways corresponding with significant decrease of FEV_1. Expiration time is prolonged because narrowed airways represent increased resistance to air flow. At the same time, retention of inhaled air occurs in terminal respiratory units (↑ FRC). In accelerated breathing, air retention as well as FRC markedly increase, because the obstruction of airways slows expiration down and also quells its termination. In repeating such breathing cycles respiratory level at rest shifts towards inspiration level (barrel chest).

Increased frequency makes the conditions for gas exchange worse, therefore slow and deep breathing is advantageous for patients with ORD. Total lung capacity is comparable to normal values or is increased due to increased RV.

Reversibility of obstruction

If we find OVD in spirometric examination, it is necessary to determine whether the obstruction is reversible or not, and to conclude level of reversibility. It is important for choice of treatment because in these two forms of obstruction, different pathomechanisms are involved. Assessment of reversibility of obstruction and its degree are based on bronchodilation test (test is done after the examination without administration of bronchodilator agents). Significant reversibility, change of measured parameter greater than its variability, is defined as **increase of 0.20 l or more for FEV_1.** European Respiratory Society recommends to express degree of reversibility in increase of FEV_1 as percentage of predicted values. Increase in **FEV_1 ≥12%** is considered significant.

Increased bronchial reactivity

In previous paragraph, we described reaction of airways to bronchodilator stimulus. The other side is reaction to bronchoconstriction agents. This type of disorder is common in early stages of various ventilatory diseases. Test goes as follows – first we record FEV_1 without administration of bronchoconstriction stimulus, then bronchoconstriction agent, e.g. methacholine in increasing concentration is administered until we observe at least 20% decrease of measured parameter. **If that happens already when using low dose of methacholine or other bronchoconstriction agent, then the airways are hyperreactive.**

Bronchial hyperreactivity is defined as 20% decrease of FEV_1 after inhalation of histamine or methacholine in concentration lower than 8ng/L.

The shape of flow-volume loop registered pneumotachographically is helpful to determine the site of airway obstruction. In extrathoracic obstruction, e.g. tracheal stenosis, trachea has tendency to collapse during inhalation under the site of obstruction because the pressure in extrathoracic trachea is lower than atmospheric pressure (Fig. 4 and 5). Intrathoracic obstruction is more severe during expiration, when premature closure of small airways occurs caused by increased intrapulmonary pressure. Expiration part of loop has concave shape; inspiration part is comparable to normal finding. Variable extrathoracic obstruction in other hand differs from normal loop in inspiration part which is decreased. For fixed obstruction (e.g. tumour in trachea) flattened shape in both inspiration and expiration

part is typical (Fig. 4 and 5). Restrictive disorders have similar shape of loop, but smaller because of reduced VC.

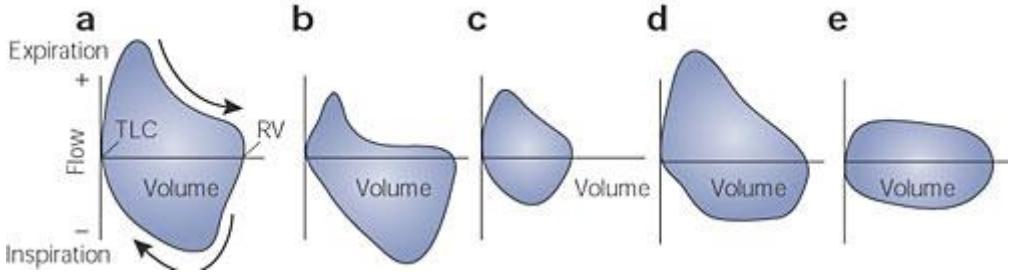


Figure 23. 4: Flow-volume loop in obstructive and restrictive disorders
a – normal; **b** – intrathoracic obstruction; **c** – restriction; **d** – variable extrathoracic obstruction; **e** – fixed extrathoracic obstruction (tumour)

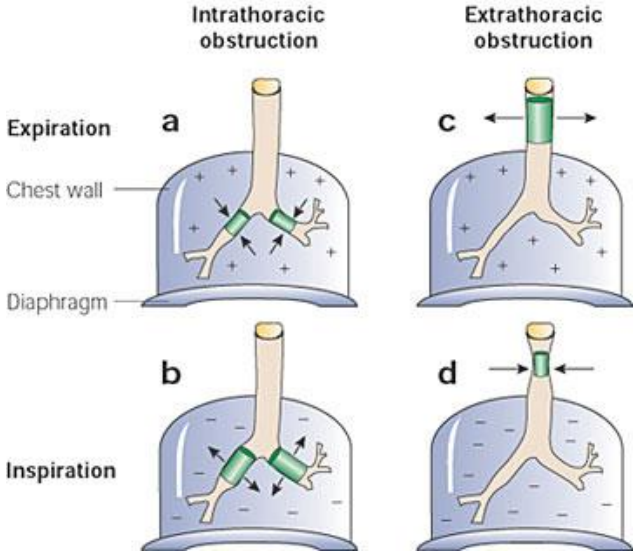


Figure 23. 5: Effect of intrathoracic and extrathoracic obstruction on airway patency

Consequences of airway obstruction depend on a cause and character of obstruction, its persistence, and localisation in the airways. Progression of disease in peripheral airways and affection of larger airways in result displays as decreased FEV_1. Serious obstruction clinically manifests mainly as severe dyspnoea with chest in inspiration position, breathing is troublesome and takes in auxiliary breathing muscles. In asthmatic patient, the obstruction can be reversed, use of bronchodilator medication can lead to increased FEV_1.

Key part of lung function test is analysis of results. Recent sophisticated machines do a basic evaluation of data, but for their realistic assessment it is necessary to have also other test and examination results, and well taken medical history. Good interpretation of gained data is result of rational thinking along with art of a doctor evaluating the results.

Conclusion

1) Obstructive ventilatory disorder is characterised by **decreased FEV_1, FEV_1 /FVC, VC can be also decreased.**

2) FEV_1 /FVC can decrease with age, therefore the value must be compared **with reference value for given age.**

3) If FEV_1 and VC are within normal range, then abnormal FEV_1 /FVC can be ignored.

Restrictive ventilatory disorder (RVD)

In RVD, there is decreased ability to ventilate lungs caused by reduced elasticity of lungs and chest wall. Loss of surfactant (ARDS) also takes part in reduced lung compliance. On the other hand, loss of elastic tissue in emphysema leads to inadequately increased compliance. As a result of restrictive ventilatory disorders, lung volumes significantly reduce. RVD is determined from examination of forced exhalation approximately as decrease of VC, FVC and TLC to less than 80% in comparison with reference values **(↓FVC less than 80%, ↓VC, ↓TLC).** Reduced TLC is the most objective parameter in determining RVD. This decrease is links with decrease of maximal inspiratory volume due to high elastic resistance of lung tissue (lung fibrosis), removal/exclusion of part of lungs (lobectomy, pulmonectomy, chest wall stiffness, enlargement of abdominal fat mass, decrease of central inspiratory effort). ERV is reduced on late gravidity (diaphragm pushed upwards). FEV_1 is lower than a reference value, FEV_1/FVC is usually within normal values or even increased. Time of expiration is shortened; shape of flow-volume loop is similar to normal but smaller (Fig. 4).

Severity of ventilatory disorder is evaluated by comparing current lung function test results in an individual with reference values.

According to established classification, there are three grades of RVD:

- **Mild RVD** ↓ FVC up to 60% of ref. value; ↓ TLC to 65% of ref. value
- **Moderate RVD** ↓ FVC 40 – 59% of ref. value; ↓ TLC 50 – 64% of ref. value
- **Severe RVD** ↓ FVC < 40% of ref. value; ↓ TLC < 65% of ref. value

Causes of RVD

- lung diseases or conditions such as lung resection, atelectasis, interstitial lung diseases (lung fibrosis, silicosis with increased lung tissue rigidity), lung oedema, tumours, pneumonia;

- respiratory centre depression – drug overdose (sedatives, narcotics), encephalitis, poliomyelitis
- pleural affection – pleural effusion, pneumothorax
- limiting of chest wall movement – obesity, kyphoscoliosis, trauma, pain, gravidity, ascites
- neuromuscular diseases – e.g. paralysed diaphragm, myasthenia gravis

Result of reduced elastic properties of lungs (fibrosis – lungs are rigid, stiff) or chest wall (kyphoscoliosis, obesity) is decreased vital capacity, patients breathe lesser volumes (lesser air inhaled and exhaled). FEV_1/FVC percentage will not be changed compared to normal values (proportional decrease of both FEV_1 and FVC) or this parameter can be even increased. Because of decreased lung and chest wall compliance, to breathe certain volume of air in, more negative pressure in pleural cavity than in healthy individual is desirable, therefore energy expended to breathe (work of breathing) must be greater.

Consequences of restriction in the airway depend on a cause and character of restriction, its intensity, duration, and localisation. In mild RRDs patients do not have troubles with breathing at rest, first signs of difficulties with breathing occur in physical strain or acute illness. In more severe diseases, patients are dyspnoeic with increased work of breathing, and are preponderant to shallow breathing of higher frequency.

Conclusion

Restrictive ventilatory disorder is characterised by **decreased FEV_1 and VC with normal or increased FEV_1/FVC.**

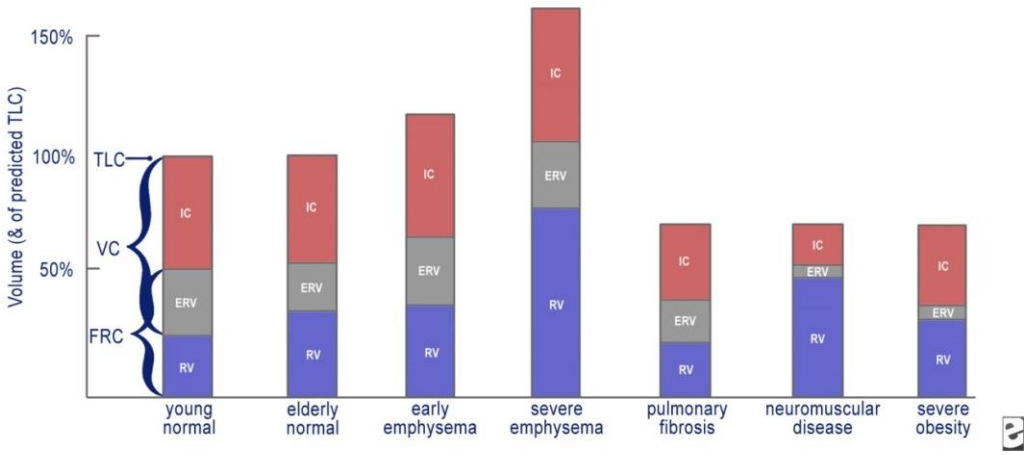


Figure 23.6: Lung volumes and capacities in healthy individuals and in different diseases

We repeatedly pointed out how important is patient's cooperation with personnel during lung function test. It happens frequently that in full spirometric exam, PEF is decreased due to low velocity during exhalation. Fig. 7 demonstrates other mistakes occurring in flow-volume loop recordings, both in inspiration and expiration.

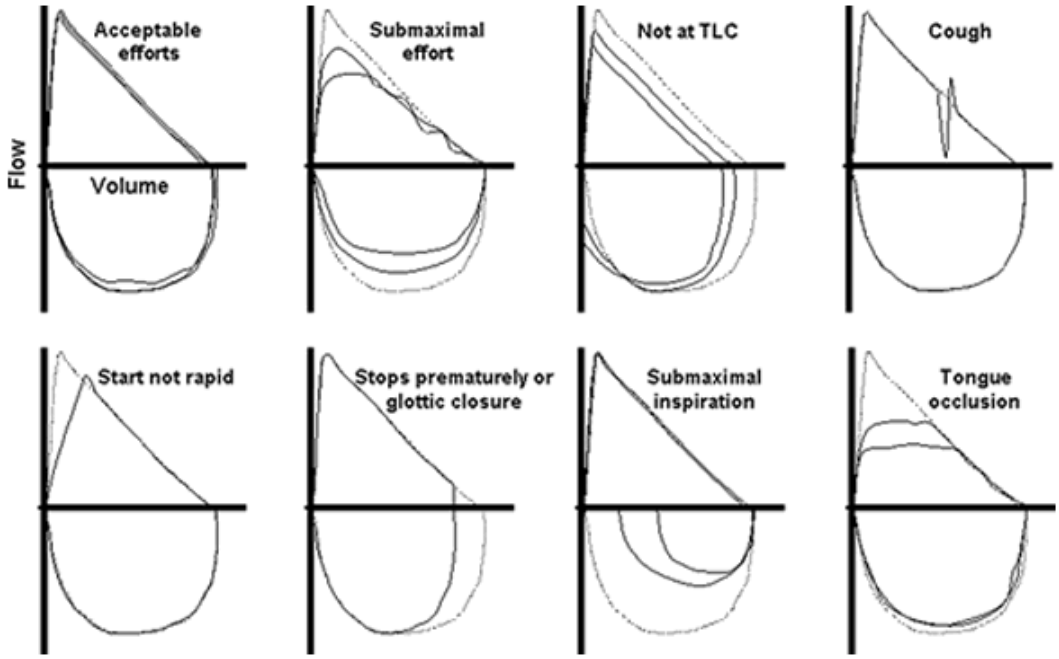


Figure 23.7: Most frequent problems in FVC examination

To prevent progression of severe chronic respiratory diseases, we should not forget to use lung function testing as an essential tool of identification of early and still reversible stages of illnesses. Spirometric examination can be repeated frequently allowing doctors to see dynamics of changes, e.g. in narrowing of the airways. Repeated testing (daily in practice) is important in asthmatic patients. Patients themselves can measure basic parameters using peak flow meter or personal spirometer. Worsened values are indicator to use bronchodilator treatment or to visit a physician to refine therapeutic regimen.

CASE REPORTS

Case report 1

62-years-old Mrs. A.B., was admitted to emergency department with dyspnoea. She reported she has been suffering from flu approximately for a week and a half, and her breathing worsens every day. Today she noticed her ankles are swollen. During sleep, she

needed one more pillow than usually to ease her breathing. She also reported she woke up repeatedly at night because of breathing difficulties. These episodes of dyspnoea resolved after few minutes when she sit up. When she felt it was hard to breathe for her, she helped herself with breathing through round mouth.

During illness production of yellow sputum increased as well as frequency of cough. Her tolerance of physical strain reduced to 20 steps. Mrs. A.B. smoked for 15 years 2 packs a day; because she had breathing issues along with cough, she decided to give up smoking 2 years ago.

Treatment at home: bronchodilator therapy, xanthines, oxygen therapy 1 L/min.

Laboratory parameters: pH 7.32; $Pa0_2$ 6.6kPa; $PaC0_2$ 8.2 kPa; HCO_3^- 30 mmol/L; SaO_2 85%; Hb 165g/L

Lung function tests:

	[l; l/min]	(% of reference value)
FVC	1.90	58%
FEV1	1.02	39%
FEV1/FVC		53%
FEF25- 75	0.74	31%
TLC	5.87	117%
RV	3.97	226%
RV/ TLC		67%
FRC	4.33	120%
DLCO	6,4mL/min	26%

Questions & Tasks

1) What kind of ventilatory disease is it in this case?

2) Which grade is the ventilatory disorder?

3) Based on medical history and rest results, what is the diagnosis?

4) Interpret the laboratory results.

5) Why was the patient waking up at night and assumed orthopneic position?

6) Why were patient's ankles swollen?

7) Why did she breathe through round mouth?

Case report 2

50-years-old Mr. M.T. has one-year history of productive cough with mucoid sputum. He hasn't had fever or lost weight. He smoked 1 pack of cigarettes a day for 30 years, his

tolerance of physical activity decreased. In medical history, he reported gastro-oesophageal reflux disease.

Physical examination: Temperature 36.9 °C, BP 125/75mmHg, pulse 78/min, regular, breathing frequency 15/min; BMI 25. Breathing was clear, chest x-ray normal.

Spirometry: FEV_1 – 85% of reference value, FEV/FVC – 75%, no change after bronchodilator test

Questions & Tasks

1) Does this patient have a ventilatory disorder? If so, which grade?

2) Which ventilatory disorder do you consider?

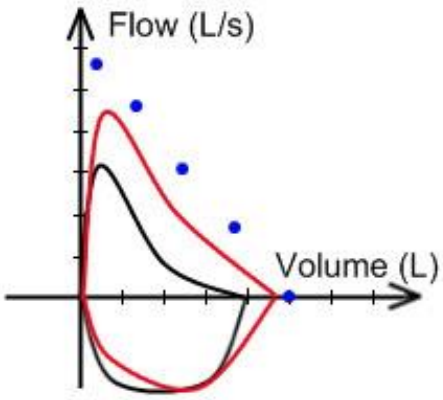
3) What diagnosis could this be?

4) What does negative bronchodilator test result mean?

Case report 3

25-year old man saw allergist in April presenting with acute respiratory disease which manifested as dyspnoea at night and wheezing. He suffers from rhinitis and his eyes are itchy since March. Rhinitis is escalating, swelling of eye lids and conjunctivitis are present. For past week, he has been dyspnoeic at rest, had trouble breathing when climbing stairs, he reports wheeze and dry cough.

Spirometry: Flow-volume loop – the black loop was recorder before administration of bronchodilator medication, the red one was recorded after. Blue points mark reference expiratory area of F/V loop.



	Predicted	**Before**	%	**After**	%	Diff. in %
FVC	5.15	4.03	78%	4.48	87%	11
FEV1	4.35	2.18	50%	3.31	76%	51
FEV1/FVC%		82.7	54%		74%	37
FEF25-75	5.04	1.71	34%	3.12	62%	83
PEF	9.88	6.03	61%	8.40	85%	39
FET		6 s		6.5 s		

Questions & Tasks

1) What kind of ventilatory disorder does our patient have?

2) Interpret the lung function test results.

3) Characterise the shape of F/V loop.

4) Was the bronchodilator test positive?

5) What is the most likely diagnosis in this patient?

Case report 4

33-year old woman, weight – 99 kg, BMI 34 has trouble breathing, mainly during physical activity, e.g. when climbing stairs, she felt great exhaustion. That is why she visited her doctor.

Questions & Tasks

1) Do you think there could be a ventilatory disorder in this patient?

2) If so, what kind of ventilatory disorder would you expect?

3) Which spirometric parameters would be most likely changed?

4) What pathomechanisms could lead to dyspnoea in this patient?

Chapter 24

PROTECTIVE AND DEFENSIVE MECHANISMS OF RESPIRATORY TRACT

Respiratory system, even though it is directly exposed to noxious or potentially noxious factors from **outer** (e.g. cigarette smoke, viruses, bacteria, allergens, dust particles) and **inner** environment (e.g. inflammatory mediators, tachykinins, oxidants), is able to maintain homeostasis in the airways and the lungs thanks to effective cooperation of protective and defensive mechanisms. They can be divided in two groups – **reflexoric and non-reflexoric.** Different noxious substances stimulate nerve endings of vagus and trigeminal nerve in mucosa of upper and lower airways, which leads to activation of defensive and protective mechanisms.

Nerve endings in the airways can be divided into:

- chemosensitive (sensitive to chemical substances, e.g. to acid),
- thermosensitive (sensitive to temperature changes of inhaled air),
- mechanosensitive (sensitive to mechanical stimuli, e.g. foreign bodies),
- polymodal C-fibres (sensitive to more types of noxae).

Protective mechanisms – protect the airways and lungs from incursion of noxious or potentially noxious factors into peripheral airways. They are activated by stimulation of nerve endings localized in mucosa of upper airways. These mechanisms involve apnoeic reflex, laryngoconstriction, filtration of pollutants in the nose and pharynx by physical and electrostatic mechanism.

Defensive mechanisms – their role is to eliminate and/or degradation/detoxication of exogenous and endogenous noxious factors in the airways, e.g. elimination of mucus, tissue detritus by cough, sneezing, mucocilliary transport or by antioxidants, proteases and other mechanisms of non-reflexoric nature.

Table 24.1: Reflexoric and non-reflexoric protective and defensive mechanisms of the airways

Reflexoric mechanisms	Non-reflexoric mechanisms
1. changes of breathing pattern	1. physical defence (filtration, warming, humidification)
2. apnoeic reflex	2. local immune defence mechanisms
3. laryngoconstriction, bronchoconstriction	3. mucocilliary transport
4. sneezing	4. surface fluid of the airways and the lungs
5. aspiration reflex	5. surfactant
6. sniffing	6. system of proteases and antiproteases
7. expiration reflex	7. system of oxidants and antioxidants
8. cough reflex	

Reflexoric mechanisms

Changes of breathing pattern – are reflexoric response caused by activation of chemosensors of trigeminal nerve in upper airways by chemical irritants (cigarette smoke, ammonia, xylol, and other aromatic volatile substances). Activation of chemosensors leads to change of breathing pattern – breathing becomes faster and its amplitude decreases, which in turn decreases the amount of irritants which infiltrate alveolar space.

Apnoeic reflex – originates in stimulation of trigeminal and olfactoric nerve endings by mechanic, chemic or cold stimuli in the nose. Kratschmer's apnoeic reflex is analogous to diving reflex which occurs in submersion of face into cold water. Response to such stimulation is apnoea – interruption of breathing in expiration phase with relaxation of inspiratory muscles. Part of the response is bronchoconstriction and cardiovascular reactions as well – occurrence of hypertension, bradycardia and peripheral vasoconstriction with redistribution of circulation.

Sneezing – is defensive reflex of the airways induced by stimulation of nerve endings in nasal mucosa and is characterized by forced expiratory effort, which is usually preceded by inspiration. In sneezing, inspiration is done primarily through mouth in order to prevent inspiration of noxious substance that is already present in nose to lower parts of the airways. Receptors for the initiation of sneezing are nerve endings of I. and II. branch of trigeminal nerve. Stimuli for sneezing are chemical substances (perfumes, chemicals, inflammatory mediators and others) and mechanical stimuli (accumulation of mucus).

Mechanism of sneezing begins with one or more inspirations (inspiration phase), which is followed by activation of expiratory muscles with closed glottis, which causes increase of intrathoracic pressure (compressive phase). After release of glottic and pharyngeal constriction the air is released from lower airways and lungs (expulsive phase), which flows with high velocity mainly through nose and thus removing noxious substance from the nose which initiated the reflex.

Aspiration reflex – is defined as burst of repeated, fast consecutive strong inspiration efforts which are not interrupted by forced expiration. Reflex occurs in irritation of nasopharyngeal nerve endings of glossopharyngeal nerve. Basic role of this reflex is to move irritant from nasopharynx to oropharynx or hypopharynx, from where it can be eliminated by cough, swallowing or vomiting. Aspiration reflex plays an important role in resuscitation and autoresuscitation as well, because it is accompanied by strong arousal reaction in brainstem and other parts of CNS. Prof. Tomori and his co-workers from medical faculties in Košice and in Martin have substantial merit on description of this reflex.

Expiration reflex – was discovered on Department of Pathophysiology of JFM CU by prof. Korpáš in 1972 in experiments on anaesthetized cats. He found that in mechanical irritation of medial rim of vocal cords a strong expiration occurs, which is not preceded by inspiration as in cough. Expiration reflex is also present in humans and in later studies it was shown that it can be evoked also by mechanical irritation of tracheal mucosa. The main role of this reflex is assumed to be the maintenance of patent larynx and prevention of aspiration of fluids and foreign bodies from hypopharynx to lower airways. Expiration reflex can manifest as a single expiratory effort or in a form of short bursts and can be followed by apnoeic pause or cough.

Cough reflex – is important defensive reflex of the airways and lungs, which occurs as reflexoric response to mechanical (dust particles, larger foreign body, mucus or other fluids) or chemical (air-born irritants, acid fumes, inflammatory mediators, low temperature and others) irritation of afferent nerve endings in large lower airways. Cough reflex is exclusively mediated by vagus nerve. These afferent nerve endings, which mediate cough reflex, include thin myelinated A-δ fibres of nodose ganglia, which play role mostly in **physiologic cough.** These fibres are sensitive to mechanical stimuli: pressure, foreign bodies, mucosal oedema, from chemical stimuli only to acid. They are localized mostly in upper part of lower airways. Cough can be provoked also by stimulation of unmyelinated C fibres, which originate in jugular ganglia of vagus nerve. They are localized mainly in bronchi. They are activated by air-born irritants from atmosphere or by inflammatory mediators (histamine,

bradykinin, adenosine, hydrogen ions) which are present in inflammation of the airways. Chemosensitive type of cough is often associated with diseases of the airways, therefore it is also considered as **pathologic cough.** In activation of cough, the important role is also played by activation of transmembrane ion channels with transient potential on vagal neurons (Transient Receptor Potential): TRPA1 and TRPV1. Pathologic cough, which is a symptom of severe respiratory diseases, can be accompanied by pain which is mediated by aforementioned vagal nociceptive C fibres. Main tussigenic areas include larynx (glottis, supraglottic area), trachea and major bronchi (mostly in their branching area).

After irritation of tussigenic receptors, electric signal occurs which spreads through afferent pathways of sensory vagal fibres to central structures of cough regulation in CNS. This "centre" is located in brainstem and it is composed of **neuronal network,** which cooperates also on regulation of tidal breathing and other respiratory and non-respiratory actions. Therefore, we cannot determine some isolated and specialized cough centre. From this "centre", the efferent information is mediated via motor and secretory nerves to effectors, which include diaphragm and other respiratory muscles, laryngeal muscles, smooth muscles of bronchi as well as mucus producing glands of airway mucosa.

During chronic diseases of the airways and lungs, there are structural and functional changes of parts of reflex arc of cough e.g. increase of density and sensitivity of receptors in airway mucosa or sensitization of central part of reflex arc. These changes are overall termed as **neuroplasticity of cough reflex.** The result is increased sensitivity, strength and duration of cough reflex. Such hypersensitive cough becomes pathologic, because it loses its defensive function.

Phases of cough reflex

Classic cough burst consists from several phases, which can be recognized on cough recording. These phases are:

Inspiration phase is characterized by deep inspiration. Large volume of air inhaled into lungs provides better mechanic efficacy of expiratory muscles and is a precondition for creation of optimal intrathoracic pressure throughout compressive phase.

Compressive phase begins with activation of laryngeal muscles followed by glottis closure. Simultaneously, contraction of expiratory muscles and muscles of abdominal wall begins. The result is an increase of intrathoracic pressure up to + 4.0 kPa.

Expulsive phase begins with sudden opening of glottis by activation of laryngeal adductors. High transpulmonal pressure leads to fast expiration of large volume of air with

velocity 150-280m/s. In this phase the mucus and substances it contains are ripped from the airway wall by turbulent airflow and eliminated from organism.

Disturbances of defensive reflexes

Defensive airway reflexes fulfil their physiologic function only when adequately regulated. Enormous increase or reduction/absence of defensive mechanisms can cause disturbances of functions of respiratory tract. For example, cough reflex can be enormously increased in airway mucosa inflammation with decreased production of mucus (unproductive cough), which can cause damage of epithelial integrity, damage of mucosal capillary network (presence of blood in sputum – haemoptysis), pneumothorax and other complications. List of causes of disturbances of cough reflex and complications resulting from these disturbances is shown in table 2.

Table 24.2: Causes and consequences of disturbances of cough reflex

Extreme increase of cough	Extreme reduction of cough
Causes increase of epithelial permeability inflammation of airway mucosa, pneumonias increased expression of receptors (stimulation of neurotrophic factors) increase of nerve endings sensitivity (airway hypersensitivity) increase of excitability of nerve fibres increase of neurotransmitter activity increase of activity of CNS centres contributing to neurogenesis of cough (pertussis toxin)	**Causes** damage of nerve endings in the airways (heavy smokers) damage of afferent nerves (diabetic neuropathy) damage of CNS (unconsciousness, conditions after strokes damage of efferent pathways and effectors (paresis of motoric nerves, myasthenia gravis) damage of effectors (muscle dystrophies, parkinsonism, neuromuscular disturbances)
Consequences sleep disturbances, disturbances of circulation, cough syncope, rib fractures internal pneumothorax headache, chest pain	**Consequences** stasis of mucus in the airways / infections obliteration of small airways with disturbance of V/Q ratios development of respiratory failure hypoxia, hypercapnia, acidosis

eating disorders nausea/vomiting provoking of bronchospasm gastro-oesophageal reflux urine incontinence decreased quality of life	refluxate aspiration / aspiration pneumonia

Extreme reduction of cough reflex occurs in damage of reflex arc by pathologic process (morphologic or functional damage of receptors, afferent pathways, centre or effector system). Reduction of defence mechanisms can have more significant consequences than their increase. Reduction results in stasis of mucus and spreading of infection, formation of mucous plugs in the airways, inflammatory infiltration, mucosal oedema which narrows the airways and leads to disturbances of V/Q ratios. Reduction of defence mechanisms occurs in neurologic diseases, trauma to brain or spinal cord, diabetic neuropathy or attenuation of respiratory centre by medication. For example, patients with disturbances of consciousness (alcohol intoxication) or after stroke are endangered by aspiration of stomach contents (refluxate) with development of aspiration pneumonia or asphyxia, which is often the cause of death.

Non-reflexoric protective and defensive mechanisms

Physical mechanisms – include modification of inhaled air in nasal cavity by warming/cooling, humidifying and by electrostatic and aerodynamic filtration system.

Local immune mechanisms

Mucosa of respiratory tract is equipped by cellular and humoral immune mechanisms, which contribute to complex defence of the airways against potentially pathogenic and pathogenic factors. Cellular protection/defence involves alveolar macrophages which contribute to phagocytosis of noxious agent which infiltrated terminal parts of respiratory tract (cigarette smoke, smoke and particulate matter as a result of combustion of solid fuels at home). Part of local immune system involves neutrophils (in capillaries and in mucosa of the airways) which produce proteases and free oxygen radicals which directly inactivate microorganisms. Substances with local protective/defensive properties include proteins with bacteriostatic and bactericidal properties, e.g. lysozyme, lactoferrin, opsonins, interferons,

complement system. Examples of specific immune response are antibodies (e.g. IgA) which are a component of surface fluid in the airways. Epithelial and dendritic cells also play an important role in immune response within the airways, where they contribute to protection/defence against viruses and other microorganisms.

Mucocilliary transport

Mucus on the mucosal surface of the airways consists from two layers – layer of **gel** (thicker) and **sol layer** (thinner). It is produced by goblet cells, sero-mucinous, serous glands and transudate of blood plasma. Mucocilliary transport (MCT) is an important defensive mechanism, which lies in transport of mucus and substances trapped within, which is potentially dangerous or dangerous for airway mucosa, from terminal bronchioli towards pharynx. MCT begins on level of respiratory bronchioli and continues in larger airways by cylindrical ciliary cells. Cellular cilia are submerged in sol layer adhering to epithelial surface and their endings are in contact with gel layer. Coordinated oscillation of cilia moves the mucus towards pharynx, where it is eliminated by swallowing or coughing. For proper function of MCT, undamaged ciliary epithelium, which is in contact with gel layer only by its endings, is necessary. Therefore, ideal thickness of sol layer is approximately equal to length of cilia. Overall, increased or significantly reduced thickness of sol layer, as well as increased thickness or density of gel layer reduces the efficacy of MCT.

Disturbances of MCT can occur in **structural and/or functional changes of cilia or ciliary cells,** which can be a result of congenital or acquired diseases.

An example of congenital disease is Kartagener syndrome (primary ciliary dyskinesia, which is caused by mutation of gene encoding synthesis of tubulin – a protein, which comprises internal structure of cilia). The result is inadequate and uncoordinated oscillation of cilia. Ciliary epithelium can be destroyed in smokers and in people exposed to higher concentration of pollutants, where it is replaced by metaplastic squamous striated epithelium which lacks cilia and therefore the islets of metaplasia in the airways limit MCT.

Transient ciliary dyskinesia can be caused by bacterial and viral infection which damage epithelium; as well as after intubation or bronchoscopy; it is also mediated by effects of different medication (e.g. beta blockers, medication with atropine effect, halothane anaesthesia).

Another disturbance of MCT is **inadequate viscoelasticity of mucus and thickness of periciliary fluid.** If the periciliary fluid, in which cilia oscillate, is too thick, the oscillation of cilia in ineffective and the result is decreased MCT. This kind of disturbance occurs is

patients with pulmonary or bronchial oedema and in these patients the diuretic treatment can improve MCT. On the other hand, if the thickness of periciliary fluid is too reduced or the viscosity of mucus is increased (cystic fibrosis, asthmatic inflammation, acute inflammation of the airways), mucociliary movement is reduced as well.

Other factor, which inhibits MCT, is **morphologic change of epithelium** (proportion between ciliary and goblet cells, as well as bronchial glands). Chronic inflammation, e.g. chronic bronchitis, lead to destruction of ciliary cells, hypertrophy and hyperplasia of glands and goblet cells, which results in overproduction of mucus with changed viscoelastic properties.

Surface fluid of the airways and lungs

Mucosa of the airways is covered with mucus, which contains, apart from mucins, proteins with antimicrobial properties (antibodies – mainly IgA, lysozyme, lactotransferrin, antioxidants). Defensive function of mucus lies in binding of microorganisms to mucins (glycoproteins) to their saccharide chain and removal of these complexes by effective mucociliary transport.

Pulmonic and bronchial surfactant

Surfactant coats alveoli and the airways and it contains phospholipids (90%), proteins (SP-A, SP-B, SP-D - 10%) and saccharides. Pulmonic surfactant is produced by II. order (granular) pneumocytes. Bronchial surfactant has similar composition as pulmonic; difference is in decreased content of proteins. Surfactant protein A plays an important role in airway defence by contribution to bacterial damage and increase in phagocytic activity of macrophages. But the main role of surfactant is to maintain morphologic integrity of alveoli and bronchi, to reduce surface tension in the wall of alveoli and terminal bronchioli. It also contributes to MCT and has a function of barrier and antioedematous function. Dysfunction of surfactant plays important role in pathogenesis of pulmonary diseases associated with airway obstruction and development of atelectases.

System of proteases and antiproteases

Another defensive system of the airways and lung is system of antagonistically acting systems of proteases and antiproteases. In a healthy individual, there is a **dynamic balance** in their action in the airways and lungs. Their defensive potential lies in the fact that different types of cells (including immunocompetent) can produce wide range of enzymes, e.g.

elastase, collagenase, cathepsin G, protease B, matrix metalloproteinases. These enzymes have proteolytic activity and, apart from destruction of bacteria, in case of their increased concentration they can damage the tissue of airways and lungs.

Against protease system, their natural antagonists act upon – antiproteases, which bind to protease molecules and thus inactivating them. Most known antiproteases are **α1-antitrypsin, antichymotrypsin and antileukoprotease.**

Disturbance between these two systems occurs if the production of proteases is increased (chronic inflammation) or if the amount or efficacy of antiproteases decreases, either from congenital (congenital deficiency of α1-antitrypsin), acquired antiprotease deficiency or their combination. For example, tobacco smoking causes activation of immunocompetent cells in the airways and lung coupled with increased production of proteases and simultaneous oxidation of α1-antitrypsin molecule, which in turn decreases its efficacy to neutralise elastase. The result of these processes is superiority of protease system with gradual destruction of extracellular matrix (destruction of alveolar septa) and development of emphysema.

Important antiprotease in respiratory tract is **neutral endopeptidase (NEP),** which degrades neuropeptides – proinflammatory factors released from afferent nerve endings in neurogenic inflammation. It is localized in epithelium, endothelium, submucosal glands, smooth muscle cells and neurons. In NEP deficiency, e.g. in epithelial damage, neuropeptides (SP, NKA, CGRP) facilitate neurogenic inflammation and cause vasodilation, bronchoconstriction and oedema.

System of oxidants and antioxidants

Free oxygen radicals produced in redox reactions have antimicrobial effect, but if overproduced they will disturb balance between oxidants and antioxidants and oxidative stress with production of highly reactive oxygen metabolites will develop, which damages lipid peroxidation (damage of membranes), depolymerisation of carbohydrates, oxidation of proteins containing –SH group followed by inactivation of enzymes and damage of DNA.

Table 24.3: Sources of reactive oxygen species

Endogenous	Exogenous
• activity of enzymes	• air-born pollutants
• transport of electrons in mitochondria	• hyperoxia

• activation of inflammatory cells • accumulation of reduced metabolites	• cigarette smoke • radiation • inflammation • excessive physical activity • medication

In disturbance of dynamic balance in this system the destructive influence of reactive oxygen species (ROS) manifests in all respiratory diseases, including ARDS, chronic bronchitis, emphysema, cystic fibrosis and so on.

Organism is equipped with contraregulatory mechanisms against ROS (antioxidant system) which includes enzymatic defence system: superoxide dismutase, catalase, glutathione peroxidase/reductase and non-enzymatic antioxidant defence system: albumin, transferrin, ceruloplasmin, glutathione, uric acid, L-ascorbic acid (vitamin C), tocopherols (vitamin E), beta-carotene (vitamin A), flavonoids, minerals and trace elements (Mn, Fe, Cu, Zn).

Increase of antioxidant capacity of respiratory tract by administering aforementioned substances can exhibit favourable preventive and therapeutic effect. Nowadays, there are many ways of increasing antioxidant capacity of organism, e.g. by supplementation of antioxidant-acting enzymes by administration of N-acetylcysteine, as well as supplementation of non-enzymatic antioxidants – vitamins C, E, A and trace elements, which contribute to reduction of oxidative stress.

Defensive antioxidant system is complex mechanism, in which the functions of individual antioxidants are interconnected and their antioxidative activity is most prominent in use of mixture of antioxidants. Unsuitable diet or reduction of antioxidant intake increases the risk of oxidative damage to the lungs.

CASE REPORTS

Case report 1

J.H. is 69-years-old man, who has been smoking 2 packs of cigarettes for 50 years. In last 5 years, he suffers from severe dyspnoea coupled with hypersecretion of mucus in the airways. Sputum which he expectorates is purulent, of yellowish colour. Cough wakes the patient up during the night; it is most intense early in the morning (4-5 AM) and when he wakes up from the bed. Dyspnoea was present only in physical activity at first, but nowadays

it occurs even at rest. In last two years, he suffered from repeated bronchitis which was treated by antibiotics.

Present complaints: His dyspnoea has become even more intense and auxiliary respiratory muscles are involved in breathing. He complains about weakness and fatigue. Results of his last spirometry showed **significant decrease of FEV1 and FEV1/FVC ratio was 0.38**.

Laboratory results: pO_2 9.7kPa; pCO_2 6,6kPa; pH 7.32; SpO_2 84%, Hct: 59%

Questions & Tasks

1) Identify all the signs and symptoms which manifested in this patient.

2) Explain mechanisms of development of identified signs and symptoms.

3) Which defence mechanisms of the airways and lung are disturbed in this patient?

4) Why does he complain about increased weakness and fatigue?

5) Analyse the laboratory results – explain the mechanisms of development of aforementioned changes.

6) Another symptom of the disease is cough bursts, which increase during disease exacerbation and bother the patient mostly during the night and early in the morning. In cough bursts, J.H. states, that he feels chest pain and headaches. Explain the pathomechanisms of development of cough and other symptoms.

7) What is the diagnosis in this patient?

Case report 2

13 years old female patient was deferred from ENT clinic to specialized department of Clinic of Paediatrics after bronchoscopy examination, which was indicated due to excessive mucus production in the airways and long-lasting productive cough. Sputum cultivation showed presence of Neisseria meningitis.

Personal history: Prematurely born in 34th pregnancy week; prenatal hypotrophy with birth weight 1750 g. From early childhood, repeatedly treated by antibiotics because of frequent respiratory tract infections, excessive mucus production and chronic productive cough. Until the age of 13, she did not undergo complex examination to determine the cause of her problems.

After admission, apart from other examinations focused in differential diagnosis of chronic respiratory illnesses, electron microscopic (ELMI) examination of cilia from bronchial mucosa was performed. Sample of mucosa was taken during one of repeated

bronchoscopies. Folded cilia, abnormal cilia with frequent vesiculations of ciliary membrane, as well as abnormal basal bodies, mostly with normal configuration (9+2) of microtubules, sporadic signs of missing internal dynein arms. Subsequent frequent hospitalizations were necessary due to exacerbations of purulent bronchitis. Cultivation findings still showed N. meningitis.

Within complex treatment, these therapeutic strategies were applied: systemic and inhalational antibiotics, inhalational corticosteroids (ICS) and bronchodilators, respiratory physiotherapy and repeated therapeutic bronchoscopies, administration of different mucolytic medications. After administration of erdosteine (medication which modifies chemical composition of mucus, improves its rheological properties and reduces its daily volume), significant decrease of mucus production was observed and cultivation findings were negative. It is supposed to have antiphlogistic, antioxidant and antibacterial properties – by inhibition of bacterial adhesion and it simultaneously exhibited synergic effect with antibiotics. In primary ciliary dyskinesia (PCD) its mucomodulation effects is extremely important, which reduces viscosity of bronchial secretion. From the time of erdosteine treatment, patient did not suffer from exacerbation of chronic respiratory disease caused by PCD.

Questions & Tasks

1) Pick all important signs and symptoms from the case report.

2) Explain possible mechanisms of their development.

Chapter 25

DISTURBANCES OF GLOMERULI AND TUBULI

Damage of kidneys can affect **renal blood flow, function of glomeruli and/ or function of tubular system.** It can also lead to the presence of pathological substances in urine, which are normally not detected in urine laboratory analysis (glucose, amino acids, proteins, casts) or presence of certain substances, which when elevated, may predispose to **urolithiasis**. Decrease of renal functions, which is extensively discussed in next chapter lead to **insufficient excretion of metabolites** (e.g. uric acid, urea, creatinine), and their concentration in plasma increase. It will also lead to the **imbalance in water and electrolytes metabolism and acid-bas balance.** Disturbed regulation of sodium and water metabolism leads to **dysregulation of blood pressure**, which is precisely controlled by kidneys via elimination of Na^+ and water.

Main function of kidneys is to **maintain homeostasis** – constant volume of body fluids and composition of extracellular fluids. This function depends on ability to filter sufficient volume of blood flowing through the glomerular system with subsequent resorption of substantial part of primary filtrate, ions, low-molecular weight substances essential for the body and excretion of metabolites. Volume of excreted urine (~ 1.5 l/24 hours, or 1ml/min) is the outcome of two processes. First of them is **glomerular filtration** – glomeruli filter more than 180 l of fluids/24 hours (125 ml/min) through glomerular membrane. The second process is **tubular resorption** of more than 99% of primary filtrate by various transport processes. Blood flow through the kidneys is roughly 20% of cardiac output at rest conditions, while kidneys represent only 1% of total body weight. Blood flow per gram of tissue shows, that kidneys have higher perfusion rate that brain or heart. The reason is not so high energy demands, but maintenance of optimal blood flow for sufficient filtration of blood.

Normally, the amount of the filtered water and solutes is several times greater than the volume which is finally excreted. Tubular epithelial cells have enormous reabsorbing capacity – they reabsorb total plasma water in 20 min and total volume of extracellular fluids in 3 hours. Excretion capacity of the kidneys thus is far from exhaustion. Therefore, GFR – volume controlled by kidneys - could be significantly limited without negative consequences for the organism. The decrease in GFR, however, is **coupled with limited possibilities of**

homeostasis regulation, which may manifest after certain load. During aging, the **plasma creatinine (P_{Cr}) does not increase even if the glomerular filtration rate decreases**. This apparent contradiction is caused by aging and reduction of muscle mass and thus the production of creatinine. In case of reduced renal function P_{Cr} rises in hyperbolic fashion.

Excretion of water and other substances in kidneys is **regulated by hormones** (e.g. antidiuretic hormone ADH (vasopressin), aldosterone, atrial natriuretic peptide (ANP), parathormone, calcitriol, calcitonin, cortisol, prostaglandin E_2, insulin, oestrogen, progesterone, T3, growth hormone, etc.). Disturbances of hormonal loops can cause changes in excretory and regulatory functions of kidneys.

Kidneys are not only a target for many hormones, but they also **produce hormones** themselves. Via these hormones kidneys influence their own functions, metabolism of minerals (calcitriol) and regulation of blood pressure (renin-angiotensin-aldosterone). Hormone erythropoietin produced in kidneys regulates production of red blood cells in bone marrow.

Disturbance of glomerular functions

Disturbance of glomerular filtration

The role of glomeruli is production of glomerular filtrate (GFR). Glomerular filter (endothelial cells of glomerular capillaries, basal membrane and podocytes) is selectively permeable, therefore the filtrate does not contain proteins (negligible amount). Entire blood flowing through the kidneys must go through glomerular vessels, therefore change of their lumen considerably influence renal perfusion (RPF) and glomerular filtration (GFR). Volume of primary filtrate is determined by three factors:

1) **relationship of pressure forces across glomerular membrane** (glomerular capillary hydrostatic pressure and oncotic pressure in Bowman´s capsule enhance filtration, glomerular capillary oncotic pressure and hydrostatic pressure in Bowman´s capsule decrease it),
2) **velocity of blood** flowing through glomerular vessels,
3) **permeability and total surface of glomerular capillaries.**

Reduction of GFR can be expected when:

a) **glomerular hydrostatic pressure is decreased** (e.g. hypotension),
b) **tubular hydrostatic pressure** (and pressure in Bowman´s capsule) **is increased (**e.g. obstruction of urine outflow from urinary bladder),

c) **plasmatic oncotic pressure is increased** (haemoconcentration in dehydrated subjects),
d) **reduction of renal (**therefore also glomerular) **blood flow** (shock, heart failure),
e) **permeability** and/or **total filtration surface is reduced** (e.g. acute or chronic glomerulonephritis).

Disturbances of glomerular filter permeability

Glomerular filter is nor permeable for all components of blood. Molecules with diameter bigger than pores in the membrane cannot cross the barrier. Molecules smaller than pores cross the barrier as good as water. Molecules only a bit smaller than the pore can follow the water only partially. This is the **size selectivity of glomerular filter**. Not only the size of molecule matters, but the charge of components is important, as well. Glomerular filter has **charge selectivity**. There are electrostatic interactions between the glomerular membrane (pores have negative charge) therefore molecules with negative charge cross the membrane with difficulties (or not at all) in contrast with molecules with positive or no electric charge. These electrostatic interactions prevent filtration of plasma proteins, mainly **albumin**.

Urine of otherwise healthy adults contain only 150 mg of proteins and this amount is not detectable by stripe indicators routinely used in GP´s practice. The threshold for these routine stripe indicators is about 200 mg/L – in healthy subjects detectable only in case of severe dehydration. Periodic preventive check-up at GP´s practice often reveals proteinuria and in majority of cases it is an accidental finding. This type of **proteinuria** is often a manifestation of functional changes in glomerulus related to the body position (**orthostatic proteinuria**), or intense physical workout (**exercise proteinuria**), eventually emotional stress (**emotional proteinuria**). However, accidental finding of proteinuria may indicate so far asymptomatic renal disease.

Glomeruli can be damaged by:

- **inflammation** (glomerulonephritis),
- **deposition of pathological material** (amyloid in amyloidosis),
- **high concentration of filterable proteins in plasma** (plasmocytoma),
- **high pressure in glomerular capillaries** (e.g. arterial hypertension, thrombosis of renal veins, venous congestion in congestive heart failure),
- **low perfusion** (atherosclerosis of renal arteries).

Damage of mechanical and electrostatic barrier will lead to filtration of high amounts of plasma proteins, which are finally present in urine in detectable amount. Damage of integrity of glomerular membrane allow a leak of red blood cells to the Bowman´s capsule. Presence of red blood cells in urine is called **haematuria.**

Disturbance of excretion function

Elimination (excretion) of substances normally eliminated by kidneys **decreases** in case of reduced GFR and reduced tubular secretion. A vice versa, limitation of tubular resorption and increase of tubular secretion lead to **increased elimination** of certain substances in kidneys. **Plasma concentration** of given substances either increases or decreases according to the rate of renal excretion. Plasma concentration however, depends also on **extra-renal factors,** e.g. production and metabolism of given substance, its resorption in intestine or extra-renal elimination (stools, sweat).

Correct interpretation of changed plasmatic concentrations requires understanding of relationship between **plasma concentrations versus renal elimination.**

This relationship is quite simple in substances, which are only filtered in glomeruli, but tubular activity does not influence their final elimination (no tubular secretion and no resorption), e.g. creatinine. Decrease of GFR in general lead to **progressive rise of plasma concentrations of substances normally eliminated by kidneys** (urea, creatinine). Plasma concentration of creatinine (P_{Cr}) is basic laboratory test used to detect abnormalities in renal functions. It is important to detect exact values of GFR mainly in initial stages of renal insufficiency, when rise of P_{Cr} is minimal or negligible.

Substances, which are reabsorbed in tubular system by transport processes with high affinity (e.g. glucose, amino acids, phosphates, sulphates) are completely resorbed unless their plasma concentration exceeds normal values. Low plasma concentration guarantees complete resorption, and substance is not present in final urine. When the concentration of given substance in primary filtrate exceeds maximal transport capacity of tubular epithelium, the excess which was not reabsorbed persists in final urine. Plasma concentration of a substance at which filtered concentration equals with reabsorbed amount is called **renal threshold**. For example, when plasma concentration of glucose increases (in diabetes mellitus) so it exceeds the renal threshold for reabsorption, it will lead to **glycosuria** (presence of glucose in urine).

Disturbances of concentration function

According to the conditions in the human body, kidneys can excrete hypotonic urine (< 100 mOsmol/L) or hypertonic urine (> 1200 mOsmol/L). Osmolality of plasma is ~ 300 mOsmol/L. Concentration and dilution of urine, as well, are main functions provided by **ascending part of the loop of Henle,** which transports NaCl to the renal interstitial space without water following it. **Hyperosmotic renal interstitial space** thanks to this process, and other special transport processes in descending loop and vasa recta are crucial to regulate osmolarity of urine (counter current multiplicative mechanism).

ADH increases permeability for water in distal tubule and collecting duct. Osmolality of fluid in distal tubule is close to the osmolality of plasma and osmolality of interstitial space is high. Therefore, water leaves the lumen of distal tubule via osmotic gradient and **urine in tubular system becomes concentrated.** Physiologic role of concentration function is to eliminate salt, even in case of low water intake. Renal disturbances with limited concentration function can only **excrete salt in high volume of urine**, which will lead to dehydration without optimal substitution of fluids.

Deficit of **ADH** (central diabetes insipidus) or insensitivity of distal nephron to ADH (renal diabetes insipidus) are characterized by low permeability of distal nephron to water, therefore it cannot leave the tubular system via osmotic gradient and kidneys then excrete up to 20 l of hypotonic urine per day. Diabetes insipidus is characterized by polyuria with polydipsia to substitute renal water loss.

Urea follows water resorbed in the proximal tubule, loop of Henle and distal tubule only partially, therefore its concentration in the collecting duct is increased. Permeability of the collecting duct in the medulla is quite high, and urea diffuses into the interstitial space. High concentrations of urea in the medulla drags water from the descending arm of Henle's loop. Urea partially diffuses into the lumen of loop of Henle and distal tubule, so it will get back to collecting tubules. Increase blood flow in renal medulla washes away osmotically active substances. Mediators released in inflammation (e.g. kinins, prostaglandins) cause vasodilation with the same effect, which decreases osmolarity of the medullary interstitial space. This limits concentration of urine. Caffeine also has vasodilating effect on the vasa recta.

When tubular fluid (primary filtrate) contains molecules which are poorly resorbed, it increases **osmolality of tubular fluids**. Based on osmotic forces, these molecules become concentrated and hold the water inside the tubular lumen – **osmotic diuresis**.

In general, decreased resorption leads secondary to reduced resorption of NaCl and urea. Since these two substances determine osmolality of renal medulla, osmolarity becomes lower, so does the ability to drag the water from tubular lumen and to concentrate urine. This situation is present e.g. in diabetics – increased excretion of glucose with osmotic diuresis leads to polyuria and polydipsia (increased water intake via thirst. **Decreased concentration function manifest in general by nocturnal urination (nycturia), thirst and high volume of extremely diluted urine.**

Pathophysiology of transport processes in kidneys

Genetic or toxic factors, drugs or hormonal disturbances can cause damage of tubular transport systems.

Glucose is normally reabsorbed in proximal tubule. Genetic defect of specific transporter leads to **renal glycosuria.** Plasmatic concentration of glucose is normal in this disturbance. Na^+ is reabsorbed in distal tubule and collecting ducts via action of aldosterone. Lack of aldosterone (hypoaldosteronism) or limitation of its effect in kidneys lead to the loss of Na^+ by urine**,** reduction of effective circulating volume and low blood pressure.

Kidneys considerably influence regulation of acid-base balance by excretion of hydrogen ion (acidification of urine) and resorption of bicarbonates, which are a component of the most important buffer system. Renal disturbances are characterized by onset and progression of metabolic acidosis. There are also genetic defects of hydrogen ion transport, which limit acidification of urine. This condition is described as **renal tubular acidosis.**

Renal hypertension

Majority of renal diseases can cause hypertension. Substantial condition participating in pathogenesis of renal hypertension is **renal ischemia**. Reduced perfusion of kidneys lead to the onset of hypertension, but it does not matter what part of kidneys is affected by ischemia. Limitation of renal blood flow can occur due to pathological process within the parenchyma (e.g. glomerulonephritis, pyelonephritis), problems with renal artery (stenosis, clamping, and atherosclerosis) or aorta above the branching of renal arteries (stenosis or aortic isthmus).

Reduced perfusion of kidneys lead to stimulation of system **renin-angiotensin-aldosterone**. Renin cleaves plasmatic angiotensinogen (produced in liver) to angiotensin I, which is converted by ACE (angiotensin converting enzyme) present in many tissues to

angiotensin II. Angiotensin II causes sever vasoconstriction and elevates blood pressure. It also stimulates secretion of aldosterone and ADH, which finally act in kidneys increasing reabsorption of sodium and water. Expansion of volume due to sodium and water retention elevates blood pressure even without RAA system. Hypervolemia always leads to hypertension.

Urolithiasis

The most common component of renal stones is calcium-oxalate (~ 70%) or calcium-phosphate (~ 30%) uric acid or urate (~ 30%). Frequently, other substances also contribute to the formation of renal stones, because this process start by precipitation of particular substance – forming crystals. These crystals further promote precipitation and sedimentation of other substances dissolved in urine. Causes leading to the formation of renal stones can be **prerenal and renal.** Prerenal cause is e.g. increased filtration and excretion of substances with high affinity to precipitation when their concentration in plasma (and urine) increases. **Prerenal hypercalciuria** and **phosphaturia** are consequences of their increased resorption in intestine or mobilisation from bones in subjects with excessive production of calcitriol or parathormone. Hyperoxalaemia can be caused by metabolic defect of amino acids break-down, or by increased resorption of oxalate in intestine. Hyperuricaemia is caused by increased intake, facilitated synthesis or break-down of purines. The cause of increased excretion in hypercalciuria and cystinuria is always defect of renal resorption. Secretion of ADH after drop of circulating volume or in stress increases concentration of substances which can form the stones through "retention" of water in the body, while the concentration of substances in tubules logically increases.

Solubility of certain substances depends on pH of urine. Phosphates are well soluble in acidic urine, but not in alkalic. That's why phosphate stones are typically present in alkalic urine. Stones made of uric acid and urates are rather present in acidic urine, because it has higher solubility in dissociated form.

Another important factor contributing to formation of urine stone is the time - how long are the crystals present in "hypersaturated" urine. This time depends on diuresis (reduced production of urine also means prolonged presence of urine in urinary tract (post-renal cause).

Consequence of urolithiasis is blockage of urinary tract. Contraction of musculature of ureter and its dilation above the obstruction cause very painful "**renal colic**". Obstruction of the continual flow of urine leads to stagnation of urine and it may interrupt renal functions.

Kidneys may remain damaged even after the removal of the stone. Stagnation of urine contributes to infectious complications of urolithiasis e.g. infection of urinary bladder or **pyelonephritis**. Bacteria typically break-down urea. Ammonia as a product of this reaction shifts the pH of urine to alkalic side. This situation promotes precipitation of phosphates a formation of phosphate stones (vicious circle).

Nephritic syndrome

Combination of laboratory findings in urine, nephrogenic hypertension and oedemas is typical for acute and chronic nephritic syndrome. The most common causes of these conditions are acute and chronic glomerulonephritis with primary dysfunction of glomerular apparatus. **Acute nephritic syndrome** is characterized by sudden onset of haematuria and proteinuria, which are often accompanied by oedema, oliguria, hypertension and reduction of GFR. **Chronic nephritic syndrome** is characteristic clinical manifestation of chronic glomerulonephritis. Typical manifestation is erytrocyturia, proteinuria, casts made of red blood cells in urine sediment and hypertension. **When proteinuria gets worse, clinical manifestation may change to nephrotic syndrome. In case that disease caused considerable damage of nephrons, patient develops chronic renal insufficiency.**

Nephrotic syndrome

It is a **complex of metabolic changes** characterized by proteinuria, hypoalbuminemia, hyperlipidaemia, and generalized oedema. Nephrotic syndrome can be caused by various kidney diseases of any aetiology. It is always accompanied by **damage of glomerular membrane** that manifests by **increased permeability**.

A serious consequence of increased permeability of glomerular membrane is loss of protein in the urine - **proteinuria**. Patients lose **more than 3.5 grams of protein per d**ay (sometimes 10-20 g). Increased excretion of protein in urine leads to reduced amounts of plasma proteins. Since the renal protein loss affects mainly albumin, patients develop **hypoalbuminemia**.

Hyperlipidaemia and hypercholesterolemia are other characteristic findings in nephrotic syndrome. The cause is not fully known - it is **probably a reduced transport capacity for lipids in the blood due to failure of the lipase activity in the tubular cells**. The increase in the concentration of lipid levels is also influenced by reduced plasma protein as plasma lipids are forming complexes with plasma proteins.

Generalized oedema is the most prominent symptom of nephrotic syndrome. One factor that contributes to the formation of oedema is the loss of albumin in the urine, thereby permanently reducing the **colloid-osmotic pressure of plasma**. Starling forces in the microcirculation are affected by reduction of the colloid-osmotic pressure and fluid leaks from the intravascular into the interstitial space. Reduction of the volume in intravascular space (effective arterial volume) stimulates the renin-angiotensin-aldosterone system. This mechanism will step up tubular reabsorption of sodium and water. Moreover, increased concentration of sodium ions in the extracellular fluid increase release of antidiuretic hormone, thereby increasing the tubular reabsorption of water.

Increased resorption of sodium ions is accompanied by the loss of a potassium ion, the patient is often in a state of a **potassium depletion**. It is important to note that nephrotic syndrome itself is not a clinical entity, but rather a manifestation of various renal diseases.

Defects of glomerular filter result into a loss of protein by the kidney, failure of tubular resorption leads to a loss of substances essential for the body (electrolytes, minerals, bicarbonate, glucose, amino acids). For substances, which cannot be secreted by tubular cells, controlled volume corresponds with **glomerular filtration rate (GFR)**. All substances present in the primary filtrate can be resorbed by tubular epithelium or eliminated. For substances, which can be secreted by the epithelium (e.g. potassium), controlled volume corresponds with the total volume of the plasma flowing through the kidney (**renal plasma flow - RPF**).

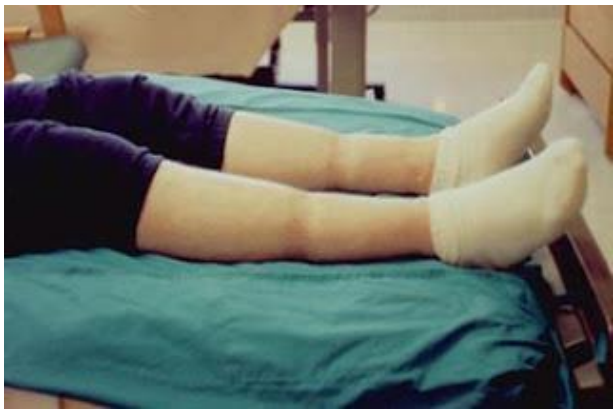
CASE REPORTS

Case report 1

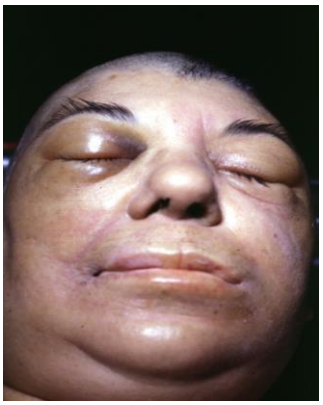
28-years-old man with Down syndrome was admitted to hospital because of fatigue and progressive weakness. Parents observe these changes for 2-3 weeks, and now they spotted oedema of his face. He is otherwise healthy and according to the parents, he was never seriously ill.

Clinical findings: Patient is responsive, communicates at the level of his mental defect, eupnoeic, afebrile, 170 cm, 68 kg, skin and conjunctival mucosa are pale, no icterus, no cyanosis, heart action regular 78/min, systolic murmur at the apex, BP140/90 mmHg, breathing rate 15/min, lung auscultation – physiologic findings, abdomen – no pathology, lower extremities – oedema of both legs to the knee level.

Laboratory findings: albumin 16.6 g/L; cholesterol 12.5 mg/L; urea 6.9 mmol/L; creatinine 75 μmol/L; in urine – nonselective proteinuria 6.425g proteins/24 hours. Inflammatory activity is not elevated FW 5/12, CRP 2.7 mg/mL, nonspecific inflammatory markers are not elevated, ANA and ANCA (antibodies) are not elevated, concentration of immunoglobulins in serum is not elevated, C3 a C4 components of complement are normal, no paraproteins in urine



Oedema of lower extremities



Oedema of face

Questions & Tasks

1) Based on the amount of proteins in urine, quantify severity of proteinuria.

2) Characterize individual clinical and laboratory findings typical for nephrotic syndrome

3) Explain, why concentration of cholesterol is elevated

4) Explain pathogenesis of oedema in nephrotic syndrome

5) Is it possible to detect somehow whether our patient has primary or secondary oedema?

Chapter 26

PATHOPHYSIOLOGY OF RENAL FAILURE

Definition

Renal failure means that kidneys are not able to maintain normal volume and composition of body fluids (homeostasis) in subjects with normal intake of proteins (~ 0.5 g/kg/day). Disturbance of homeostasis is manifested mainly by **reduced elimination of protein metabolism end-products and impaired metabolism of ions.** Kidneys also considerably reduce their **regulatory and endocrine functions** (regulation of erythropoiesis, acid-base balance, volume of circulating fluids, concentration of calcium in bones). This condition represents an end-stage of diseases of kidneys and urinary tract and it affects all systems of the body.

Classification of renal dysfunction

Renal insufficiency, renal failure, azotaemia, and uraemia – all of these terms belong to the terminology describing reduced renal functions. They are often used inappropriately, because they clearly define distinct situations. In general, term **renal insufficiency** describes a condition when renal functions are reduced to 25 % of their normal functions. Glomerular filtration (GFR) is reduced to approximately 25-30 $ml.min^{-1}$ (normal value of GFR is 120 $ml.min^{-1}$). Concentration of serum creatinine and urea are slightly elevated. It means that one healthy kidney is effective enough to maintain normal renal functions and renal insufficiency develops only in case that both kidneys are damaged. Term **renal failure** is typically used to describe more severe loss of renal functions, according to some sources it is around 10% of normal renal functions**.** Renal insufficiency can be **acute** with fast progressions even though this condition is fully reversible after optimal treatment. Renal failure also has a **chronic form** which is typical rather for long lasting, slowly progressing renal disease towards end-stage, and it may last for years. **Uraemia** is a clinical term describing clinical syndrome developing in a subject with renal insufficiency. Biochemical parameters such as elevated urea and creatinine are accompanied by fatigue, anaemia, nausea, vomiting, skin itching, neurological, haematological, cardiovascular and bone signs and symptoms. Terms azotaemia and uraemia are often mixed up, but azotaemia only describes biochemical changes – elevation of urea and creatinine in the blood.

Acute renal insufficiency

It is sudden nearly total loss of renal functions, usually of otherwise healthy kidneys, which is fully reversible after optimal treatment. This condition is caused by:

a) failure of renal circulation,

b) considerable dysfunction of glomerular and/or tubular functions.

It manifests by sudden **oliguria** (reduced production of urine below 500 ml/24 h) or **anuria** (less than 50 ml of urine/24 h). There is also a special type of renal insufficiency, which is characterized by normal volume of urine, however homeostasis is disturbed and nitrogen containing metabolites are not excreted from the body (**non-oliguric type**).

Pathogenesis

Acute renal insufficiency can be a consequence of three distinct chains of mechanisms:

1. **Prerenal acute renal insufficiency** is characterized by reduction of GFR caused by renal vasoconstriction and reduced renal perfusion. Typical causes leading to this condition are hypotension in shock, surgeries of the heart, aorta, and long lasting surgeries in abdominal cavity, heart failure or dehydration. Function of nephrons is not disturbed, simply said, kidneys are not producing urine, because they do not have optimal filtration pressure due to low perfusion. There is no functional nor morphological damage of the nephrons, and when the blood flow restores by optimal therapeutic interventions, glomerular filtration and tubular functions normalize, so does the diuresis.
2. **Intrarenal acute renal insufficiency** is caused by direct damage of nephrons, **mainly epithelial cells of renal tubules**. Typical causes are:
   a) ***long-lasting renal ischemia*** e.g. in complicated surgeries with poorly controlled hypotension, severe shock states mainly is extensive burns or sepsis,
   b) ***severe haemolytic reactions*** (leak of haemoglobin to circulation) or long-lasting ischemia of striated muscles (leak of myoglobin to circulation) lead to precipitation of mentioned proteins in renal tubules and influence glomerular filtration by tubulo-glomerular feedback,
   c) ***nephrotoxic medication*** (antibiotics, anaesthetics, X-ray contrast materials, analgesics, chemotherapeutic drugs, immune-suppressive drugs) cause primarily damage of tubular system,
   d) **severe clinical course of glomerulonephritis or malignant hypertension** can cause primary damage to the vascular system of glomeruli, what lead to reduction of GFR.

Disturbance of renal functions persists even after the circulation problems were fixed, or after the exposure to nephrotoxic substances was interrupted. Renal functions are typically restored in 1-2 weeks after the primary insult which caused acute renal failure. In case that tubular functions are not restored successfully, renal functions remain very low and this condition may eventually progress to chronic renal failure.

3. **Postrenal acute renal insufficiency** appears as a consequence of reduced excretion of urine caused by complete obstruction of urinary tract. This can happen in diseases which cause considerable narrowing of urethra (e.g. benign prostatic hypertrophy, tumours in urinary bladder, urolithiasis occluding urethra etc.). Acute renal failure does not develop in case of occlusion of ureter at one side, while the other side has normal urine flow. However, if this occlusion persists, it will proceed to the pressure destruction of the renal parenchyma and irreversible failure of renal functions at affected side (hydronephrosis).

Cells with the highest sensitivity to ischemic damage and nephrotoxic substances are cells of the **proximal tubule and ascending part of the loop of Henle**. Cells of distal tubule and collecting duct are less sensitive. This is the reason why the consequence of tubular damage manifest by **impaired reabsorption of sodium, chlorides, bicarbonates and glucose** (proximal tubule). Impaired function of the loop of Henle will manifest by **inability to concentrate urine** with osmolality of urine very close to osmolality of plasma.

Reduction of renal functions is often manifest in subjects with circulation problems, with subsequent renal hypoperfusion. In majority of cases renal functions improve after normalization of circulation. Presence of decreased renal functions after this point is an evidence of ischemic damage of renal tubular cells, which happened during circulation problem and indicates that initially "prerenal" renal failure changed to "intrarenal". Even though acute renal insufficiency is serious and life endangering condition, it is fully reversible in majority of cases. Determinants of reversibility are:

a) Damaged of tubular epithelial cells, but with **intact basal membrane** - this is the optimal condition for regeneration of tubular epithelium.

b) During the period of regeneration of tubular epithelium, it is necessary to provide **optimal perfusion of kidneys, therefore optimal condition for regeneration**.

c) It is also necessary to **maintain homeostasis by medication and dialysis** (whenever indicated) to prevent accumulation of toxic metabolic end-products in the body.

It is possible to recognize **three stages of acute renal failure (intrarenal) in clinical conditions**:

a) Oliguric stage

Plasma concentrations of urea, creatinine, uric acid, organic acids and intracellular cations, mainly potassium elevate due to reduced diuresis. Hyperkalaemia and metabolic acidosis are potentially life threatening situations. This stage lasts about 10-15 days, until the tubular cells are not regenerated. Then, production of normal volume of urine will start again. At this point renal function is sufficient to eliminate metabolic products, which are normally eliminated by kidneys. Some of patients with typical manifestation of decreased renal functions and retention of nitrogen containing molecules do not have oliguria, they rather produce two or even more litres of urine daily. It is "**non-oliguric**" type of acute renal failure and it develops mainly in subjects after the exposure to nephrotoxic antibiotics, burns and anaesthesia with certain type of anaesthetics.

b) Diuretic (polyureic) stage

Volume of excreted urine is progressively increasing, what indicates improvement of glomerular function. Although the volume of urine normalizes, or it is slightly higher, renal functions are not fully recovered. The reason is a bit delayed tubular epithelium recovery. Resorption capacity of not fully recovered tubular epithelium is low, therefore patient can lose substantial amount of electrolytes and water. Patients are prone to **dehydration and hypokalaemia** in this stage of acute renal failure.

c) Recovery of renal functions

This stage can last 3-12 months. Glomerular filtration rate and concentration of urine may remain reduced permanently.

Clinical manifestation

Failure of renal regulatory function influences all systems of human body. Patient´s condition is usually critical, patient is lethargic with nausea, vomiting and diarrhoea. Skin and mucosa are dry from dehydration, the breath has typical "urine-like" smell. Disturbances of CNS manifest by lethargy, somnolence, headache and muscle cramps. Patient with oliguria has typically reduced ability to excrete potassium. Hyperkalaemia is further promoted by catabolism of proteins, which is responsible for release of potassium from the cell to the interstitial space. Metabolic acidosis has similar effect, because potassium is replacing

hydrogen ion which is transported towards cells, therefore concentration of potassium in extracellular compartment increases (distribution hypokalaemia). Hyperkalaemia is dangerous, because it may lead to the disturbances of heart rhythm, eventually it may cause cardiac arrest. Metabolic acidosis develops in subjects with renal failure due to inability of kidneys to eliminate daily metabolic production of acid, including sulphates and phosphates. Anaemia is common sign. It is caused by bleeding to the gastrointestinal system, reduced osmotic resistance of red blood cells in uremic plasma and decreased production of erythropoietin, which stimulates bone marrow to maintain optimal production of red blood cells.

Chronic renal insufficiency

Clinical manifestation of chronic renal insufficiency depends on the degree of reduction of renal functions and underlying diseases, which caused the insufficiency. Decline of glomerular filtration is good indicator of clinical manifestation of chronic renal insufficiency.

Chronic renal insufficiency and it´s end-stage chronic renal failure, represent progressive irreversible damage of renal functions, which is characterized by inability to maintain a balance of metabolic processes, volume and composition of body fluids, leading to uraemia. The most common causes of chronic renal insufficiency are un-treated hypertension, complication of diabetes mellitus, chronic glomerulonephritis, chronic pyelonephritis, congenital disturbances such as polycystic kidneys, complete obstruction of urinary tract, complications or certain systemic diseases (lupus), and chronic medication with certain drugs (phenacetine kidneys).

Pathogenesis

While in acute “intrarenal” renal insufficiency tubular epithelial cells are damaged and this damage is potentially fully reversible, chronic renal insufficiency is characterized by **destruction of entire nephron.** This leads to the reduction of number of functioning nephrons. **Residual nephron** is a term used for nephrons left intact (approximately 30%) after considerable destruction of renal parenchyma (about 70% of nephrons). Blood flow through the kidneys is not reduced, therefore, it is redistributed to residual nephrons. Increased perfusion of residual nephrons leads to hyper-filtration and hypertension, which both contribute to the damage of residual nephrons. Since the nephrons cannot regenerate, this process lead to their progressive irreversible loss. Hyper-filtration in residual nephrons

manifests as polyuria. Loss of renal function in the progression of renal disease is usually associated with changes in renal morphology. Despite the structural reconstruction, glomerular and tubular function remains in close connection (glomerulo-tubular balance) as in normal functioning body, and also in the final stages of chronic renal failure. The essential feature of the **intact nephron hypothesis** is that renal function is preserved after the loss of a certain quantity of nephrons by function of other preserved normally working nephrons. Chronic renal insufficiency manifests clinically when the number of residual nephrons drops and renal functions are reduced to about 25% of their normal function. Clinical manifestation includes imbalance of metabolic processes, damage of cardiovascular, hemopoietic, gastrointestinal, nervous systems, and bones. There are also disturbances of lungs and skin.

Maintenance of water and ion balance

Decreasing number of residual nephrons leads to inability of kidneys to concentrate urine. Osmotically active substances are not optimally resorbed in tubules, because of the hyper-filtration and fast flow of primary filtrate through tubular system, therefore they drag water to the lumen, and volume of excreted urine increases. Patients are prone to dehydration in this initial and progressive stage as long as they do not increase their water intake. Vomiting and diarrhoea may also contribute to the water loss. Total inability to excrete sodium appears when glomerular filtration drops below 10% of normal values. Later stage is characterized by tendency to generalized oedema, hyperkalaemia with similar pathogenesis as it is in acute renal insufficiency.

Abnormalities of acid base balance

Metabolic acidosis appears when glomerular filtration drops to 20-30% of normal values. Ability of residual nephrons to excrete hydrogen ion and resorb bicarbonate, which is a component of the most important buffer system, decreases. With a progression of disease, kidneys are not able to excrete sulphates, phosphates and other acid metabolites. Metabolic acidosis thus becomes more severe.

Uremic encephalopathy

Neurologic complications of chronic renal insufficiency are caused by **uraemia** (electrolyte imbalance, acid-bas imbalance), **inability of kidneys to excrete administered medications** (possible risk of overdosing) and also by **hypertension**. Common symptoms and signs are considerable fatigue, sleep during the day, with nocturnal insomnia,

disturbances of speech, confusion, hallucination. Uremic coma represents the most advanced stage of renal encephalopathy.

Anaemia

Anaemia is common manifestation of chronic renal insufficiency. It is caused by low production of erythropoietin in damaged kidneys, therefore reduced production of red blood cells in the bone marrow. Red blood cells have also reduced osmotic resistance in uremic serum, so they are haemolysed earlier than expected. Patients with chronic renal insufficiency have tendency to bleeding, because of disturbances of platelets caused by uraemia. Frequent blood sampling prior and after dialysis (e.g. three times each week) contributes to anaemia, as well.

Renal osteodystrophy

Impaired metabolism of phosphate and calcium with subsequent changes in parathormone production lead to the changes in bones. They belong to typical manifestation of chronic renal insufficiency. There are several mechanisms leading to the decrease of calcium concentration in the blood. Most important mechanisms rely on reciprocal relationship between phosphates and calcium. Since the phosphates are not effectively eliminated, they push calcium to the bones forming calcium sulphate. Calcium concentration therefore decreases. Parathormone release as a response to this change activates osteoclasts to increase plasmatic concentration of calcium. This process, however, lead to the demineralization of bones. Other mechanisms which influences bones is lack of biologically active vitamin D (activation should happen in kidneys). Bones become fragile and sensitive to innocuous mechanical force, which may lead to the bone fracture.

Cardiovascular manifestations

Hypertension, often present in subjects with chronic renal insufficiency can be a direct consequence of renal disturbances (expansion of circulating volume, production of renin). Vascular resistance, as the second determinant of blood pressure is also increased in subjects with renal problems, due to accelerated atherosclerosis and mediocalcinosis of arteries. On the other hand, hypertension is a factor which considerably contributes to the decline of renal functions via destruction of nephrons.

Increased volume of circulating blood represents an extra work for heart, which work with higher preload and/ or against higher afterload. This may lead to the heart failure. Coronary atherosclerosis, which is accelerated due to disturbances of lipid metabolism

typically present in subjects with renal diseases, also contributes to this process. Uremic pericarditis may develop.

Clinical manifestation

Progressive destruction of nephrons is clinically silent for long time. Signs and symptoms appear after the total count of residual nephrons drops to ~ 25%. Patients are firstly fatigued and lethargic. They later develop gastrointestinal problems (nausea, vomiting, and diarrhoea), increased tendency to bleeding and confusion. If this condition is not treated, somnolence and Kussmaul's breathing appear (compensation of acidosis). This condition terminates in coma and cramps.

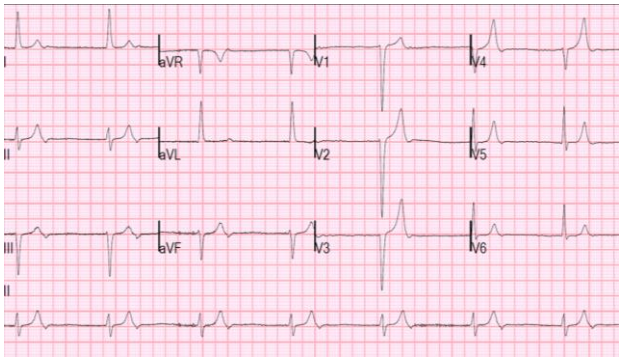
CASE REPORTS

Case report 1

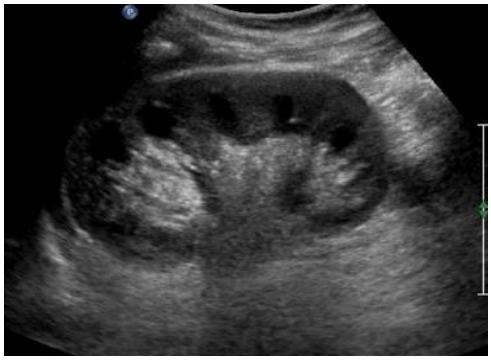
70-years-old woman with DM type 2 on insulin treatment, with hypertension, hyperlipidaemia and generalized atherosclerosis was admitted to emergency department with progressive weakness, fatigue, headache and anorexia, which become complicated this morning by repeated vomiting. Patient finally fainted. She is on diuretics, hypolipidemic and antihypertensive treatment, she regularly visits her DM specialist and she monitors her glucose every day.

Clinical findings: Patient is responsive, oriented, without breathlessness, skin has anaemic colour, and conjunctival mucosa is also pale. Patient´s height is 167cm, weight is 65kg. Heart action regular 50/min, no murmurs, BP 110/60 mmHg, normal vesicular breathing without pathologic sounds, abdomen without hepatosplenomegaly, lower extremities – peripheral pulsations are present, less palpable, symmetrical oedema around both ankles.

Laboratory findings: Na 139 mmol/L; K 7.9 mmol/L; glucose 6.7 mmol/L; creatinine 398 μmol/L; urea 22 mmol/L; TnI < 0,2 ng/mL (normal) pH 7.26; BE -8; HCO_3 16 mmol/L; pO_2 12.6 kPa; pCO_2 5.1 kPa; CRP 6 mg/L; albumin 40 g/L



ECG – Bradycardia



Normal structure of kidneys

Questions & Tasks

1) Find symptoms and signs related to renal insufficiency in patient´s history, clinical and laboratory finding.

2) What do you think is the reason that led to worsening of renal functions in our patient?

3) What type of acidosis are present in our patient? What other types of acidosis can be present in subjects with chronic renal insufficiency depending on stage of the process?

4) What is the effect of high plasmatic level of potassium? What mechanisms can lead to hyperkalaemia in our patient?

5) Define differences between acute and chronic renal insufficiency?

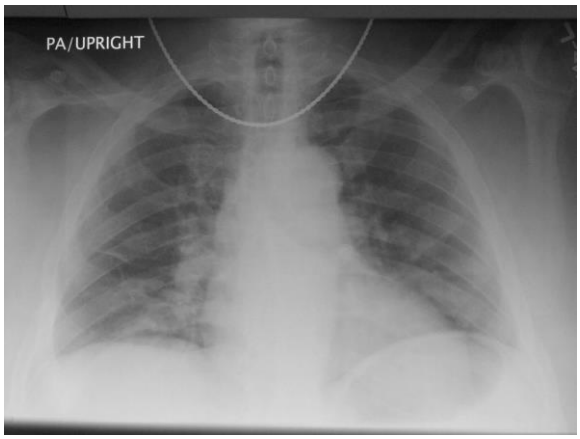
Case report 2

67-years-old patient was admitted to hospital due to dyspnoea, which is worse in supine position, patient is breathless also in the rest, and she stopped urinating. She had pneumonia 2 weeks ago, with bad clinical course, and she got two types of antibiotics to combat her lung problem. First antibiotic was Ciprofloxacin, and she could not take the medication because of severe nausea, therefore, the doctor has changed the medication to Gentamycin. She was taking the later one, cough is gone, but she is still weak, breathless and today she notices that she is not urinating.

Clinical findings: Patient is fully responsive, afebrile, breathless at rest, anxious, does not tolerate horizontal body position due to breathlessness. She has bit pale conjunctival mucosa, oropharynx is normal, filling of jugular veins also normal. Lungs – normal alveolar breathing, no pathological sounds, bilateral crepitation over lung basis and low lung fields. Heart – action regular, 110/min, BP 160/100 mmHg, normal heart sounds. Abdomen without pathology, tapotement test negative, lower extremities – bilateral oedema of calf, Homans's

sign is negative. Insertion of catheter to urinary bladder – 250 ml of roily urine – sent to laboratory for analysis.

Laboratory findings: WBC $8{,}0\times10^9$/L; HBG 110 g/L; PLT 250×10^9/L; Na 120 mmol/L; K 6.7 mmol/L; urea 25.0 mmol/L, creatinine 462 μmol/L, Ca 1.9 mmol/L; P 2.4 mmol/L; CRP 8.0; albumin 30.0 g/L. **Astrup:** pH 7.20; pCO_2 4.1kPa; pO_2 12.0 kPa; HCO_3 8.3 mmol/L; BE -15 **Urine analysis:** blood +; protein +; Na 50 mmol/L; proteinuria 0.8 g/24h; RBC 20/μl; brown granulated casts



Chest X ray

Questions & Tasks

1) What processes caused renal damage and oliguria?

2) What type of renal failure developed in our patient? (pre-renal, intrarenal, post-renal)?

3) What type of acid-base imbalance is present in our patient?

4) How do you explain low sodium and higher potassium in blood?

5) Do we have a direct evidence about acute tubular necrosis?

Chapter 27

DISEASES OF GASTROINTESTINAL TRACT

Gastrointestinal tract (GIT) has a constant direct communication with the external environment via the food or water intake, which can contain toxic compounds directly damaging the function of the GIT and after the resorption the other functions of the body, as well. Moreover, chyme contains number of potentially toxic substances. These are, first, components of secretion (enzymes, HCl), but also waste products of digestion of the food components and products of bacterial flora. This chapter will address the most important pathomechanisms of most common disorders of GIT, including:

- motor dysfunction of musculature of walls of various parts of GIT,
- disturbances of digestion and absorption of nutrients (malabsorption syndromes),
- bleeding into the digestive tract,
- perforation of the GIT wall with leak of intestinal content into the peritoneal cavity,
- slowing or complete stop of peristalsis,
- circulation disorders.

The most common symptoms and signs of GIT disorders

These symptoms and signs are a part of clinical manifestation of variety of GIT diseases. **Dyspepsia** includes abdominal pain, feeling of fullness and "indigestion", burning pain behind the sternum – pyrosis, or nausea and vomiting. These are mainly symptoms of disorders of the oesophagus, stomach and duodenum. These symptoms and signs combine in various ways for individual diseases of upper GIT. Dyspepsia is the most often manifestation of peptic ulcer, prolonged reflux of gastric contents into the oesophagus and gastritis.

Vomiting is a reflex effort which serves to empty the contents of the stomach and duodenum out of the body through the oral cavity with the support of retrograde peristalsis in the oesophagus. This reflex event is most frequently the result of:

- sudden distension of the stomach and duodenum caused by accumulation of content,
- reflex response to intense pain,
- reflex response to trauma of ovary, testis, uterus, bladder and kidneys,
- response to irritation of the stomach lining by toxic substances,
- stimulation of the vomiting centre, e.g. metabolic acidosis or brain lesions.

Nausea (feeling sick) usually precedes vomiting. It is **unpleasant subjective sensation** associated with various symptoms. Sympathetic activation causes tachycardia and diaphoresis. Parasympathetic activation causes enormous salivation, increased motility of the stomach and relaxing the upper and lower oesophageal sphincter. Metabolic consequences of vomiting are loss of water and electrolytes from the body and acid-base disturbances.

Diarrhoea is an increased frequency of defecation with increased volume of watery stools. Many factors determine the volume of stool and its consistency. They are the water content, the presence of undigested and un-resorbed food components and increased production of intestinal secretions. Diarrhoea is caused by three important pathomechanisms:

- osmotic activity of intestinal contents,
- increased secretion of fluids into the lumen of the intestine,
- accelerated intestinal peristalsis.

Osmotic diarrhoea (high-volume diarrhoea) appears when un-resorbed materials are present in the intestinal contents. These substances bind water osmotically and thus significantly increase the volume of the intestinal contents. Example of such diarrhoea is lactase deficiency, in which lactose is not decomposed to simple sugar units, they remain in intestine and drag water by their high osmotic activity. The **secretory diarrhoea** is caused by an enormous secretion of fluid and electrolytes into the lumen of the intestine with insufficient reabsorption. The primary stimuli of such process are bacterial enterotoxins (infectious diarrhoea). Common infectious agents are *Shigella, Escherichia coli* and *Campylobacter jejuni.* Small-volume diarrhoea is caused by increased peristaltic intestinal activity, typically present in chronic inflammation of the intestines (ulcerative colitis, Crohn's disease).

Constipation is an abnormal decrease in the number of defecation. It is associated with difficult emptying of solid stool, which is usually painful. It is a consequence of failure of one of the three most important functions of the colon: the transport of the contents (secretion of mucus by the colon mucosa promotes the movement of the content), smooth muscle activity and processes responsible for defecation. **Repeated ignoring of the urge for defecation** leads to insensitivity of rectal wall to the intraluminal pressure and consequently, for a defecation there must be much higher pressure in the lumen of the rectum. After several

years of such state the wall of the rectum loses tone and does not respond to normal stimuli for defecation.

Constipation is the result of **damage of nerve cells in the intestinal wall** providing regulation of peristalsis. A typical example is a congenital absence of these cells, leading to significant dilation of the colon. Such a condition also occurs secondary to spinal cord injury. **Weakened abdominal wall muscles and pain after surgery** can also cause constipation. A common cause of constipation is also inflamed haemorrhoids in the anal parts that are quite painful during defecation. Sedentary lifestyle and low-fibre diet are often associated with constipation.

Bleeding into GIT is often the result of a large number of diseases. Bleeding into the upper GI is most common for oesophageal varices, haemorrhagic gastritis and ulcers of the stomach and duodenum. Bleeding into the lower GIT or the jejunum, ileum, colon and rectum is caused by inflammation, tumours and haemorrhoids. Sudden and intense bleeding is life threatening. It is usually manifested by **hematemesis** - presence of blood in vomit. Vomiting of blood may be in the form of fresh blood or a blood clot (intense bleeding with acute gastric dilatation and subsequent rapid vomiting). Often the blood in vomit looks like a "coffee grounds". The reason is that the blood flows more slowly in the stomach, and there is time for its digestion. Haemoglobin converts to acid haematin, which has black colour. Another manifestation of bleeding into GIT is **melena** (dark tarry stool due to presence of digested blood). **Occult blood loss** is chronically repeated loss of small volumes of blood, which usually manifests as sideropenic anaemia.

Malabsorption syndromes are consequences of digestive disorders (e.g. cleavage of food components to simple compounds that can be absorbed) and also disorders of the absorption itself, when the intestinal mucosa is not able to resorb one or more components of normally digested food. Incomplete digestion of food can occur at several levels of GIT due to the disturbance of secretion of digestive juices. Problems with protein digestion appear e.g. after gastrectomy. Pancreatic diseases (e.g. chronic inflammation) lead to malabsorption of protein, polysaccharides and lipids, as the glandular part of the pancreas produces enzymes to digest all food components. Undigested proteins, polysaccharides, and lipids are present in the stool. Diseases of liver or insufficient production and excretion of bile into the duodenum. Bile has an important role in the digestion of lipids. Small intestine produces certain digestive enzymes and it is also the most important area for resorption of digested nutrients. Resorption size of this area depends on the normal structure of mucosa, which is moulded into the villi to increase resorption surface.

Celiac disease and lactose intolerance are the most common primary malabsorption diseases in our geographic area. **Celiac disease** is a protein malabsorption and it is very likely caused by allergic response of the mucosa of the small intestine to gluten, protein present in different cereals. Mucosal inflammation leads to atrophy of the villi, which significantly reduces resorption ability of mucosa. Frequently occurring carbohydrate malabsorption is **lactose intolerance**. Activity of lactase, milk sugar degrading enzyme is insufficient. After drinking milk, un-resorbed lactose present in the intestine drags water to the lumen, because it is osmotically active substance and greatly increases the volume of chyme. In addition, milk sugar is cleaved by bacteria to the gas and substances which irritate the mucosa. This results in abdominal cramps, bloating and diarrhoea.

Digestive disorders can cause **malabsorption of vitamins** and, although the food contain sufficient quantity of these micro-nutrients. Disturbances of bile secretion into the duodenum lead to insufficient digestion of lipids, therefore vitamins, which are soluble in lipids - A, D, E and K are not optimally resorbed. Fastest clinical manifestation appears in case of malabsorption of vitamin K, which is necessary for production of coagulation factors in liver. Patients have **increased bleeding tendency**. Insufficient production of "intrinsic factor" in chronic atrophic gastritis causes a lack of resorption of vitamin B-12 and folic acid. The consequence is impaired formation of red blood cells in the bone marrow and the development of **pernicious anaemia.**

The most important diseases of GIT

Oesophagus

Reflux esophagitis occurs after longer-term presence of gastric or duodenal contents in the oesophagus in case of frequent and long lasting gastroesophageal reflux episodes. HCl, pepsin and bile cause mucosal damage with subsequent inflammation, erosions and ulcerations. It is a consequence of insufficient (impaired) function of the lower oesophageal sphincter, delayed gastric emptying with an increase in the gastric pressure and insufficient cleansing function of the oesophagus (lack of saliva, poor oesophageal peristalsis, and decreased secretion of oesophageal mucosal glands). Typical symptoms are heartburn (pyrosis), regurgitation, dysphagia and chest pain.

Achalasia is a primary oesophageal motility disorder characterized by an inability of the lower oesophageal sphincter to relax and it is constantly contracted. Patients have deficit of inhibitory ganglion cells in the wall of the oesophagus. Food accumulates in the

upper part of the oesophagus, which gradually dilates, food is decomposed by bacteria and occasionally, there is also a regurgitation.

Stomach

Gastritis is an inflammatory disease of the stomach lining. **Acute gastritis** is the most common result of excessive alcohol drinking. It occurs also after the administration of anti-inflammatory drugs (aspirin, NSAIDs). **Chronic gastritis** is inflammation of the lining of the stomach, often with insidious onset and long-term clinical course. It is often the consequence of autoimmune damage to the mucosa and atrophy. ***Helicobacter pylori*** is found in a significant proportion of patients.

Peptic ulcer is related to digestion of mucosa and deeper parts of the wall of the stomach, duodenum, and lower oesophagus by hydrochloric acid and pepsin. While erosion is a flat defect that does not extend into the lamina muscularis mucosae, ulcer passes through this layer. **Chronic peptic ulcer disease** is a multifactorial disease. The main role in it is played by gastric juice (HCl and pepsin) and also bile, which are aggressive substances. Other factors promoting mucosal damage are **Helicobacter pylori infection and use of NSAIDs.**

There is a set of defence mechanisms that prevent mucosa from auto digestion. They prevent the action of aggressive agents. The layer of mucus, which firmly covers the mucosa, and is not permeable for acid and pepsin prevents penetration of hydrogen ion (H^+) into the mucosal tissue, where it can cause damage of cells and subsequent digestion of tissue by pepsin). Under normal conditions, the amount of mucus that is digested is immediately replaced by glands. The epithelial cells itself also produces a lot of bicarbonate ions, capable of buffering H^+ ions which have penetrated into the mucosa. An important part of the mucosal defence function is also good perfusion. Even if the erosion appears, it does not necessarily proceed into peptic ulcer, because the mucosa has powerful defence mechanisms related to the quick repair of the damage. Damaged microcirculation is a source of fibrin, which leaked from capillaries and the lesion is very quickly covered by cap made of mucus and fibrin. This cap firmly covers the lesion, prevents further penetration of aggressive substances to the mucosa and promotes regeneration.

Stomach and duodenal ulcers manifest either as acute or chronic. Acute peptic ulcer can be healed rapidly by mucosal epithelium regeneration. Chronic ulcer tends to penetrate deeper into the tissue and healing takes weeks to months. There is a lot of granulation tissue, which slowly matures to connective tissues forming so called “ulcus callosum”, which can

unfortunately undergo malign transformation. The main symptom is epigastric pain that occurs after a meal, very early in case of gastric ulcers and for about 2-3 hours after the meal in case of duodenal ulcer. Alarming consequences of peptic ulcer are bleeding and anaemia. Unexplained weight loss and repeated intense vomiting are often due to pyloric obstruction caused by scaring of the pyloric wall.

Intestinal system

Appendicitis occurs most frequently after obstruction of the lumen of the appendix. Irrespective of the cause, it tends to increase intraluminal pressure (secretion of mucus and fluids continues) and promotes overgrowth of bacteria with subsequent leukocytes transfer and production of pus. Further increase of luminal pressure slows the venous drainage from the wall of the appendix, thrombosis of veins appears with gangrene and perforation of the appendix. The result is either peri-appendicular abscess or diffuse peritonitis, according to the ability of omentum and surrounding structures to localize the inflammation. Pain is initially diffuse and poorly localized (visceral pain), then the transition of inflammation to the parietal peritoneum makes a difference - patient localizes pain to the right hypogastrium (somatization of visceral pain).

Chronic inflammatory bowel diseases are Crohn's disease and ulcerative colitis. Both are manifestation of inflammatory disorders caused by disturbances of immune response (autoimmune diseases). **Crohn's disease** may affect any part of the gastrointestinal tract, but most commonly terminal part of the ileum. Inflammatory process affects all layers of the wall of the digestive tract. The progression of inflammation results in the formation of ulcerations in the wall, the formation of fistulas and abscesses. Healing process lead to formation of scars, which can narrow the lumen and cause obstruction of the intestinal tract. Characteristic symptoms are abdominal pain and diarrhoea. Malabsorption is the result of loss of functional mucosal absorption surface. Most often it leads to deficit of several food components and dehydration. **Ulcerative colitis** affects the colon and rectum, which affects the mucosa and submucosa with multiple ulcerations. Compared to Crohn's disease there is not intensive accumulation of fibrotic tissue. The cardinal symptoms are diarrhoea, weight loss, abdominal pain and loss of blood in the faeces.

The most important causes of "acute abdomen"

These are diseases of abdominal organs, including the peritoneum, or retroperitoneal organs. They appear unexpectedly, patients experience a severe discomfort

and pain typically from "full health". Affected are organs of the gastrointestinal and biliary-tract, pancreas, urinary tract and female genital system.

Acute abdomen manifests mostly by intense visceral pain, nausea and vomiting and other unpleasant subjective difficulties arising from the hiccups, tympany, inhibition or stop of peristalsis, urinary disorders, dyspnoea, increased body temperature, abdominal discomfort, etc. A part of patients may quickly develop septic shock.

Hemoperitoneum

It is the accumulation of large quantity of blood into the abdominal cavity. It may result to hypovolemic shock. The most common source of bleeding is traumatic rupture of the spleen, liver and mesenteric arteries.

Acute abdomen caused by inflammation

Inflammation may be confined to one organ with minimal spread to the surrounding peritoneal structures (appendicitis, cholecystitis), which often leads to creation of **intraperitoneal abscess**. When the inflammation spreads to the peritoneal cavity, **peritonitis** occurs.

Peritonitis is an inflammation of the serous layer of abdominal cavity and the organs contained therein. Peritoneum quickly responds to various pathological stimuli by inflammatory response. These stimuli are e.g. infectious (bacteria) or sterile, caused mainly by chemical substances present in peritoneal cavity e.g. after perforation of hollow organs (gastric juice, bile). The most common cause is perforation of the stomach, intestine or bile duct with subsequent release their contents into the peritoneal cavity, and traumatic perforation is rare. Endotoxins produced by gram-negative bacteria lead to release of cytokines, damage the cells, and often are the cause of septic shock and multiple organ failure.

Diverticulitis is an inflammatory complication of diverticula (pouches) of intestinal mucosa. Mucosa most frequently protrudes through the muscle layer of the intestine under the visceral peritoneum (pseudodiverticula) at sites where arteries and nerves penetrate intestinal wall. Diverticulosis is associated with increased intraluminal pressure e.g. caused by constipation associated with a diet low in fibre and obesity. Another factor is abnormal peristalsis. Faecal material accumulates in these pouches, leading to their obstruction with subsequent inflammation. As with appendicitis, a pressure increases in the diverticula with the danger of subsequent perforation and peritonitis.

Acute abdomen caused by intestinal obstruction

This is a serious condition that can have many causes. In principle, obstruction of the intestine can be classified as follows:

a) mechanical obstruction caused by a barrier (occlusion) inside the lumen, or compression of intestine from outside,
b) vascular obstruction caused by strangulation of intestinal vasculature, by thrombosis or embolism,
c) functional obstruction caused by the "paralysis" of the intestinal muscles.

The pathogenesis of damage of the intestine involves stagnation of intestinal contents, disorders of absorption and secretion in affected part, bacterial overgrowth, and hypoxia of intestinal wall. Symptoms of intestinal obstruction vary according to the type of obstruction and its location in the intestinal system. It can be colic pain (caused by obstruction of the lumen) or permanent pain. Then, there are vomiting and abdominal distension with tympany. The rapid onset of symptoms is typical for **strangulation** (either strangulation of intestinal wall or mesenteric arteries), in contrast with paralytic ileus pain is initially lacking. Complications, such as peritonitis and circulatory shock may develop.

Ileus occurs due to hypo-motility of GIT without mechanical obstruction of the lumen. Musculature of intestinal wall is temporarily weakened and is not able to transport intestinal contents. Loss of coordinated propulsive activity results into the accumulation of gas and fluid in the intestine. The most common cause of this condition is an abdominal surgery. Physiologic ileus resolves spontaneously after 2-3 days. If it takes longer, then it is referred to as paralytic ileus. It is caused by activation of the spinal reflex inhibitory pathways.

Obstruction of small intestine is most commonly caused by postoperative adhesions, Crohn's disease and hernias. The proximal parts of the intestine above the obstruction becomes dilated due to the accumulation of fluid and ingested gas. Dilation stimulates secretion, what potentiates peristalsis and increase of intraluminal pressure. Increased hydrostatic pressure in the microcirculation leads to loss of fluid and electrolytes into the "third space". Vomiting occurs in case of the proximal localization of obstruction.

Obstruction of large intestine can be caused by tumours or anatomic abnormalities such as volvulus, incarcerated hernia, strictures or obstipation. Distension of the intestine is

followed by visceral pain, anorexia and later vomiting of intestinal fluid with faecal admixture.

If a part of the intestine completely twists around the mesenteric attachment, this process causes **volvulus**. It leads quickly to ischemia and necrosis of the intestinal wall with a fatal outcome. The process by which intestinal segment inserts (slides) into an adjacent segment is called **intussusception.** Oppression of lymphatic drainage and circulation in this segment has similar consequences as volvulus. A part of intestine, specifically in case of increased peristaltic activity of the gastrointestinal tract, may protrude through weakened parts of abdominal wall or natural apertures (e.g. **inguinal or umbilical hernia**). It becomes dangerous if there is a strangulation (incarceration) of protruded part and it becomes a cause of acute abdomen.

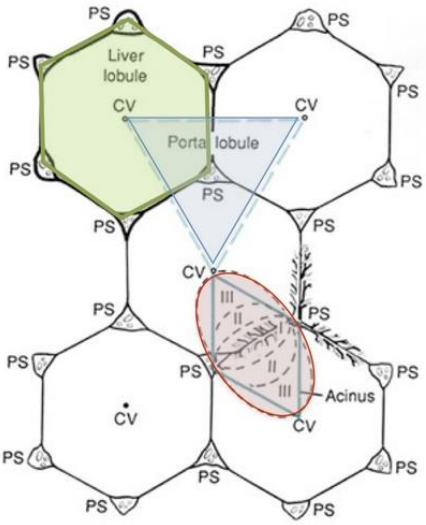
Haemorrhoids

They are the most common anorectal pathology. Rectal venous plexus is a part of the anorectal closure mechanism. Haemorrhoids cause symptoms if they are **enlarged, inflamed, prolapsing or affected by thrombosis**. The problems start with itching of the rectal area and end with rectal bleeding. Abnormal swelling of the anal plexus cause dilation and enlargement of it. Shortening of supportive rectal muscles causes a prolapse of veins through the anal canal. Anal mucosa is easily damaged, prone to bleeding, the blood has bright red colour.

Chapter 28

LIVER FAILURE

Liver is an organ with unique position in the human body. Functionally, it has dual blood supply – it is involved in the portal venous system which brings material reabsorbed in the intestine to the hepatocytes to be utilized or stored, and at the other hand it has also a blood supply via hepatic artery, which brings the oxygen to the hepatocytes. This allows effective communication of the liver with the rest of the body. Liver has many functions – biosynthetic, regulatory and it also participates in the detoxication of the body and biotransformation, produces bile acids which are necessary for digestion of lipids. Anatomical structure of the liver is characterized by hexagonal structures clustered around the central vein – and these are called hepatic lobules. Functional subunit of the hepatocytes however differs from the anatomical and it is represented by the triangle shaped structure around the portal field. There are the branch of hepatic artery, portal vein and the bile ducts in every of these spaces, also called Disse's spaces. This structure is called portal lobule.



Looking at the picture of the hepatic structure itis clear that different cells have different position when it comes to their distance from the both central vein and the hepatic artery. This is quite of significance, because cells in the different areas have different sensitivity to the pathogenetic factors, and they are at different risk of exposure to the different factors as well. For example, cells located close to the central vein are exposed to the toxins and potentially dangerous factors reabsorbed from GIT in case of alimentary

intoxication. At the other hand, they are less sensitive to the hypoxia, because they have two sources of oxygen, which is brought to the portal field by both vein and the artery.

Factors which can cause damage to the hepatic cells:

- **infections** (hepatotropic viruses, other viruses, bacteria, parasites)
- **toxins** (amanitin, paracetamol, alcohol, other drugs and chemicals
- **abnormal immune reactions** (autoimmune damage in systemic lupus or primary biliary cirrhosis)
- **hypoxia** (congestive heart failure, shock)
- **chronic inflammation, tumours, cirrhosis**

Sudden damage to the hepatocytes lead to their necrosis and logically dysfunction, because the cells are no table to provide all the functions they are supposed to. This lead to the clinical syndrome of acute liver failure. The most frequent causes of acute liver failure are severe intoxications and severe clinical course of hepatitis. Progressive, long lasting decline of the liver functions lead to the syndrome of chronic liver insufficiency/failure and it is most frequently caused by chronic hepatitis, steatosis, amyloidosis, systemic diseases, but most importantly in liver cirrhosis.

Acute liver failure is defined as sudden decline of the liver functions in previously healthy individual, which leads to the lack of detoxification, biosynthesis and regulatory functions associated with impaired vital functions. It manifests mainly by the reduced functions of the CNS, jaundice and coagulation disturbances.

Chronic liver insufficiency/failure is defined as progressive slow decline of liver functions. Clinical manifestation of this process depends on the exogenous factors such are alcohol intake, protein intake, bleeding to the GIT, medication or infections. The most common cause of this process is the liver cirrhosis. Manifestation is heterogenic and it depends on the severity and the type of dysfunction (partial/total dysfunction).

In chronic hepatic failure, the patient suffers from metabolic disturbances, homeostasis disturbances, portal hypertension, encephalopathy, jaundice, circulatory changes, endocrine disturbances and many more.

1) Disturbance of the carbohydrate, lipid and protein metabolism

Acute liver failure is characterized by **hypoglycaemia**, which is caused by inability of liver cells to produce new molecules of glucose in the process of gluconeogenesis. It develops typically after the glycogen storage has been utilized and damaged hepatic cells have limited capabilities regarding gluconeogenetic enzymatic process. **Chronic liver failure** is however characterized by tendency to hyperglycaemia, hyperinsulinemia and insulin resistance. as a consequence of impaired production of glucostatic hormones and their effects on damaged liver. The reasons are many, but one of the most important mechanisms is reduced so called „first pass effect" which is one of the key factors leading to the hyperglycaemia with hyperinsulinemia and insulin resistance. In these subjects, there is also high concentration of free fatty acids in the plasma, because they cannot be metabolized by the liver cells, what lead to the change in the lipid and lipoprotein plasma profile.

When it comes to the metabolism of proteins, liver failure is characterized by intolerance of proteins, and patients are recommended to have low protein diet. In case of acute liver failure, the concentration of plasma protein increases, because liver typically produces more proteins during the acute phase reaction. Chronic liver diseases lead to the hypoproteinaemia because of insufficient proteosynthtic function of liver cells. Manifestations of low protein synthesis are reduction of oncotic pressure and disturbances of coagulation.

2) Disturbances of homeostasis

Patients with liver failure typically develops secondary hyperaldosteronism, and the changes in this hormonal cascade are induced by loss of effective arterial volume due to drop of oncotic pressure in liver failure subjects. In response to this, renin-angiotensin-aldosterone system is activated to increase reabsorption of sodium and water in the kidney in attempt to improve circulating volume. This is not effective and this cascade becomes soon dysregulated leading to the hyperaldosteronism (inability of liver to metabolize aldosterone). Increased volume of circulating fluids leads to the overload for cardiovascular system. In case that ADH is involved as well, patients may develop rather dilution hyponatraemia. Activation of aldosterone lead to the excretion of K^+ in the renal tubuli, thus leading to hypokalaemia with the tendency to metabolic alkalosis in extracellular space and intracellular acidosis. Alkalosis is dangerous because it influences ionisation of molecules in the body fluids e.g. ammonium which is reduced in alkalic fluid, and then ammonium without a charge (NH_4^+ vs NH_3) can

much easier cross the blood-brain barrier causing severe neurological problems (tin combination with other mechanisms) in liver failure patients.

3) Portal hypertension

It is defined as permanent rise of hydrostatic pressure in the portal vein above thy physiological values (5 – 15 mmHg). This is pathology, because portal system belongs to the low pressure low resistance part of the circulatory system. Causes leading to the increased pressure in the portal vain are occlusion inside of the vain, or a compression from the outside – these intra and extra vascular occlusions lead to the limited venous outflow from the portal system thus leading to the **portal hypertension.**

Portal hypertension is considered being **primary** when it is caused by primary increased blood flow via the portal system e.g. in case of congenital a-v malformations, as a consequence of medication with drugs causing vasoconstriction of the portal system, and finally it can be found in individuals with certain haematological diseases with splenomegaly. More frequent type is however **secondary portal hypertension** which is caused by partially or completely blocked venous outflow from the portal system.

Causes of secondary portal hypertension can be divided into prehepatic (thrombosis of the portal vein, compression by fibrosis after surgeries, compression by the head of pancreas etc.). intrahepatic (caused by majority of liver diseases with infiltration of perisinusoidal space, destruction of the parenchyma with cirrhotic remodelling, metastatic tumours, extramedullary hemopoiesis etc.) and **posthepatic** (thrombosis of the hepatic veins - Budd – Chiari syndrome, constrictive pericarditis, congestive heart failure etc.).

The most common cause leading to portal hypertension is chronic progressive liver disease with cirrhosis, where new islets of proliferating hepatocytes (micro or macronodular cirrhosis) lead to the compression/destruction of the spaces for sinusoids thus leading to the reduction of sinusoidal cross-sectional area. Consequences of portal hypertension are ascites and opening of so called portocaval (porto-systemic) venous shunts

4) Ascites

It is defined as a presence of inappropriate amount of fluids in the peritoneal cavity. In case of portal hypertension, the Starling balance across the peritoneal capillaries becomes disturbed by increased hydrostatic pressure and also by reduced oncotic pressure which is caused by hypoproteinaemia in liver diseases. Resorption of fluids at the venous end of the capillary fails and the fluids move to the peritoneal cavity. This leak of fluids in the abdominal area lead to the reduced venous return to the right heart, which further lead to the

reduction of effective arterial volume and cardiac output. This will activate compensatory mechanisms which in fact do not help to improve the circulation volume, but they will lead to the progression of ascites – mainly the activation of RAA system. Activation of this axis lead to the retention of sodium and water. Imbalance of Starling forces at the capillaries in the portal system will again lead to the fluid leak to the peritoneal cavity with the creation of vicious cycle. The boost for this process is low oncotic pressure and slow breakdown of aldosterone in subjects with liver disease. All of these mechanisms lead to the increase of the ascetic fluid volume. (Fig. 2).

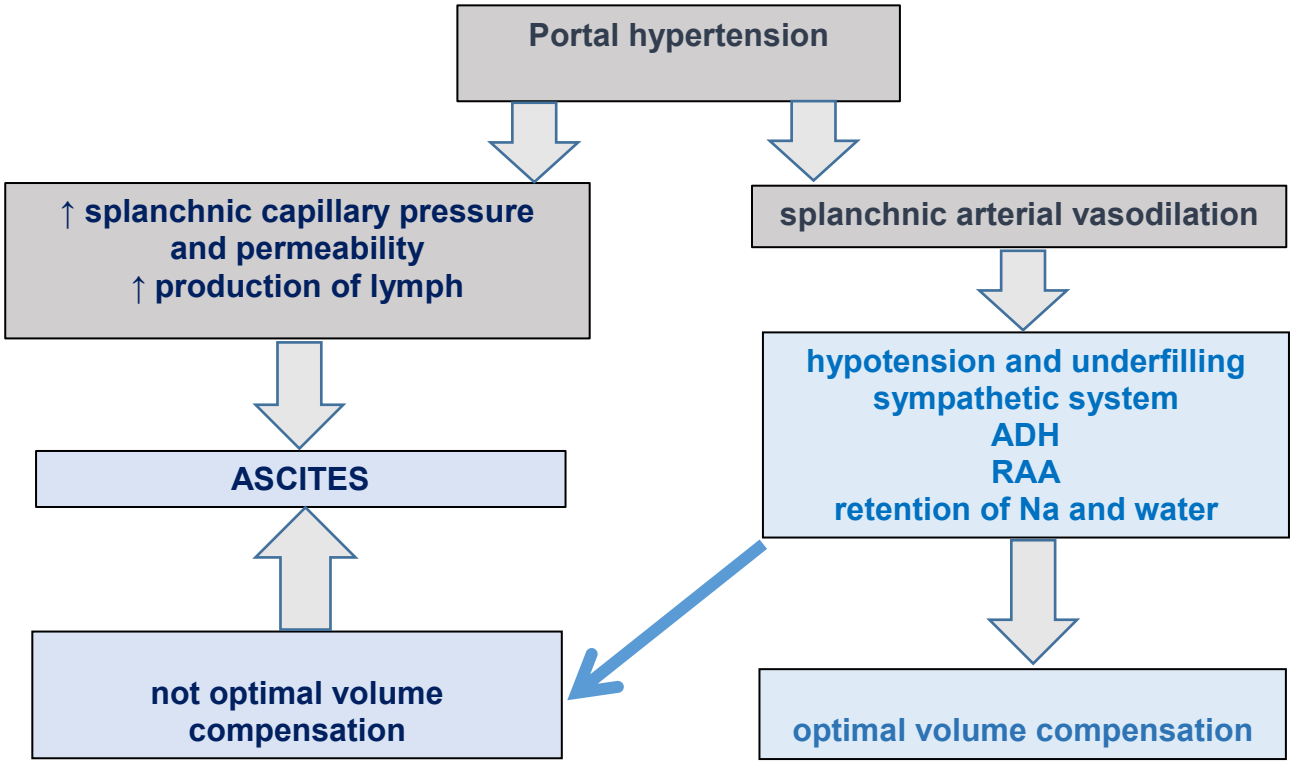


Figure 28.1: Mechanisms leading to ascites

Consequences of ascites are mainly compression of abdominal organs causing their impaired functions and the risk of bacterial peritonitis and sometimes also from respiratory failure caused by high position of diaphragm. Other negative consequences of portal hypertension are splenomegaly and hypersplenism (leading to the pancytopenia), hypervolemia with volume overload for the heart.

Portocaval anastomoses are veins located around the rectum, anterior abdominal wall and veins on the gastric fundus, distal oesophagus, veins draining venous blood from the spleen and veins of the left kidney, and finally venous connections between the diaphragm

and liver. These venous connections are normally closed in case that pre-portal venous pressure is normal, and they open only in case of increased portal venous pressure. Blood flow under higher pressure through these veins lead presence **external and internal haemorrhoids, caput medusa and oesophageal varices** – at least these have clinical significance. These veins can disrupt under the higher pressure leading to the clinically significant bleeding. The most dangerous is bleeding from oesophageal varices in combination with coagulation problems caused by liver failure/chronic liver dysfunction. The shunts between the portal and systemic circulation may have positive effect in a sense they reduce the pressure in the portal system, but, the disadvantage of these connections is that all the blood carrying bacterial products, different molecules and potential toxins from the gastrointestinal tract and these molecules are entering the systemic circulation without being effectively filtered in the liver. All of these molecules have potentially negative effect on **central nervous system and further they have negative effect on systemic circulation.**

5) Portosystemic encephalopathy

Portosystemic encephalopathy (hepatic encephalopathy) is **complex neuropsychiatric syndrome caused by metabolic damage of the CNS in subjects with advanced liver failure.** There are two main conditions for this syndrome to exist. First is the damage of the liver cells and communication of portal with systemic blood (presence of porto-systemic shunts). Mechanisms leading to this disturbance are complex and they involve **increased concentration of ammonium and its reduced ionization mainly in alkalic body fluids, disturbance of the energy production in the neurons, production of so called false neuromediators, impairment of blood-brain barrier and toxins resorbed from the lumen of intestine.**

Damage of the hepatocytes lead to the accumulation of nitrogen containing substances, mainly ammonium. Ammonium when poorly ionized, is present in the form of NH3, and it let it to cross the blood-brain barrier. Blood brain barrier permeability is influenced by the presence of NO and other bacterial toxins and both of these factors may lead to the vasogenic and toxins induced brain oedema. His may also contribute to already worsened performance of central nervous system. Ammonium influences energy production in the neurons - its high concentration activates transamination processes in which the oxoacids are used (they are substrates which normally enter the Krebs cycle). Transamination may lead to the imbalance in the neurotransmitter systems – in fact, the concentration of main inhibitory neurotransmitter - **gamma aminobutyric acid** – increase. Concentration of

glutamate – excitatory neuromediator decreases, because it is changed in the metabolic processes to the glutamine.

Furthermore, synthesis of so-called false neurotransmitters occurs, basis of which are aromatic amino acids from gastrointestinal tract, which are converted in chemical reactions into **octopamine and B-phenylethanolamine.** These false neurotransmitters influence the transmission of synaptic signals and CNS function. Source of ammonia and "toxic substances" – substrates for false neuromediators, toxins and in the end NO is the gut. Portal blood without filtration in the liver brings these substances into systemic circulation.

To cause, eventually to worsen the CNS functions in patients with liver disease can be initialized by **increased protein intake, GIT haemorrhage, alkalosis, simultaneous renal failure or effects of some medications.** Hepatic encephalopathy manifests with broad spectrum of **psychiatric symptoms** (changes in behaviour, aggressive or apathic behaviour, hallucinations, delusions) and **neurologic symptoms.** Most important is development of unconsciousness – **hepatic coma.**

6) Icterus – jaundice

One of consequences and simultaneously manifestations of hepatic insufficiency is icterus – yellow colour of sclera, skin and mucosal membranes caused by accumulation of bilirubin.

From pathophysiological point of view, icterus develops when **the balance between bilirubin production and its elimination from organism is disturbed.** Bilirubin is metabolic end product of tetrapyrrolic compounds, majority of which is represented by haemoglobin. In the metabolism of haemoglobin, the cyclic structure of tetrapyrrolic core is interrupted and linear molecule of biliverdin is synthetized, which is converted to bilirubin via other enzymatic reactions. From the place of its origin it is transported to liver in bond on albumin, as bilirubin is apolar molecule, which cannot be transported in extracellular fluid in any other way. During the passage through hepatic sinusoids it is absorbed on blood pole of hepatocyte, transported into endoplasmic reticulum and microsomes, where its **conjugation with glucuronic acid, glycine or taurine** takes place to increase its solubility and ability to be eliminated through bile. After its transport to gastrointestinal tract it is enzymatically converted by microbial flora to urobilinogen and urobilin, stercobilinogen and stercobilin – pigments which are responsible for characteristic colour of stool. Bilinogens undergo enterohepatic circulation and when the capacity of hepatocytes of their reuptake is exceeded, then they will be present in urine.

Based on presence of disturbances in synthesis, metabolism or elimination of bilirubin, jaundice is classified into three main groups: **prehepatic** (caused mainly by disturbance of synthesis – bilirubin overproduction), **intrahepatic** (disturbance of metabolic pathways in hepatocytes) and **posthepatic** (disturbance of elimination of bilirubin/bile into duodenum).

Prehepatic (haemolytic) icterus

Occurs due to disturbance of balance between bilirubin production and capacity of hepatocytes to conjugate synthetized amounts of bilirubin. This situation occurs e.g. in **massive haemolysis, resorption of massive haematomas, ineffective hemopoiesis** and so on. Synthetized bilirubin is bond to albumin and transported to liver for further metabolism. Its bond to albumin is the cause why unconjugated bilirubin is not present in urine. After processing of excessive amounts of bilirubin in liver **increased amount of bile pigments in bile and stool** (pleiochromic bile, hypercholic stool) **is present**, increased conversion of bilirubin to bilinogens in gut, their enterohepatic circulation and as the hepatocytes are overwhelmed by conjugation process, these substances do not undergo reuptake in liver and **urobilinogen together with urobilin can be detected in urine.** Specific type of haemolytic icterus is neonatal icterus, when in neonates the haemoglobin concentration decreases from approx. 190 g/L to 140-130g/L, because after childbirth the partial pressure of oxygen which oxygenates the blood changes. New-born does need so much haemoglobin after birth and eliminates it gradually. Healthy new-borns manifest with jaundice in approximately 50% of cases on 2^{nd} – 3^{rd} day and this jaundice can be considered physiologic.

Intrahepatic (hepatocellular) icterus

It is important to note in relation to metabolism of bilirubin in hepatocyte, that bilirubin undergoes three metabolic steps until it is secreted to bile – these steps depend on **presence and capacity of transport systems (blood and bile pole of hepatocyte), conjugation systems and enough energy in hepatocytes.** Hepatocellular icterus as a complex is heterogenous group of pathologic processes concerning disturbances of uptake of bilirubin by hepatocytes, disturbances of conjugation and lastly disturbances of secretion of bilirubin on bile pole of the cell. This type of jaundice can be caused by hepatocellular damage by different noxae; several genetic factors, infectious agents, immunopathologic noxae are also important as well.

Disturbances of bilirubin uptake on blood pole

Transport mechanism for bilirubin on blood pole is not specific for bilirubin, but transports many organic anions (bilirubin is present in form of bilirubinate in pH 7.35-7.45 – it has negative charge). Protein responsible for this step is called **ligandin** or protein Y. Disturbance of transport system occurs in Gilbert's syndrome, which is autosomal dominant disease. Patients with this disease do not have jaundice all the time (only hyperbilirubinemia is present); jaundice develops in case of functional overload of transport system on blood pole of hepatocyte e.g. in infection, different medication (barbiturates, NSAIDs), alcohol intoxication or fasting. This disease belongs to group of benign hyperbilirubinemias and has good prognosis.

Disturbances of conjugation

Bilirubin conjugates with glucuronic acid via enzyme UDP-glucuronyl transferase. Hereditary defects of this enzyme exist which manifest with severe neonatal icterus, e.g. **Crigler-Najjar syndrome,** which is present in two forms – either in recessive form of inheritance with total enzyme deficiency of autosomal dominant form in which the enzyme activity is present.

Disturbances of conjugation occur also in pre-term new-borns. UDP-glucuronyltransferase complex matures just prior to 10^{th} lunar month and pre-term new-borns suffer from severe disturbances of conjugation of excessive amounts of bilirubin which are synthetized as part of postpartum adaptation of oxygen transport system. **Neonatal icterus of pre-term new-borns** is more severe as physiologic jaundice, occurs on second postnatal day, lasts longer and bilirubin levels are several folds higher than normal. In levels above 300 μmol/L there is high risk of bilirubin crossing the immature brain-blood barrier and development of **kernicterus**. This type of jaundice must be distinguished from jaundice of breast-fed new-borns – in some cases breast milk contains 20,3-pregnanediol, a steroid which blocks the conjugation process.

Damage of hepatocytes – inflammatory, toxic, ischemic, immunogenic, metabolic – can manifest with hepatocellular jaundice with disturbances of conjugation. Patient has yellow colour of skin; in blood, increased concentrations of unconjugated and conjugated (direct) bilirubin are present – direct bilirubin gets into circulation via "back leak" mechanism in hepatocellular necrosis. Direct bilirubin, as well as urobilins can be present in

urine. Hepatic enzymes (ALT, AST) are typically elevated as markers of hepatic injury; in damage of bile pole the levels of ALP and GMT are elevated.

Disturbances of bile secretion

Secretion of conjugated bile is disturbed in **Dubin-Johnson syndrome** and **Rotor syndrome.** Both diseases belong to genetically determined diseases and belong to group of benign hyperbilirubinemias, which are diagnosed in children or adolescents during regular check-ups. Child is not yellow, sclera can become subicteric in intercurrent diseases, experimenting with alcohol or during medication with medicines which compete with bilirubin secretion on bile pole of hepatocyte. Both diseases have good prognosis and are not associated with any other functional disturbance of hepatocytes.

Posthepatic (obstructive) icterus

This type of icterus is caused by an obstacle in bile drainage, which occurs on the level of extrahepatic bile ducts. Disturbances of drainage e.g. in cholangitis or primary biliary cirrhosis are connected with damage to bile pole of hepatocytes and as such are categorized as a subgroup of hepatocellular icterus.

Most common cause of obstructive icterus is block of extrahepatic bile ducts by concrement, which "travelled" to bile duct during biliary colic. Mechanic problem of bile drainage can be caused by intraluminal problem (concrements, parasites) or extraluminal compression of bile duct (pancreatic tumour, scaring, strictures after inflammation and others). Aftermaths of this process are evident forwards as well as backwards.

Forwards: **bile is not secreted to gut which disturbs digestion and resorption of fats and fat-soluble substances. Results of these processes are: steatorrhea –** grey, foul-smelling stool with presence of indigested fats, **acholic stool –** stool does not have necessary amounts of pigments as the metabolism of biliary pigments in gut is not present; urobilinogen is present in urine. **Disturbances of blood coagulation –** disturbance of lipid digestion and resorption leads to disturbance of lipid-soluble vitamins (A, D, E, K) and as vitamin K is not being deposited in organism in deposit form in contrast to other aforementioned vitamins, its deficiency can soon manifest as coagulopathy. Second result which can be marked as backwards is increased pressure before the obstruction which causes increased pressure in extrahepatic and intrahepatic bile ducts **(cholestasis).** Increased pressure on bile pole of hepatocytes can lead to disturbance of intercellular junctions between hepatocytes and bile which is supposed to drain to gut leaks through damaged intercellular junctions to blood

(back leak mechanism). The results of this process are **presence of conjugated bilirubin in urine** (urine is dark as stout), **elevation of cholestatic enzymes** (ALP and GMT), which are present at bile pole of hepatocytes and they are present in blood in its damage – they serve also as markers of cholestatic liver damage, **increased concentration of cholesterol and bile acids in blood, pruritus (itching),** which develops due to deposition of bile acids into skin close to free nerve endings; bile acids do not directly activate them but only increase their sensitivity.

Severe consequences develop when the obstacle is present in the area of sphincter of Oddi, because simultaneously with pressure increase in bile ducts the pressure increases in pancreatic duct as well and **bile influx** can develop with premature activation of pancreatic enzymes with autodigestion of pancreas. If the obstacle is incomplete or intermittent, repeated pressure increase can lead to secondary biliary cirrhosis – tissue damage around the bile ducts with their subsequent cirrhotic regeneration.

7) Changes of systemic circulation

Chronic hepatic insufficiency is characteristic by development of hyperkinetic circulation – increased minute volume at rest, tachycardia, decreased vascular resistance in splanchnic area with some regional (renal) circulations have increased resistance in contrast. Insufficient filtration ability of monocyte-macrophage system leads to inadequate elimination of endotoxin from GIT by liver and (at least their part) reach systemic circulation. It is known, that endotoxin increases expression of **inducible NO synthase** (iNOS) via interaction with immunocompetent cells and endothelium. iNOS subsequently produces increased amounts of **nitric oxide, which is a strong vasodilating factor.**

Decrease of peripheral vascular resistance induced by NO activates compensatory mechanisms (sympathetic system, RAA, ADH). Sympathetic signalling is not sufficient enough to antagonize the effects of produced NO and therefore systemic hypotension persists. Combination of these pathologic processes (decrease of vascular resistance) with compensatory mechanisms (sympathetic signalling, RAA) can severely influence the circulation in **lungs or kidneys** with development of severe life-threatening processes, such as respiratory or renal failure in patients with primary liver failure – they are called **hepatopulmonal and hepatorenal syndrome.**

Hepatopulmonal syndrome is development of respiratory failure in patients with advanced hepatic insufficiency. Its development is of multifactorial origin, but the highest contribution to its development is done by changes of **systemic circulation.** Hyperkinetic

circulation with increased minute volume leads to **increased blood flow in unventilated lung compartments.** This leads to increased right-to-left shunts, which manifest with development of hypoxemia without hypercapnia. Hypoxemia can be also result of alveolocapillary membrane (interstitial pulmonary oedema caused by endothelial damage by endotoxin originating in GIT) and in case of ascites inability of diaphragm to contract properly with inadequate motion (hypoxemia with hypercapnia). Disturbance manifests with development of dyspnoea and changes in blood gases pressures.

Hepatorenal syndrome characterizes functional renal failure which develops in severe forms of liver diseases with ascites and changes in systemic circulation. Mechanisms which contribute to development of renal failure are overactivation of sympathetic nervous system and RAA system due to changes in systemic and portal circulation which leads to worsening of renal haemodynamics with subsequent decrease of glomerular filtration rate which manifests with oliguria, eventually anuria with retention of potassium, anions of fixed acids, nitrogen-containing substances (e.g. urea) and electrolytes with complex disturbance of homeostasis

8) Changes of endocrine system

Liver is the place of metabolism of several hormones; therefore, the levels of these hormones change in liver insufficiency. Clinically most visible are the changes caused by insufficient metabolism of androgens which are converted to oestrogens in the periphery. Affected men suffer from **decreased libido, impotence, gynecomastia and spider angiomas on skin.** Women in fertile age suffer from disturbances of menstrual cycle (from irregularities to amenorrhea), spider angiomas. Decreased conversion of aldosterone was already mentioned and it contributes to increased biologic effect of aldosterone on sodium and water retention.

9) Other

In patients with chronic liver insufficiency **pruritus** develops as a result of increased concentrations of **bile acids** and their deposition into skin close to free nerve endings which although not directly activated by these acids, they are significantly sensitized. Further manifestation includes **anaemia, "unexplainable" fevers, psychic changes and deficiency of vitamins (A, D, E, K, folic acid, B1, B6)**.

CASE REPORTS

Case report 1

58-years-old, unemployed man admitted to department of internal medicine due to jaundice, sudden increase in abdomen size and oedemas of lower extremities. Family history is negative and in personal history the findings of multiple admissions to hospital (lacerations, bicycle accidents, unexplained traumas – always with positive blood alcohol, also the reason why he is unemployed). He is not on any long-term treatment, he states that he has not any allergies. According to patient, he drinks 3-4 beers daily, spirits only occasionally and smokes 20 cigarettes a day. Three weeks ago, he attended a celebration of some sort, where he caught a cold and "drank a bit" and he does not feel well since. He is tired, weak, he lost his appetite – he still put on 10kg of weight, his lower extremities started to swell and his abdomen got larger. He noticed darker urine and when his relatives noticed his jaundice, they went to seek medical advice with him.

Objective findings: Patient is oriented, looks tired; has yellow skin, sclera and mucosal membranes. His extremities are atrophic in contrast with abdomen. Skin on chest has multiple spider angiomas, tongue is smooth. Breathing vesicular, without any phenomena. Heart – action regular, HR 110/min, BP 90/60 mmHg. Abdomen above thorax niveau, without pain, positive undulation phenomenon; liver is of tough consistency, exceeds right costal margin by 2cm; spleen palpable. Symmetric oedemas of lower extremities present.

Laboratory results: WBC 5.6; HBG 113 g/L, HTC 0.35; PLR 95, MCV 101.2 fL; Na 128 mmol/L; K 3.4 mmol/L; UREA 26 mmol/L; creatinine 240 μmol/L; ALT 4.3 μkat/L; AST 3.8 μkat/L; ALP 2.0 μkat/L, GMT 5.9 μkat/L; bilirubin 45 μmol/L; albumin 32 g/L. Proteins in urine are not present, but bilirubin (+++), urobilinogen (+++) are, and Na is low (8 mmol/L). HBsAg positive. Coagulation parameters suggest coagulation deficiency.

Questions & Tasks

1) Which laboratory parameters differ from normal values and explain why they change.

2) How would you explain clinical findings?

3) Given positive HBsAg, history, present disease and elevated GMT and MCV, what is the aetiopathogenesis of patients' disease?

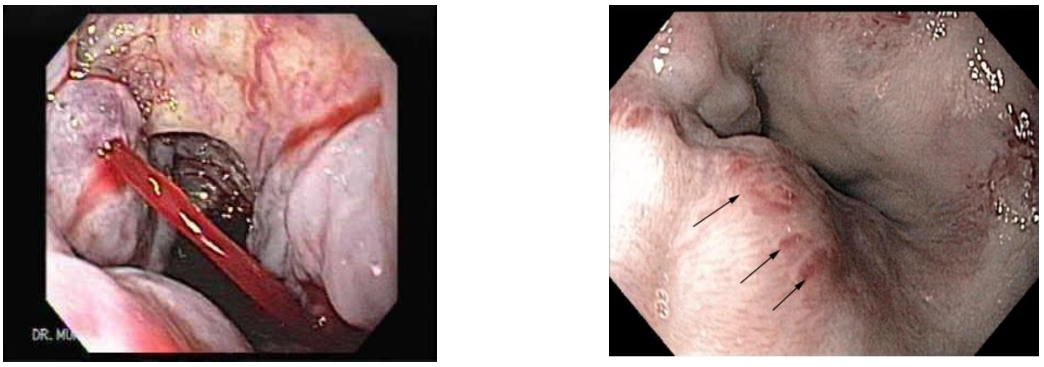
4) Explain the pathogenesis of deregulation of sodium and water balance in organism.

Case report 2

48-years-old unconscious patient was admitted to ER after an episode of massive haematemesis. Blood was dark red, was not digested. Based on indirect history given by his fiancée, the patient is unemployed and likes to drink alcohol. He does not take any medications regularly, his personal and family history are not remarkable. Furthermore, his fiancée states that he sometimes had problems with digestion. She also noticed that he is moody and aggressive lately; he sometime has memory loss; his hands are shaky and she thinks it is caused by his alcoholism.

Physical examination: Patient unresponsive, GCS 6, inserted Sengstaken-Blakemore tube, not bleeding at the moment, secured venous line with saline administration, spontaneous ventilation, sat O2 94%, BP 90/60 mmHg, heart rate 140/min, weak pulse, white and cold skin. Abdomen below the niveau of the chest wall, no palpable resistance, liver, spleen not palpable, lower extremities with mild oedema. Initiated volume resuscitation and endoscopic treatment of varices (adrenalin stings, administration of etoxysclerol). Patient with stable vital functions transferred to the intensive care unit.

Laboratory examination: Na 145 mmol/L; K 3.2 mmol/L; Cl 98 mmol/L; AST, ALT elevated, ALP, GMT elevated, Bi 32 μmol/L, albumin 38 g/L, UREA 4,5 mmol/L, creatinine 120 μmol/L; WBC $7{,}5\times10^{9}$/L; RBC $3{,}5\times10^{12}$/L; HBG 120 g/L; HTK 0.40; PLT 150; MCV 101 fL; coagulation parameters indicate severe problems with blood clotting.



Endoscopy before and after the stabilization of the patient condition. Arrows indicate the presence of massive oesophageal varices underneath the mucosa

Questions & Tasks

1) Which of the data from patient history, physical examination and laboratory findings indicate the liver damage?

2) What is the reason for smaller liver and spleen? Explain.

3) Which of the laboratory parameters can confirm chronic alcohol intake in this patient?

4) How do you explain the presence of oedema and lack of ascites in this patient?

5) Does this patient have signs and symptoms of shock? What type of shock developed in this patient?

Chapter 29

SELECTED PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM

Endocrine and nervous system create **communication network of organism.** Its function **connects, coordinates and integrates** parts of organism; **they are able to react to changing environmental conditions which maintains organism integrity.**

Endocrine system consists from several parts. They are:

a) Specialized endocrine glands – hypothalamus, thyroid gland, adrenal gland, pituitary gland, gonads, pancreas, parathyroid glands.

b) Specialized endocrine cells localized in non-endocrine organs or **tissues** – endothelial cells producing endothelins and prostaglandins; endocrine cells of gastrointestinal tract producing e.g. cholecystokinin and other hormones.

c) Non-specialized cells of different tissues – producing cytokines.

Main groups of hormones

A. Classic hormones

a) Low molecular amines – derived from tyrosine (catecholamins, thyroid hormones, leukotrienes, prostaglandins, dopamine, serotonin).

b) Steroids – derived from cholesterol (glucocorticoids, mineralocorticoids, sex steroids).

c) Polypeptides and proteins (insulin, bradykinin and others).

B. Group of novel hormones

a) Hypothalamic hormones (liberins, statins).
b) Polypeptides produced in GIT (more than 26).
c) Endogenous opioids (endorphins, enkephalin, dynorphin).
d) Tissue growth factors (epidermal, neuronal, platelet and others).
e) Natriuretic factors (atrial - ANF, brain – BNF).
f) Transformation growth factors (e.g. TGF).
g) Haemopoietic growth factors.
h) Cytokines.

Concentrations of hormones in serum are expressed in range from pg (10^{-12} g) to μg (10^{-6} g) in 1 ml of serum. Concentration depends on speed and amount of secreted hormone,

on speed of its inactivation and on mechanism of its transport via blood.

Transport of hormones in blood

- Polypeptide and protein hormones are soluble in water and are transported as solutes.
- Steroid hormones – are insoluble in water and are transported in bond with albumin as a non-specific transporter or in bond with specific transporter (e.g. thyroxin binding globulin - TBG, sex hormone binding globulin - SHBG). Only free fraction of hormone is biologically active – it is approx. 10% of its total amount.

To understand disturbances of endocrine system as a whole and its parts the knowledge of **general properties of hormones** is necessary. These include the following.

Mechanism of hormone release

- Rate of secretion is different in different hormones - diurnal, pulses, cyclic, dependant on concentration of hormone itself or substrate which they influence, and each hormone has specific properties.
- Their secretion is regulated by feed-back systems.
- They influence only cells which have specific receptors for given hormone.
- They stimulate ion and glucose transport through membranes.
- They stimulate or inhibit cellular enzymes.
- They influence genetic information of cells.
- They are catabolized mainly by liver and kidneys, but they may be inactivated also in tissues where they exhibit their function.

Basic mechanisms contributing to development of disturbances of hormonal functions

If some hormonal disturbance develops, usually it is caused by one of three following mechanisms:

1) primary failure of regulatory mechanisms (e.g. feedback) **controlling synthesis and release of hormones.** This regulation is normally mediated by, e.g. different hormones, nervous system, changes of plasmatic solutes – ions, organic nutrients.

2) Primary disturbance of endocrine gland itself or endocrine activity of tissue cells. It is caused by damage of endocrine gland by pathological process – inflammation, tumour, degenerative process or existence of ectopic site of hormone production.

3) Primary failure of target cells to react adequately to hormone. In these cases, the

target cells have lost (mostly due to pathological process) the ability to adequately react to hormone – they are either hyporeactive or hyperreactive; e.g. due to changed number of receptors or function of intracellular pathways.

These mechanisms can lead to two main types of hormonal disturbances:

I. Increase of concentration/effect of hormone

II. Decrease of concentration/effect of hormone.

An overview the pathophysiology of endocrine system

1. Pathogenesis of disturbances of hypothalamus and pituitary gland

Hypothalamus plays an important role in regulation and coordination of whole endocrine system. Its main function is maintenance of **organism homeostasis.** This function is fulfilled by stimulation or inhibition of many processes in organism, such as heart rate, stability of blood pressure, stability of volume and composition of body fluids, appetite, body weight, secretion of glands of stomach and intestine, function of pituitary gland, sleep cycle and many others. **Hypothalamus is considered to be a connection between nervous and endocrine system**. It produces hormones which promote or inhibit synthesis and release of other hormones in whole organism. Hypothalamus also contributes to many functions of **autonomous nervous system.**

a) Hypothalamic hormones and their disturbances

Antidiuretic hormone = arginine vasopressin (ADH or AVP) **–** increases reabsorption of water in collecting ducts in kidneys and in higher concentration in blood causes vasoconstriction. Its synthesis is increased by systemic hypotension, hypovolemia, hyperosmolarity of extracellular fluid, stimulation of sympathetic nervous system and increased concentration of angiotensin II. Disturbances in its synthesis and release manifest with typical syndromes. These are:

Syndrome of inappropriate ADH secretion (SIADH)

Excessive amount of ADH is synthetized in hypothalamus, which is transported to posterior lobe of pituitary gland and from it to blood, and increases reabsorption of water in kidneys which leads to its accumulation in organism. The result is expansion of extracellular fluid volume and its dilution which manifests by **hypotonic hypervolemia and hyponatremia.** If SIADH is the cause of **severe hyponatremia,** it can manifest by wide

array of signs and symptoms, such as increased irritability, nausea, vomiting, tremor, cramps, coma, generalized muscle weakness.

It is obvious, that there is a contribution to aforementioned symptoms by shift of water from extracellular fluid to intracellular (because cells fluid is hyperosmolar in comparison to extracellular fluid), therefore, intracellular oedema develops (especially the oedema of brain cells is dangerous).

SIADH is most often caused by either **inappropriate hypersecretion of ADH from its normal hypothalamic source or by ectopic production**. The causes of SIADH can be divided into four broad categories: nervous system disorders, neoplasia, pulmonary diseases, and drug induced. Neoplastic causes, as are small cell lung carcinoma, prostatic cancer, ovarian cancer, urinary bladder cancer, breast cancer, lymphomas, melanomas, inflammation causes - brain, meninges, lungs, which are the places of **ectopic ADH synthesis**, as well as (left) heart failure and psychoses.

Diabetes insipidus (DI)

It is syndrome caused by inadequate synthesis of ADH or its inadequate effect at the level of cells. Insufficient synthesis, "storage" and release of ADH are caused by damage to the hypothalamus (or pituitary gland), e.g. in surgery in respective brain area, by tumour, inflammation or trauma. This DI type is called **central** or **neurogenic.** Decreased ADH synthesis also occurs after ingestion of alcohol-containing beverages or due to decreased environmental/body temperature. It is not DI in these cases, but rather natural/physiologic reaction of hypothalamus to mentioned noxae.

Nephrogenic DI develops in different way. In this case, the amount of synthesized ADH is normal, but renal tubules react to it less, or not at all. Such a tubular defect can be congenital, but can develop within chronic renal diseases or under the influence of some medication (e.g. lithium-containing medication, tetracycline ATBs).

Main manifestations of DI are: extreme polyuria (excretion of hypotonic urine – up to 20 L/day, specific density 1.000 – 1.005), which leads to development of **hypertonic dehydration** and intensive thirst, which results in excessive intake of fluids (polydipsia). Patients suffer from nycturia and enuresis. Manifestations of syndrome are caused by mainly hypertonic dehydration (more info in chapter related to control of fluids in the body)

Figure 29.1: Main symptoms and signs of SIADH and DI

Other hypothalamic hormones are liberins (CRH, GnRH, GHRH, PRH, and TRH) and statins (e.g. PIH**)** and oxytocin. They are hormones synthetized in hypothalamus, and apart from oxytocin and PIH, they stimulate synthesis of hormones in pituitary gland – ACTH, gonadotropins, STH, prolactin and thyrotrophic hormone.

Hypothalamus is supposedly the most important part of the endocrine system, because it regulates the quality of other parts of endocrine system via synthesis of specific hormones. This provides the balance of internal processes of organism which are performing according to organism demands in any given situation.

Pathophysiology of anterior lobe of pituitary gland

In anterior pituitary gland, the **tropic hormones** are synthetized – **adrenocorticotropic hormone, gonadotropic hormones, thyrotrophic hormone, growth hormone and prolactin.**

From pathophysiologic point of view, two major pathologic conditions which affect anterior pituitary gland functions can be distinguished. These are:

A. Hypofunction - hypopituitarism

B. Hyperfunction - hyperpituitarism

A. Hypopituitarism

It is a name for insufficient synthesis and/or secretion of one (partial) or more hormones of pituitary gland (panhypopituitarism). Whole array of causes which can induce these changes are known, and may be localized directly in anterior pituitary gland: e.g.

tumour, which causes destruction of anterior pituitary or specific type of cells, pressure to the anterior pituitary from surrounding tissue, ischemia (caused by hypotension, thrombosis, embolism), bleeding, surgery in the area, as well as those which are primarily localized in hypothalamus. The result/manifestation of these processes depends on **type and degree of hormonal insufficiency.** It may manifest as **adrenal cortex insufficiency,** severe **thyroid insufficiency, disturbances of gonadal functions, growth retardation**, as well as non-specific symptoms as is fatigue (malaise).

In partial ACTH deficiency, the basal secretion of cortisol in adrenal cortex is normal, but during stress (e.g. infectious disease, surgery...), when ACTH concentration physiologically increases, the increase in cortisol concentration does not reach level which is necessary for to resist the stressor, so the manifestations of adrenal cortex insufficiency develop (Addison disease).

In complete ACTH deficiency, the synthesis of this hormone is fully stopped or is very low. This results in loss of basal cortisol secretion which leads to life-threatening disturbance of defensive functions of organism (Addison crisis).

In panhypopituitarism, the synthesis of not only ACTH, but also gonadotropic, thyrotrophic and other hormones is affected, which manifests by hypocorticalism, hypogonadism, hypothyroidism, growth retardation (if panhypopituitarism developed in childhood) and hypoprolactinaemia.

ACTH deficiency manifests with an array of **non-specific signs and symptoms,** e.g. nausea, vomiting, headaches, as well as **specific ones** – tendency to hypoglycaemia, orthostatic hypotension caused by loss of extracellular fluid volume (BP when measured in horizontal position can be physiologic), loss of axillar and pubic hair in women caused by loss of effect of gonadal hormones, decrease of aldosterone production (ACTH has tropic effect on zona glomerulosa of adrenal cortex), hyponatremia and eosinophilia (due to decreased levels of glucocorticoids).

In gonadotropic hormone deficiency (FSH – follicle stimulating hormone, LH – luteinizing hormone), anovulation cycles in women in fertile age develops, other signs and symptoms can include amenorrhea, vaginal and uterine atrophy, hot flashes and decrease of libido. In post-pubertal men, testicular atrophy, decrease of typical masculine hair growth, gynaecomastia and fine facial wrinkles develop.

Deficiency of growth hormone manifests differently when it occurs in childhood (nanism) **and differently in adulthood** (loss of muscle strength, decreased tolerance of exercise, increased content of adipose tissue).

B. Hyperpituitarism

This term describes overproduction of anterior pituitary gland hormones. Main causes of hyperpituitarism are adenoma of pituitary gland or its increased stimulation by hormones from hypothalamus. The result is manifestation of, e.g. **overproduction of prolactin –** hypogonadism (PRL inhibits synthesis and release of gonadotropins from anterior pituitary), galactorrhoea – production and spontaneous secretion of breast milk from mammary glands outside of lactation period in women, in men it can cause erectile dysfunction and infertility. Long-term overproduction of prolactin is a risk factor for hyperglycaemia which is a risk factor for diabetes mellitus development.

Overproduction of growth hormone before epiphyseal slit closure in long bones (in puberty) leads to excessive growth in length – **gigantism.** Overproduction of STH in adults manifests as **acromegaly** – enlargement of acral parts of the body (feet, hands, ears, chin) as well as internal organs (heart, tongue, liver). Enlargement of jaw can lead to development, eventually enlargement of spaces between teeth (see pictures). Patients with this disorder have also increased risk of diabetes mellitus development.

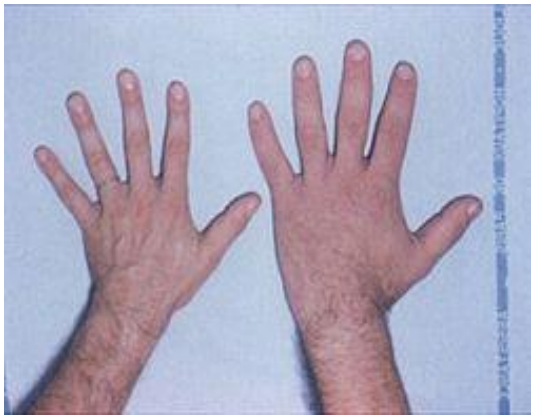


Figure 29.2: Comparison of hand size of healthy person and patient with acromegaly

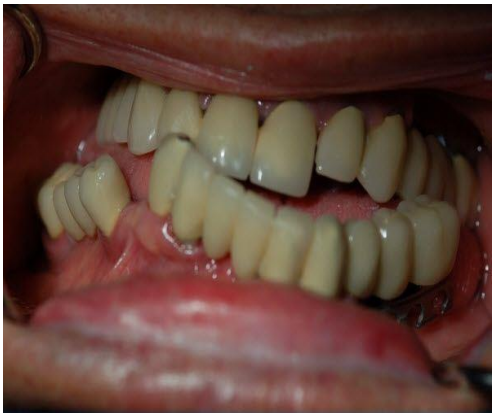


Figure 29.3: Teeth deformities in patient with acromegaly

ACTH overproduction can be caused by overproduction of CRH from hypothalamus (e.g. in permanent stress), by adenoma localized in anterior pituitary gland or ectopic ACTH synthesis e.g. in bronchial carcinoma. The most important effect of ACTH is stimulation of adrenal cortex, especially its middle layer (zona fasciculata), in which the glucocorticoids are synthetized. ACTH also influences the outer layer of adrenal cortex (trophic effect), but does not directly stimulate the synthesis of mineralocorticoids within the layer. The result of such stimulation is hypertrophy of adrenal cortex as well as increased synthesis of glucocorticoids

(cortisol). These have many side effects, especially in increased levels, manifesting in different tissues and organs. Their summary is called **Cushing's syndrome.** The main effects of glucocorticoids include:

a) Stimulation of gluconeogenesis in liver and inhibition of glucose utilization in peripheral tissues which leads to increased risk of diabetes mellitus (so-called steroid DM).

b) Stimulation of lipolysis, proteolysis in tissues and synthesis of plasmatic proteins in liver. This manifests with hyperlipidaemia (atherosclerosis acceleration), loss of muscle mass (e.g. thin lower extremities), muscle weakness, loss of cutaneous collagen (skin becomes fragile and gets torn easily – striae distensae develop - striae – stretch marks, if skin vessels are also affected, striae rubrae occur), osteoporosis (loss of bone matrix). Due to different sensitivity of adipose tissue to glucocorticoids in different parts of the body, the redistribution of adipose tissue occurs – thin extremities and accumulation of adipose tissue on trunk, face and back of the neck. Given the fact, that due to increased levels of glucocorticoids the catabolic processes prevail over anabolic ones, the wound healing is slowed. In children, it can cause growth retardation.

c) Glucocorticoids also promote production of erythrocytes, platelets and neutrophils and supress production of eosinophils, monocytes and lymphocytes. They also inhibit release of histamine (from mast cells), interleukins, lymphokines and antibodies (anti-inflammatory effect). Increased production of red blood cells leads to polycythaemia (resulted in increased blood viscosity), increased platelet count increases the risk of thrombosis and decreased number of lymphocytes predisposes these patients to infections.

d) Glucocorticoids in stomach increase production of HCl and pepsin, they limit mucus production (protective factor against gastric HCl) – the result is increased risk of peptic and duodenal ulcers.

e) Increased excitability of nervous system (development of endocrine psychosyndrome). Patients with this disorder usually have increased blood pressure, because glucocorticoids increase sensitivity of cardiomyocytes and vascular smooth muscle cells to catecholamins (increased cardiac output and vasoconstriction).

f) Glucocorticoids also cause hypervolemia (sodium retention in kidneys together with water caused by mineralocorticoid effect of glucocorticoids).

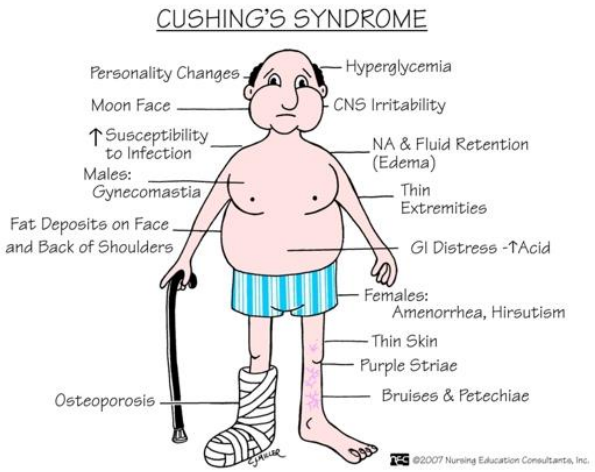


Figure 29.4: Symptoms and signs of increased production and effects of glucocorticoids

From the list of signs and symptoms caused by overproduction of ACTH followed by overproduction of glucocorticoids it is obvious how strong and broad are the effects of these hormones throughout the body. Apart from causing an array of damage in overproduction or inadequate therapy dosage, the effects of these hormones are positive as well and these are utilized in not only regulation of physiologic processes as well as in therapy of many diseases.

Hyperfunction and hypofunction of adrenal cortex can also develop independently on function of hypothalamus and pituitary gland. Causes are usually **primary hyperplasia and tumour of adrenal cortex** or **atrophy or destruction of adrenal cortex, e.g. by infection, autoimmune process or bleeding.** In all these cases, the changes in adrenal hormones production are **autonomous,** therefore regulatory mechanisms independent.

Hyperfunction manifests with overproduction of hormones synthetized by cells of different layers of adrenal cortex. In hyperfunction of cells in **zona fasciculata** the concentrations of glucocorticoids in blood are increased, their effects are listed above. In hyperfunction of **zona reticularis** cells the **androgen synthesis** increases, which can cause **signs and symptoms of masculinization and amenorrhea** in women and **acceleration of masculine secondary sex characteristics** (pseudopubertas praecox) in boys. Increased cellular activity in **zona glomerulosa** (Conn's syndrome) leads to **overproduction of mineralocorticoids** (mainly aldosterone) which manifests by sodium and water retention by kidneys, systemic arterial hypertension, hypokalaemia, hypomagnesemia, alkalosis and increased neuromuscular irritability.

Hypofunction of adrenal cortex can be generalised (all layers are insufficient) or

localized in one or two layers. In **zona glomerulosa hypofunction, the production of mineralocorticoids is decreased** which manifests by severe loss of sodium and water and retention of potassium, magnesium and hydrogen ions. The resorption of NaCl form gastrointestinal tract is decreased as well. The result is hypotonic dehydration, hypovolemia, decreased BP, possible intracellular oedema development.

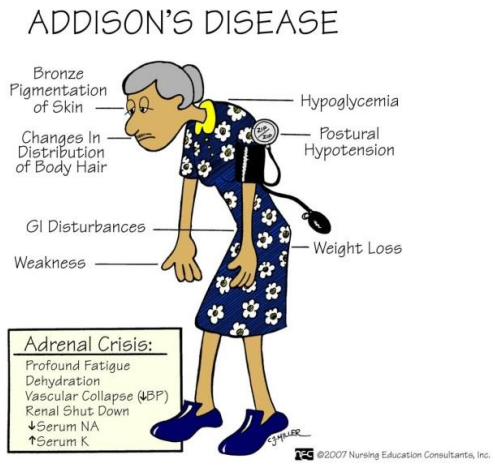


Figure 29.5: Symptoms and signs induced by hypofunction of adrenal gland cortex

Hyperfunction and hypofunction of thyroid gland

Hyperfunction of thyroid gland is characterized by increased synthesis and/or effects of thyroid hormones - T_3 and T_4. It is caused by several mechanisms:

- overproduction of TRH in hypothalamus,
- overproduction of TSH in anterior pituitary gland,
- toxic adenoma of thyroid gland,
- inflammation of thyroid gland,
- ectopic tumours producing T_3 and T_4.

Hyperfunction of thyroid gland (hyperthyroidism) is **complex pathologic process.** Main forms of this disease are **Graves' disease and autonomous toxic adenoma.**

Graves' disease is hyperthyroidism connected with hyperplastic goitre. It is caused by antibodies (long acting thyroid stimulator – LATS, thyroid stimulating immunoglobulin - TSI) binding to TSH receptors of cells of thyroid gland. Overproduction of T_3 and T_4 together with glandular growth leads to **complex of signs and symptoms,** basis of which is **increased metabolism in tissues.** These include:

- Merseburg triad – goitre, exophthalmos, tachycardia,
- nervousness, emotional lability, fine tremor (fingers),
- heat intolerance, excessive sweating,
- dyspnoea, thirst, dryness in mouth,
- disturbed renal functions – increased glomerular filtration with polyuria and frequent urination,
- functional changes of GIT – achlorhydria, increased motility with diarrhoea,
- changes in blood composition – slight anaemia (due to achlorhydria or effect of antibody on intrinsic factor),
- disturbance of cardiac function – apart from tachycardia also atrial fibrillation is common, decreased myocardial contractility (ATP production is decreased – cardiomyopathy),
- bones and calcium metabolism are affected – osteoporosis,
- nervous and muscular systems are affected – encephalopathy, muscle weakness, myopathy,
- skin changes are present – warm, wet, soft skin, palm erythema, vitiligo, pretibial oedema (anterior to shin),
- ophthalmologic changes – non-infiltrative ophtalmopathy (retraction of eyelid and "terrified" appearance of eyes), - infiltrative ophtalmopathy – oedema of retracted eyelids, eyeball protrusion

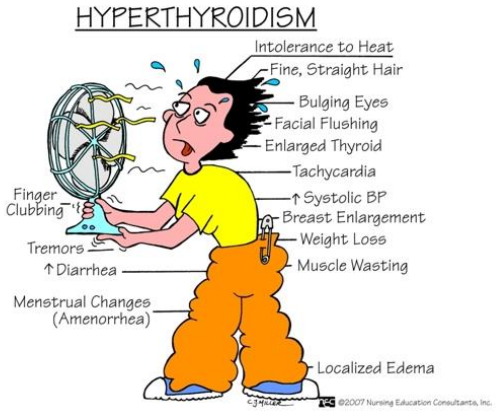


Figure 29.6: Symptoms and signs induced by increased thyroid hormones

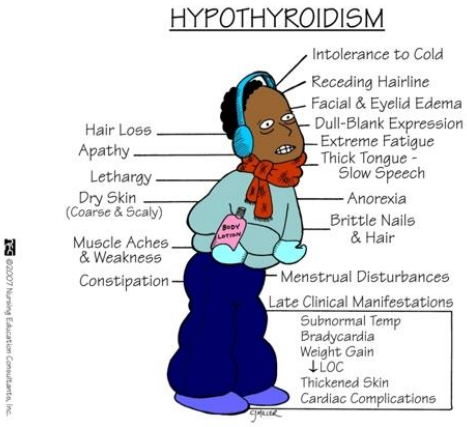


Figure 29.7: Symptoms and signs induced by decreased thyroid hormones

Thyreotoxic crisis

It develops as an aftermath of sudden and rapid release of thyroid hormones from thyroid gland or their sudden release from bounds on plasmatic proteins in blood. It manifests

by severe increase of metabolism intensity and most of aforementioned signs and symptoms of hyperthyroidism. Tachycardia can reach up to 150/min, patient is restless with possibility of delirium development, has increased body temperature, stomach ache, nausea, vomiting, diarrhoea (can lead to dehydration).

Hypofunction of thyroid gland

Is characterized by decreased production of thyroid hormones based on pathologic process within thyroid gland itself (**primary hypothyroidism),** based on decreased production of TSH in anterior pituitary gland **(secondary hypothyroidism)** or based on decreased production of TRH in hypothalamus **(tertiary hypothyroidism).**

Primary hypothyroidism is caused by autoimmune Hashimoto's thyroiditis, iodine deficiency (rare nowadays – salt iodization), after strumectomy, increased consumption of strumigens or after treatment by radioactive iodine (treatment of malignancies of thyroid gland). Development of secondary and tertiary forms of hypothyroidism is determined by pathologic processes on respective levels of thyroid gland regulation.

Primary hypothyroidism of adults is usually the result of pathogenetic chain which begins with autoimmune thyroiditis resulting in subclinical hypothyroidism and later into manifest hypothyroidism. Its development is slow and lasts for years (even a decade).

Main manifestations of primary hypothyroidism are:

- changes of mental functions (decreased memory capacity, slower thinking, loss of interest in surroundings, increased sleep), neuromuscular irritability is decreased,
- slower and monotonous speech,
- hoarse voice (due to changes of vocal folds – accumulation of glycosaminoglycans),
- body temperature is lower (around 35^0 C – heat production is decreased), decreased tolerance of cold,
- wax-like, dry skin (yellowish colour – deposition of carotene and development of myxoedema), hyperkeratosis of skin, fragile hair and nails, oedema of eyelids,
- myxoedema – accumulation of glycosaminoglycans in tissues in general, leads to morphologic changes in heart (heart is enlarged, dilated), changes of its function (decrease of contraction strength, bradycardia, decreased cardiac output),
- decrease of lipolysis, which contributes to weight gain and development of hyperlipidaemia (increased cholesterol, mainly VLDL and LDL fractions, decreased HDL cholesterol – result is acceleration of atherosclerosis – development of arcus lipoides

corneae),

- breathing is lowered and reactivity of respiratory system to its natural stimulants is decreased – increased $PaCO_2$ and decreased PaO_2 are the consequences,
- renal functions are lowered – glomerular filtration is decreased - retention of salt and water,
- protein synthesis in liver is decreased and degradation of steroid hormones is lowered,
- gastrointestinal motility is decreased (development of constipation), difficulties with swallowing.

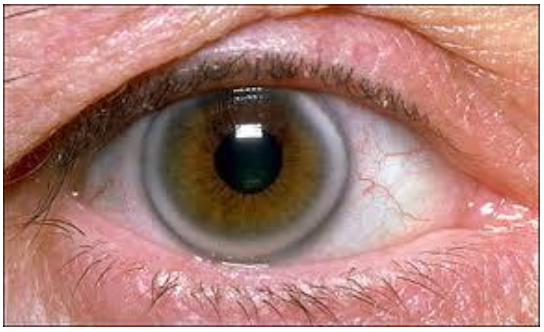


Figure 29.8: Arcus lipoides corneae

Pathophysiology of parathyroid glands and calcium metabolism

Homeostasis of calcium, phosphate and magnesium in organism is maintained by integrated and complex endocrine system, which consists of three regulatory parts:

1) Parathyroid glands synthetizing parathormone (PTH).
2) Parafollicular cells of thyroid gland synthetizing calcitonin.
3) Vitamin D.

PTH synthesis is regulated by concentration of ionized calcium, phosphates and magnesium in plasma. Decreased concentration of calcium and magnesium stimulates PTH synthesis and vice versa, increased levels of phosphates also increase secretion of PTH – not primarily, but secondarily due to decreased levels of ionized calcium in plasma. Other factors which stimulate PTH secretion include adrenaline, gastrin, ethanol, growth hormone, cortisol or vitamin A. On the other hand, some factors inhibit PTH synthesis – such as somatostatin or $PGF_{2\alpha}$. PTH is degraded mainly in liver and kidneys, therefore especially in renal insufficiency the PTH levels can increase to dangerous values. Physiologic concentrations of serum calcium are – ionized calcium 1.12 – 1.45 mmol/L, total calcium 2.2 – 2.6 mmol/L.

Hyperparathyroidism

It is a disorder characterized by **increased production of parathormone.** This can be a result of hyperfunction one or more parathyroid glands - **primary hyperparathyroidism.** It can develop as a result of primary hypocalcaemia, vitamin D deficiency in patients with intestinal malabsorption syndrome or with chronic renal failure - **secondary hyperparathyroidism.** One of the manifestation of increased production of PTH is development of **brown osseous tumours** and a disease called **osteitis fibrosa cystica,** also called renal osteodystrophy or von Recklinghausen disease. The results of primary hyperparathyroidism include:

Renal syndrome - characterized by kidney stones, renal colics, polyuria, polydipsia – it resembles diabetes insipidus (due to hypercalciuria the sensitivity of tubular cells to ADH decreases; nephrocalcinosis – deposition of calcium salts in kidneys).

Osseous syndrome – osteitis fibrosa cystica manifesting as diffuse pain of bones, growth retardation in children, development of pathologic fractures.

Gastrointestinal syndrome – functional dyspeptic syndrome (constipation, anorexia, vomiting), duodenal ulcers (hypercalcemia stimulates gastrin production), pancreatitis (conversion of trypsinogen to trypsin in pancreas), cholelithiasis (in bile oversaturated by calcium the crystals of calcium salts develop).

Hyperuricaemia syndrome – it is a result of decreased renal function, which manifests by increased concentrations of uric acid and deposition of its salts to synovial membrane and joint cartilage.

Neuromyopathy – develops as a result of increased concentration of calcium, which manifests as muscle weakness, increased exhaustion and decreased neuromuscular irritability. Its parts are apathy, depression, development of parasomnia with possibility of psychosis development as well.

Cardiovascular changes – bradycardia, shortening of QTc interval, increased sensitivity to digitalis-like compounds, arterial hypertension.

Hypoparathyroidism

It is a pathologic process caused by insufficiency of parathyroid glands, which manifests by decreased PTH secretion to physiological stimuli. The result is weakening or loss of ability to maintain calcium homeostasis with development of hypocalcaemia. **Causes of this process can be** damage during surgery or removal of parathyroid glands in surgery on

thyroid gland, autoimmune process, hypomagnesemia (development of resistance of peripheral tissues to PTH).

Manifestation of hypoparathyroidism includes:

- Alopecia, squamous skin, nail deformities,
- increased neuromuscular irritability due to decreased concentration of ionized calcium (sensitivity of sodium channels increases, which predisposes to increased excitability of membranes of muscle cells and neuron, as well as to their easier depolarisation). It manifests as paraesthesia around mouth, tingling of extremities, carpo-pedal spasms. These signs and symptoms are called **tetany.** Hypocalcaemic tetany caused by hypoparathyroidism in adults does not manifest by tetanic convulsions, but rather by organic, bizarre signs and symptoms, e.g.:
  - Anxiety and depression,
  - Migraineous headaches,
  - Parkinsonism (due to calcification of basal ganglia),
  - Hoarse speech and spasms of larynx, feeling of constricted chest and suffocation,
  - Epigastric pain,
  - Development of cataracts,
  - Elongation of QTc interval (risk of development of severe dysrhythmias).

CASE REPORTS

Case report 1

57-years-old woman came to the GP's office. The patient complained about increased fatigue during several last weeks. She also noticed increased heartbeat; she had and still has diarrhoea – 3-4 times per day. Within last few days she was barely able to walk up the stairs to her apartment or do some shopping. She noticed that she has swollen/enlarged frontal lower part of the neck. She was sweating more than usual and she tried to stay in colder parts of her apartment because she was hot everywhere. She lost 5kg of weight in the last month.

Upon physical examination, the GP found the following: 48kg body weight, irregular heart action, HR 120/min, BP 140/65 mmHg, atrial fibrillation (from ECG recording). He ordered a set of laboratory examination: red blood count normal, sedimentation 15/41, cholesterol 3.2 mmol/L, TSH 0.001; fT3 8 nmol/L; fT4 54 nmol/L; albumin 32g/L. She was referred to endocrinology specialist. He ordered another set of examinations: ultrasonography

of thyroid gland – diffuse enlargement without presence of nodules or foci and immunological examination which confirmed the presence of antibodies against TSH receptors

Questions & Tasks

1) Identify all relevant signs and symptoms of disease in this patient.

2) Which pathomechanisms contribute to development of individual signs and symptoms of the patient?

3) What type of immune disorder is described?

4) The patient can develop heart failure. Is this statement correct? If you think so, justify your opinion. If not, state why.

Case report 2

71-years-old woman, who is extremely sleepy within last few years. Her children noticed, that peripheral part of eyebrows had fallen out and both her forearms are swollen – the oedemas are stiff. One recent morning, when she barely got out of bed her children called the family doctor due to health concerns. Upon examination of the patient he found these signs and symptoms: BP 80/60 mmHg, peripheral pulses palpable - 46/min, stiff oedemas on both forearms and tibial regions. Arcus lipoides corneae was also present. Heart sounds were weakened upon auscultation. Thyroid gland was not palpable. ECG confirmed the heart rate 46/min; regular sinus rhythm, decreased voltage of QRS complexes, without any signs of acute myocardial infarction. TSH was18 nmol/L; therefore, blood was drawn to measure levels of T3 and T4. Cholesterol was 8.2 mmol/L.

Questions & Tasks

1) Summarize important signs and symptoms of this patient.

2) What are the mechanisms which contribute to development of individual signs and symptoms?

3) What kind of oedema is described in this patient?

4) What disease is described?

Case report 3 (Author: Dr. Lier)

18-years-old student, who visited her GP because she felt severe decrease of energy within last 6 months. Before that she was very active, she met with friends a lot and she was an active football player. Presently she can barely get out of bed in the mornings and her absence in school increases. She also reports repeated upper respiratory tract and urinary tract infections. Within last months she was repeatedly treated by various antibiotics, but after the treatment was finished the infection relapsed and she had to start another round of treatment. She is depressed and also reports decreased quality of life. Her doctor is convinced that she has some sort of chronic infection which is the cause of her weakness as well as repeated infections. The patient and her family lost faith in the doctor.

Over time, her condition slightly improved so she could go on vacation to Crete. Within two week she got intense tan – more intense than her friends. Colour of her skin was not only darker, but also local differences were visible in the intensity of colour. Skin was darker in the area of skin lines on hands and feet, around joint of upper extremities and knees. Her mother noticed this after her arrival home and remembered that her sister had similar skin manifestations. They visited the GP again, who referred the patient to endocrinology specialist. Before that he ordered laboratory examinations of blood and urine which shown following results: Na 119 mmol/L; K 4.7mmol/L; Cl 98 mmol/L; HCO_3^- 23 mmol/L; glucose 4.1 mmol/L; creatinine 103 μmol/L; serum osmolality 36 mOsm/L; urine osmolality 163 mOsm/L; Na in urine < 20 mmol/L, serum cortisol test used in this examination did not reveal significant changes of cortisol level.

Based on performed examinations the endocrinologist concluded that there is no disturbance of adrenal gland function, but mother requested that another test for determining the cortisol level was used or the previous test was repeated. Endocrinologist agreed, because upon further interview with the patient he found out that she was and is taking oral contraceptives and this can interfere with the accuracy of cortisol test. The result of repeated test showed that cortisol was less than 0.1 and ACTH was massively increased. Presence of autoantibodies was tested and positivity of anti-21OH was found (1:50/L).

Questions & Tasks

1) List all signs and symptoms which occurred during the course of disease.
2) Which pathomechanisms did contribute to development of individual signs and symptoms?
3) How would you explain extremely strong tan after sunlight exposure in this patient?
4) Which of the laboratory parameters could indicate the cause of signs and symptoms of this patient?
5) What diagnosis can be determined in this patient?

Case report 4

56-years-old woman visited the GP's office. She reported progressive fatigue, weakness and diffuse bone pain. These problems are present for longer time, but their intensity increased within last two months.

Personal history: arterial hypertension, well-controlled, kidney stones repeatedly

Physical examination: without pathologic findings; laboratory examination: serum calcium 4.95 mmol/L

Questions & Tasks

1) Identify signs and symptoms which the patient reports and explain the mechanisms of their development.
2) What causes can lead to hypercalcaemia?
3) What diagnosis can be determined in this patient?

Case report 5

69-years-old man visited the GP's office, who reported increased fatigue, nausea, weakness and diffuse bone pain. He also stated that these problems got worse within last two months. He also mentioned that during this time he lost 7kg of body weight. His wife, who accompanied him, added that he seems more and more confused.

Personal history: well-controlled arterial hypertension, chronic obstructive pulmonary disease (COPD). In the past, he was a smoker – he smoked approximately 100 packs per year (20 cigarettes per pack).

Physical examination: visibly sick, skinny. Vital functions: BP 120/80mmHg, heart rate 98/min, breathing rate 16/min with prolonged expiration rate and moderate crackles and

wheezes. In left basal pulmonary segment the respiratory sounds are weekend. Other parameters of physical examination are without noticeable changes.

Laboratory examination: serum calcium 5.76 mmol/L.

Questions & Tasks

1) Identify all the signs and symptoms of this patient.

2) Explain possible mechanisms of development of individual signs and symptoms.

3) How does hypercalcaemia influence neuromuscular irritability?

Case report 6

32-years-old woman in 6th month of pregnancy came to the ER department due to sudden cramp of right arm. She reports that it occurred during the folding of laundry, it developed suddenly, lasted for several minutes and ended spontaneously.

Personal history: Thyroidectomy due to tumour of thyroid gland 3 years ago. She is taking substitution therapy of synthetic thyroid hormones and prenatal multivitamins.

Physical examination: Chvostek sign positive, Trousseau sign positive, other findings without pathological changes.

Laboratory examination: serum calcium 1.25 mmol/L.

Questions & Tasks

1) Identify all signs and symptoms of this patient.

2) Explain the mechanisms of development of individual signs and symptoms.

3) What could be the cause of hypocalcaemia in this patient?

4) What levels of ionized calcium do you expect in this patient?

Case report 7

ER department was visited by 30-years-old woman after she scratched the neighbouring car while parking. She stated that this had already happened before and she feels that the cause of this can be her decreasing vision, because she noticed the neighbouring car only after she scratched its side. To the question whether she is injured she answers no, but she complains about headaches but not due to injury of any kind during the accident. Further she reported that the intensity of headache present occurred everyday within last three

months. She describes the pain as striking in the forehead area which intensifies when laying down which is also the cause that it sometimes wakes her from sleep.

Personal history: does not seem to be significant, denies drinking alcohol, smoking or taking drugs. She noticed that her period is irregular, but she denied having other health conditions-

Physical examination: vital functions normal, breast examination – galactorrhoea; Neurologic examination – bitemporal hemianopia present.

Questions & Tasks

1) Identify all important signs and symptoms in this patient.
2) Can you explain the mechanisms of development of these signs and symptoms?
3) Could there be a connection between the patient's headaches and her driving abilities?
4) What pathological process can cause vision field disturbances?

Case report 8

60-years-old man was admitted to the ER by an ambulance. Based on his wife's interview, his health was fine until yesterday – he only seemed confused a bit. Next morning, he did not wake up in his usual time, he was still sleeping and she could not wake him up and therefore, she had called an ambulance.

Personal history: long-time smoker – smokes 40 packs/year (20cigarettes/pack).

Physical examination: patient reacts only to painful stimuli, but does not talk or respond to commands.

Laboratory examination: serum Na 120 mmol/L; chest X-ray: 2 cm circular shadow on right lung.

Questions & Tasks

1) Identify all signs and symptoms in this patient.
2) Which causes and mechanisms could contribute to patient's health problems?
3) What pathologic process needs to be considered in given X-ray finding?
4) In this patient, there is a disturbance of consciousness – what could be its cause? Explain the contribution of individual pathomechanisms.
5) What do you understand under the term "paraneoplastic syndrome"?

Chapter 30

PATHOPHYSIOLOGY OF BLOOD

Hematologic system is the most diverse, most adaptable, most coordinated and most effective system that nature has ever created. It is a system equipped by control mechanisms which can be envied even by engineers of Apollo project (Isbister JP & Harmening D, 1988. *Clinical haematology: A problem-oriented approach*. Baltimore: Williams & Wilkins).

Volume of blood in human organism correlates with its lean body weight (without adipose tissue), which represents 3.6 L in women and 4.5 L in men on average. Blood fulfils many important functions:

- transport of different substances to or out of tissues – oxygen, carbon dioxide, nutrients, vitamins, electrolytes…,
- transport and distribution of heat and signals (e.g. hormones),
- works as a buffer and defensive system,
- exhibits coagulation and anticoagulation properties,
- contributes to maintenance of homeostasis in organism (e.g. volume of fluids, acid-base balance)

Both formed elements, as well as substances dissolved in fluid compartment of blood (plasma) contribute to these functions. Erythrocytes (Er) maintain the transport of O_2 and CO_2, leucocytes – neutrophils (Ne) contribute to non-specific immunity, monocytes (Mo) and lymphocytes (Ly) contribute to specific immunity. Platelets (thrombocytes – Tr) are important for normal blood coagulation. Plasmatic proteins play an important role in humoral immune defence, in maintenance of adequate oncotic pressure, in transport of substances insoluble in water and their protection from degradation by active substances present in blood. Bond of hormones, medications and toxins to plasmatic proteins decreases the intensity of their immediate action and decreases their elimination from organism. Whole array of proteins contributes to blood clotting and fibrinolytic processes.

Pathophysiology of red blood cells

Disturbances of Er can be quantitative or qualitative, structural and functional. The most important disturbances from them are **anaemias and polycythaemias.**

Anaemias

Anaemias are pathological processes, which are characterized by decreased Er count, decreased amount of haemoglobin (Hb) in Er and decreased haematocrit (Hc) in unit of blood under reference values in normal total blood volume.

Different causes and mechanisms, which contribute to development of anaemias, exist. Based on etiopathogenetic criteria, following types of anaemias are known:

a) caused by increased Er loss,

b) caused by decreased production of normal Er or production of defective Er

First group includes anaemias caused by **bleeding** (acute and intense or chronic and weak), **haemolysis** (caused by defective Er or by noxae present in blood).

Second group includes anaemias occurring in disseminated malignant processes (e.g. leukaemia), in severe non-malignant chronic diseases of inflammatory and non-inflammatory origin, hypovitaminoses (vitamin $B_{12,}$ folic acid, vitamin C), in iron deficiency and in bone marrow failure.

Genetic factors can also contribute to development of anaemias in both groups. The type of anaemia depends on the phase Er creation in which action the haemophilic noxa acts. If it acts on pluripotent haematopoietic stem cell and causes stoppage differentiation it, the result will be **panmyelopathy -** disturbance of production of all types of formed blood elements. Noxa (e.g. viruses, antibodies against erythropoietin or against membrane proteins) can also act on later developmental stages of blood elements, e.g. on precursor of red line, and its result is **isolated aplastic anaemia.** Erythrocyte precursor cell cannot develop further if erythropoietin (EPO) is missing which can happen in severe renal damage – **renal anaemia** develops. Proerythroblast – next stage of Er development can be blocked by a genetic defect or deficiency of important vitamins (vitamin B_{12}, folic acid, and it can manifest negatively by development of **megaloblastic anaemia.** Under physiologic condition proerythroblast turns into erythroblast with synthesis of hem and globin. If the components for Hb synthesis are missing (iron deficiency, defect in synthesis of hem or globin), then **microcytic hypochromic anaemia** develops. Even after the release of mature Er from bone marrow to blood their deficiency can occur due to defect in their composition/structure or they are released into environment with conditions unfavourable for newly released Er. Both situations shorten their life span in blood. The result is than a group of **haemolytic anaemias.**

They are divided into **corpuscular –** the reason of shortened life span is within the Er itself (e.g. in their composition) and **non-corpuscular –** the reason of their shortened life span is outside of Er (e.g. mechanic, immunologic, toxic factors). Haemolytic anaemias are accompanied by increased synthesis of EPO and its concentration in blood which leads to compensatory stimulation of Er production.

Important and/or common types of anaemias include **iron deficiency anaemia, pernicious anaemia, aplastic anaemias, sickle-cell anaemia, haemolytic anaemias, anaemias in chronic diseases and thalassemias.**

1) Iron deficiency anaemias

Iron present in organism is bond mainly in Hb (2/3); the remaining third is represented by iron storage (ferritin, hemosiderin) and iron in myoglobin and in enzymes. In physiologic conditions, the iron intake and its loss are balanced. Main **source of iron** is food of which 3-15% of iron is resorbed, in iron deficiency up to 25%. The form in which iron is easiest resorbed is in **hem form (heme-Fe^{2+})**, which is contained e.g. in red meat and fish. After division from hem the Fe^{2+} is resorbed into blood or stays in intestinal epithelial cells in form of ferritin – Fe^{3+}. This form of iron returns into intestinal lumen inside of desquamated epithelial cells. **Non-hem iron** contained in plants is absorbed by intestinal mucosa only in Fe^{3+} form in symport with H^+ carrier. It is obvious, that low pH for this absorption is necessary. On the surface of mucosa, Fe^{3+} must be reduced to Fe^{2+}, which can be absorbed by epithelial cells. Iron transport from intestinal mucosa to blood requires oxidation of Fe^{2+} to Fe^{3+}. Iron reacts in blood with apotransferrin to creation of transferrin by which it is transported into bone marrow, where transferrin binds to transferrin receptors of erythroblasts and releases iron from its bond. Iron subsequently binds to hem in Er. Storage forms of iron are ferritin (fast supply) and hemosiderin. Iron in organism is recycled from malformed erythroblasts and erythrocytes after their haemolysis.

Main causes of iron deficiency anaemias include:

- Loss of blood from damaged GIT, in stronger menstrual bleeding, in chronic infections (due to proinflammatory cytokines IL-1, IL-6, $TNF_{\alpha)}$ the amount of reused iron absorbed by macrophages decreases,
- Low iron intake in food,
- Decreased iron absorption due to achlorhydria and types of malabsorption (e.g. due to

pathological processes located in upper part of small intestine) or due to bond of iron to phytates, cereals, vegetables, gallic acid (teas) and oxalates,

- Increased needs of iron, e.g. in children during growth, in pregnancy, during breast feeding.

The relationship between tannins contained in teas and intestinal iron resorption is interesting. Resorption of iron contained in plant sources is decreased significantly by tannins, e.g. 1 cup of tea decreases iron resorption from plants by 30-60%, but does not change the resorption of hem iron. This effect should be noted especially by vegetarians, because combination of diet exclusively of plant origin and tea drinking can result in iron deficiency anaemia. Iron deficiency anaemia is **microcytic and hypochromic.**

2) Megaloblastic anaemias

This group, apart from others, includes **pernicious anaemia** as well. Basic disorder which leads to development of anaemias of this type is insufficient intake or disturbance of metabolism of **folic acid** (vitamin B_9) or **cobalamin** (vitamin B_{12}). The result is limitation of DNA synthesis and lowered cell cycle of hematopoietic (but not only these) cells. Development of nuclear mass of erythroblasts is slowing down whereas the synthesis of Hb in their cytoplasm continues normally, which leads to development of large erythroblasts called **megaloblasts** and after the decay of their nuclear matter large, ovoid Er called **megalocytes** (volume > 100fl). Production of **granulocytes and megakaryocytes** is disturbed as well. Anaemia develops due to slower proliferation of Er, as well as haemolysis of megaloblasts (decreased resistance) in bone marrow (ineffective erythropoiesis) and premature decay of megalocytes in peripheral blood (premature haemolysis). The following population groups are at increased risk of development of this type of anaemia - seniors (> 60 years), people consuming a lot of antacids, adolescents with vegetarian diet, patients with chronic diseases of stomach, small intestine and after surgery on these parts of GIT, patients with chronic infections and alcoholics. Deficiency of folic acid for Er formation can develop due to **decreased intake** of folic acid (it is degraded by long cooking times of food which contain it – beans and other legumes, greens, poultry, pork, liver and sea food), low intake of citrus fruits and citrus fruit juices, whole-grain pastry and wheat bran. Folate is stored in liver and its insufficient intake will not manifest immediately, but after 2-4 months. Other reasons for its deficiency can be **increased demands** of organism (e.g. pregnancy) or **malabsorption**

caused by dysfunction of small intestine or therapeutic administration of methotrexate and **vitamin B_{12} deficiency.**

Causes of **cobalamin** deficiency are mainly **insufficient intake** (e.g. in strictly vegetarian diet, in deficiency of **intrinsic factor** due to damage of gastric mucosa – atrophic gastritis, decreased availability of intrinsic factor in intestine due to **bacterial or parasitic infection, damage or absence of terminal ileum).** Due to sufficient supply of cobalamin in organism (in physiologic conditions) the manifestations develop after years of decreased supply to the organism. The result is **megaloblastic type of anaemia.**

3) Aplastic anaemias

This type of anaemias is caused by **inability of bone marrow to produce sufficient quantity of new Er.** In development of these disorders more factors which have the potential to **cause damage to haemopoietic stem cells** of bone marrow can be involved. The result is not only anaemia, but leukopenia and thrombocytopenia as well. Bone marrow, according to degree of damage, can be **hypoplastic** (it contains only small amount of stem cells) or **aplastic** (bone marrow is "empty" – does not contain any hematopoietic stem cells).
Following steps are suggested in development of aplastic anaemia:

a) genetically determined change to bone marrow,
b) hypoproliferation of haemopoietic cells,
c) development of immune reaction against changed cells.

Aplastic anaemia can be a result of direct toxic influence of ionizing radiation, chemotherapy, some specific chemical compounds (e.g. benzene) and intermediary metabolites of some medication to bone marrow. Immune reaction against haemopoietic cells develops, e.g. after transfusion of inadequate blood (group mismatch), eosinophilic fasciitis, in some forms of hepatitis, in pregnancy, but it can also develop without any know cause (idiopathic form).

4) Sickle-cell anaemia (SCA)

It is a disease which has two forms – **haematogenic and vasoocclusive form.** Main disturbance in SCA is production of abnormal Hb – **HbS.** This form of Hb exhibits different properties than normal form of Hb – e.g. HbS forms polymers in low partial pressure of oxygen environment, what causes the change or Er shape (see picture). HbS also causes changes of Er membrane function, which manifests by decreased elasticity and flexibility of

Er, which leads to worsened transport of such Er through capillary network – they can even block it. These Er are also more fragile, which leads to shortening of their life span to approximately 15-20 days. The result of obturation of capillary network by rigid Er is tissue hypoxia followed by tissue damage accompanied by pain and organ changes (e.g. autosplenectomy). The result is haemolytic anaemia.

Figure 30.1: Sickle-cell anaemia – typical change of shape of Er.

5) Post haemorrhagic anaemias (PHA)

Their causes are different types of bleeding. It can be **acute bleeding** (internal or external), usually with massive blood loss. This kind of blood loss can primarily manifest as hypovolemia or hypovolemic shock. Anaemia – usually **normocytic and normochromic** – develops sometime after blood loss in case the lost blood was not sufficiently substituted by Er production in bone marrow. Anaemia develops as a result of activation of compensatory mechanisms evoked by blood loss. First of them is supplementation of lost intravascular volume from blood reservoirs, fluid from interstitial compartment and water retained by kidneys, which leads to blood dilution – **dilution anaemia.** Another compensatory mechanism is the replacement of missing Er by their increased production in bone marrow (for 4-6 weeks). But these elements can contain less Hb – they are hypochromic and they can be also smaller – microcytes and can be also "young" – reticulocytes; **microcytic hypochromic** anaemia develops. Complete replacement and correction of acute PHA takes 6 to 8 weeks – the last one to be corrected is the Hb level, because its synthesis takes the longest time from aforementioned processes. In **chronic bleeding** with small, repeated blood losses (e.g. occult bleeding from GIT) rather **iron deficiency anaemia** than PHA develops.

6) Haemolytic anaemias (HA)

Their characteristic sign is **premature destruction of Er** in normal erythropoietic process. The result is **premature destruction of Er and decreased concentration of Hb.** Erythropoiesis can be significantly accelerated, but does not necessarily have to be sufficient to adequate substitution of Er lost due to haemolysis.
HA are divided into **acquired and hereditary.**

The **causes of acquired HA** include:

- infections – bacterial (*Clostridium sp., Salmonella typhi* ...), protozoal provenance (e.g. malaria, toxoplasmosis),
- systemic diseases, e.g. lupus erythematosus,
- some medications, toxins,
- diseases of liver and kidneys,
- abnormal immune reactions, e.g. post-transfusion reactions, haemolytic disease of new-borns, autoimmune haemolytic anaemia.

Hereditary HA can have plenty of reasons. The basic one is **production of abnormal Er – e.g.** membrane defects, missing of some metabolic enzymes, disturbance of globin synthesis. For example, deficiency of glucose-6-phosphate dehydrogenase, which maintains oxidation stability of Hb, is the most common inherited erythrocyte enzymopathy carried by approximately 400 million carriers and it leads to haemolysis, which occurs in intravascular space or in lymphoid tissue.

Main pathomechanisms of HA development include:
a) Autoimmune mechanism – e.g. HA caused by heat or cold antibodies, HA caused by medication. HA caused by heat antibodies include anaemias occurring in chronic lymphatic leukaemia, tumours of lymphoid tissue, systemic lupus erythematosus. HA caused by cold antibodies occur as a complication of mononucleosis, in pulmonary infection caused by Mycoplasma pneumoniae.
b) Other types of pathomechanisms – e.g. physical destruction of Er (trauma, artificial heart valves), heat and radiation (thermal haemolysis, radiation haemolysis), hypophosphatemia**.**

7) Anaemias in chronic diseases

They develop in severe chronic infectious and non-infectious diseases. Primary cause of their development is decreased production of Er. Anaemia is **usually normocytic and normochromic,** but approximately 30-50% of patients can have hypochromic and microcytic type of anaemia, too. **Three mechanisms** contribute to development of this form of anaemia – **failure of erythropoiesis, disturbance of iron metabolism and shortened life of Er.**

8) Thalassemias

This is group of genetically determined anaemias, which belong to group of haemoglobinopathies. Basic disturbance is abnormal globin chain synthesis - α or β chain, which manifests by changes of Hb properties, damage to Er membrane and haemolysis. **Hypochromic microcytic anaemia and haemosiderosis** will develop. Haemosiderosis causes damage to myocardium, liver, β-cells of pancreas, spleen and lymph nodes. Thalassemia manifests by **anaemic syndrome** - weakness, breathlessness, pale skin, vertigo), enlarged spleen and sometimes jaundice.

Pathophysiology of white blood cells

White blood cells (leukocytes – Le) are a part of immune system and their role is to fight against infection and other types of antigens. Approximately 70% of Le are polymorphonuclears and 30% mononuclears. They are divided into 5 subtypes: basophils, eosinophils, lymphocytes, monocytes and neutrophils. Their pathological changes have three main forms:

- increased count
- decreased count
- changed structure and function

Combination of aforementioned forms are common. Basic disturbances include:

Agranulocytosis – decreased count of granulocytes (neutrophils, eosinophils, basophils) in blood, which can be caused by increased loss or decreased production these types of cells in bone marrow. In the case of decrease of granulocytes (namely neutrophils) to 2,000 – 500/mm^3 the defence mechanisms of organism against bacterial infections will be decreased. The result can be even neutropenic sepsis.

Leukopenia – decreased count of Le in blood below 5,000/mm^3, which is associated with increased risk of bacterial and fungal infections. It is caused by several factors, e.g. prior infection, chemotherapy, radiotherapy, as well as by some antibiotic medication.

Infectious mononucleosis – disease also known as **glandular fever** transmitted for example by kissing, occurs in children and adolescents. It manifests by lymphocytosis (mononuclears) with large proportion of morphologically changed lymphocytes, fever, headaches sore throat, enlarged lymph nodes, loss of appetite and malaise. Sometimes it is accompanied by complications, such as rupture of spleen or liver, development of haemolytic anaemia.

Myelodysplastic syndrome – it is haematological disorder manifesting by ineffective production (dysplasia) of myeloid cells in bone marrow. Its cause is suggested to be gene mutation at a level of pluripotent stem cell. However, definitive identification of gene mutation factor was not found yet. The result of disorder (based on type) can be anaemia, thrombocytopenia and/or acute myeloid leukaemia.

Myeloproliferative diseases – is a group of disturbances of haemopoiesis characterized by transformation of hematopoietic stem cell which manifests by uncontrolled proliferation and disturbed differentiation of erythrocytic, granulocytic a megakaryocytic line. The result is development of metaplasia and myelofibrosis. Transformation of normal haemopoietic stem cell into leukemic requires two mutations to take place – mutation of gene for receptor tyrosine kinase (leads to increased proliferation ability) and mutation of genes for haemopoietic transcription factors (development of differentiation block). By combination of both disorders e.g. acute myeloid leukaemia develops. To this group belong diseases such as chronic leukaemias – myeloid, granulocytic, eosinophilic; myelofibrosis, polycythaemia vera, primary thrombocytopenia.

Myelofibrosis – is clonal neoplastic disturbance of haemopoiesis and is a part of myeloproliferative disturbances. Abnormal clone of haematopoietic cells (especially megakaryocytes) produces cytokines, e.g. fibroblast growth factor, which leads to substitution of haemopoietic tissue of bone marrow by collagen fibrosis followed by loss of ability of bone marrow to produce formed elements of blood – pancytopenia develops. Extramedullar haemopoiesis occurs, which manifests by hepatomegaly and splenomegaly.

Leucocytosis – is name for increased Le count in blood and belongs to most common changes of blood count; it is a laboratory finding not a disease. Causes can be infectious and non-infectious. Based on causative agent, increase of individual types of Le can be seen (most commonly neutrophilia, but also eosinophilia, basophilia, monocytosis,

lymphocytosis). Infectious causes of leucocytosis are commonly known, the non-infectious causes are lesser known. They include extreme exercise, cramps (epilepsy), emotional stress, pregnancy and labour, anaesthesia, administration of adrenaline. Neutrophilic leucocytosis develops in intense bone marrow stimulation by inflammatory mediators with "left shift", what means increased proportion of young developmental forms of Le in blood. Opposite situation occurs in bone marrow function suppression; so-called "right shift", what means prevalence of "older" and decreased proportion of "young" Le in blood. This happens e.g. in pernicious anaemia or radiation sickness.

Healthy bone marrow can react to extreme stress, trauma or infection by production of large amounts of Le, e.g. $25 – 30 \times 10^9$ /L, what is called **leukemoid reaction.** Change in blood count resembles leukaemia (hence the name), but it differs by absence of immature, or mature but dysfunctional Le, respectively.

Not only count, but function of Le can be changed as well. Disturbances of neutrophils include:

- Disturbance of their migration ability and chemotaxis – syndrome of "lazy" Le develops and it manifests by delayed Le invasion in the area of damaged tissue,
- Disturbance of phagocytosis and destruction of microbes – is determined by e.g. myeloperoxidase deficiency in neutrophils and it manifests by chronic granulomatosis.

Disturbances of haemostasis

Haemostatic system protects the organism from excessive blood loss by means of external or internal bleeding. It consists of **plasmatic factors, platelets and vascular wall**. Their interaction secures closure of wound in vascular wall by development of "white thrombus" from platelets followed by development of fibrin network ("red thrombus") by the action of plasmatic coagulation system, which stabilizes the primary thrombus. This system is also equipped by some "brakes" – inhibitory mechanisms, which prevent inadequately strong coagulation reaction; to fulfil this balance in healthy people the balance between procoagulation and anticoagulation mechanisms exist. Disposal of redundant thrombi is maintained by fibrinolytic system of blood.

Function of these systems can be disturbed by **action of internal and/or external noxae**. It manifests by **tendency to bleeding or thrombosis.**

Risks for increase tendency to bleeding (haemorrhagic diathesis) can be following mechanisms:

a) disturbance of coagulation system,
b) disturbance of fibrinolytic system,
c) decreased count and/or function of platelets,
d) defects of vascular wall.

Processes listed under a) and b) lead to development of massive haemorrhages to soft tissues and joints (development of haematomas and haemarthros), whereas the disturbances listed under c) and d) manifest rather by small haemorrhages – point haemorrhages (petechias).

Plasmatic haemorrhagic diatheses (listed under a and b) can be of hereditary origin. Most well-known of these are haemophilias and of them especially haemophilia A, which is caused by factor VIII deficiency. Development of congenital coagulopathies is related to decreased synthesis of coagulation factors, their inhibition, e.g. by heparin, with synthesis of autoantibodies against coagulation factors, e.g. against factor VIII or to high consumption of these factors (consumption coagulopathy – e.g. in septic shock). Very common causes of acquired coagulopathies are severe liver diseases as well as vitamin K deficiency or its inhibition.

Haemorrhagic diatheses of thrombocytic origin develop in thrombocytopenias or thrombocytopathies. These can be both congenital and acquired. Acquired are more common and their causes can be processes such as aplastic bone marrow, phosphate and cobalamin deficiency, their increased degradation (e.g. in enlarged spleen – hypersplenism). When the Tr count decreases below 20×10^3 /μl of blood, the risk of bleeding increases. Whole array of other causes, which can cause decreased count or quality of Tr students can find in textbooks on haemostasis. From these, at least acetylsalicylic acid needs to be mentioned which prevents Tr aggregation and is used in prevention of thrombosis in arterial system of organism.

According Thiagarajan (2016), platelet disorders lead to defects in primary haemostasis and produce signs and symptoms different from coagulation factor deficiencies (disorders of secondary haemostasis). The body's reaction to vessel wall injury is rapid adhesion of platelets to the subendothelium. The initial haemostatic plug, composed primarily of platelets, is stabilized further by a fibrin mesh generated in secondary haemostasis. The arrest of bleeding in a superficial wound, such as the bleeding time wound, almost exclusively results from the primary haemostatic plug.

Hence, primary haemostatic disorders are characterized by prolonged bleeding time, and the characteristic physical examination findings are petechias and purpura. In comparison, defects in secondary haemostasis result in delayed deep bleeding (e.g., into muscles and joints) and the characteristic physical examination finding is haemarthrosis. Haemarthrosis and muscle hematomas are not present in primary haemostatic disorders (Thiagarajan, 2016).

Haemorrhagic diatheses of vascular origin develop in defects of vascular endothelium, in which the production of von Willebrand factor (vWF) is decreased or completely absent. vWF is carrier of factor VIII; therefore, the result is increased risk of haemorrhage caused by absence of aforementioned factor. Other types of disturbances of vascular wall quality (e.g. abnormality of connective tissue) exist, which weaken the vascular wall and results in bleeding in skin and mucosal membranes, e.g. in vitamin C deficiency or in immune reactions in vascular wall.

CASE REPORTS

Case report 1

52-years-old man complains about chest pain, breathlessness when walking up the stairs and nausea. Patient is depressed and is reporting frequent cough. Physical examination of the patient revealed jaundice, ataxic gait, dysdiadochokinesis and positive Babinski's sign. Furthermore, massive subcutaneous haemorrhage was found in area of left hip.

Laboratory results: HCl is missing in gastric juice (both fasting and after pentagastrin test). Hematologic examination showed presence of large Er in peripheral blood – many of them contain nucleus. Er count 1.4×10^{12} /L, haematocrit 0.21, Hb 4 mmol/L (reference values for men 8.6 – 11.2 mmol/L). Bleeding time was 90 min and platelet count was 50×10^{9} /L. Vitamin B_{12} concentration in serum was 90ng/L. Total bilirubin was 18mg/L (unconjugated form was increased). Decreased production of intrinsic factor from parietal cells of gastric mucosa was also found (special test which utilizes radioactive vitamin B_{12} was performed)

Questions & Tasks

1) Identify all signs and symptoms in the presented case report.

2) Explain the mechanisms of development of individual signs and symptoms.

3) Do you expect changes of white blood count in this patient? If so, what kind of changes do you expect? If not, then why?

4) Do you expect some activation of compensatory mechanisms in this patient? If so, which ones? If not, why?

5) What is the possible diagnosis in this patient?

Case report 2

65-years-old patient previously healthy was admitted to Clinic of Internal medicine. Now he complains about severe fatigue, which gradually increased during last three months. Upon further interview, it was revealed that patient fells diffuse fatigue and breathlessness while walking up the stairs from ground floor to 1st floor. These difficulties were becoming more intense over time. Patient denies other health problems.

Physical examination: pale skin, vital function normal; per rectum examination – dark brown stool, occult GIT haemorrhage test positive; laboratory examination: decreased Er count.

Questions & Tasks

1) Identify all relevant signs and symptoms of the patient.

2) Which mechanisms contribute to their development?

3) Do you mean that patient may suffer from anaemia? If yes, what type of anaemia it is and what is its possible cause?

4) What kind of blood count changes can be seen in evaluation of blood smear of this patient?

5) Which other examinations should be performed to confirm the diagnosis?

6) Explain the pathomechanisms contributing to patient's increased fatigue, paleness, dyspnoea.

7) Which other signs and symptoms could be present in this patient?

Case report 3

The ER was visited by 20-years-old woman with history of gum bleeding for 2 weeks and very strong menstrual bleeding.

Physical examination: pale skin and conjunctiva, enlarged spleen, petechias on lower extremities.

Laboratory examination of blood: Le 178,000/mm^3, Hb 78 g/L, Tr 25,000/mm^3, blasts - 30% of white blood cells.

Questions & Tasks

1) Identify all signs and symptoms of this patient.

2) Which pathomechanisms contribute to development of these signs and symptoms?

3) Which causes can be responsible for aforementioned problems of this patient?

4) What is the probable diagnosis?

5) Which other signs and symptoms could develop in this patient?

6) Which other examinations need to be performed for diagnosis confirmation?

Case report 4

Mother came to the hospital with 6-years-old son due to three days long nausea and fever approximately around 38.5°C. The boy does not have any localized problems.

Personal history: repeated febrile states. According to his mother he is ill practically every month.

Physical examination: manifestations of cervical lymphadenopathy, visible ulcerations of oral mucosa.

Laboratory examination: blood Ne count is 200/µl

Patient was admitted to the hospital. Cultivation of blood, urine and cerebrospinal fluid was negative. Repeated examination of blood after 48h revealed that Ne count went back to normal. Given the history information this seems to be repeating in cycles.

Questions & Tasks

1) Identify all signs and symptoms in this child.

2) Try to explain the mechanisms of development of individual signs and symptoms.

3) Can this case report present cyclic neutropenia? What is it?

4) What manifestation supports aforementioned diagnosis?

Chapter 31

AGEING AND TERMINAL STAGES

Ageing is continuous biologic process, which begins with birth of an individual. It is one of basic developmental manifestations of life and senescence is only life's final stage. Ageing is a complex of changes in structure and function of organism, which determine its increased vulnerability, decrease of abilities and endurance of an individual and which result in terminal stage and death. Ageing is not a pathologic change, but normal biologic process of all organisms.

It is important to note that demographic data show significant ageing of population, which is caused by both changes of lifestyle of seniors as well as more effective healthcare and prevention (survival of seniors is longer) coupled with decreased natality. Ageing is characterized by some specific features – changes in biochemical reactions, increased morbidity and mortality, decreased ability of reparation processes (wound healing), decreased adaptation to changes and progressive weakening of physiologic processes. It is very hard to determine whether the changes seen in seniors are caused by ageing or by associated pathologic processes (diseases), which increase with age. We assume, that final condition of an individual is a combination of both ageing and results of illnesses which affect the individual.

In ageing population, we state the individual's age. We can distinguish chronologic, biologic, psychologic and social age. **Chronologic age** is given by birth date. **Biologic age** is determined by physic state of an individual. Examples of indicators of biologic age can be blood pressure, vital capacity of lungs, grip strength of fist, reaction to visual/audible stimuli, vision, cholesterol levels and many other. **Psychologic age** is determined by agility and comfort. Intensity of social life and social interactions determines **social age.**

Based on age, several categories can be distinguished in the process of ageing, but their definitions are unclear. There are great interindividual differences in both manner and speed of ageing. For the dynamics of ageing, the genetic, ecologic, nutritive, social and many physiologic and pathologic factors of the environment play an important role.

Definition of age categories by WHO

World health organization defines age categories as follows: middle age 45-59 years, higher age (presenium) 60-74 years, old age (senium) 75-89 years, very advanced age (longevity) – above 90 years. Although ageing has more dimensions – biologic, psychologic

and sociologic, the focus of medicine is mainly healthcare of ageing population. Within medicine, a distinct specialty occurred – **geriatrics** – a medical speciality which focuses on diseases of ageing and assessment of degenerative changes that accompany ageing.

Causes of ageing, theories explaining ageing of organism

The effort to maintain youth and slow the ageing process has always fascinated scientists. The result of these activities is existence of approximately 300 theories at the moment, which explain ageing based on different mechanisms. The simplest theory is the theory of **deterioration of organs** by their repeated use. In general, these theories can be divided into two groups as follows:

1) Pre-programmed (determined genetically and regulated by some endogenous "clock")
2) Caused by damage (error theory) and response to it, which mostly assumes environmental factors and their influence on organism as a whole.

Although **genetic theories** state, that each species has given lifespan, but importance of **genetic predisposition** and its influence on ageing is showed by **longevity in some families,** as well as progeria (a disease characterized by rapid onset of ageing in childhood), which highlights the role of genes in this process. These theories of ageing explain, that each cell has **limited number of mitoses**, which can be repeated and afterwards it will stop.

Furthermore, the theories of ageing point to increased occurrence of **mutations of some genes with limited ability of DNA reparation mechanisms.** Mutations of somatic cells can lead to **change of surface antigens,** which cells manifest to surroundings. Antigen change activates immune system, which initiates autoimmune response to this changed tissue (cell clones) which leads to tissue damage – these mechanisms are basis of **immunity theory** explaining ageing. It is proven that occurrence of autoimmune diseases increases with age. Immunity theories also explain overproduction of intercellular matrix with simultaneous apoptosis or necrosis of cells in form of overproduction of growth factors, e.g. bFGF (basic fibroblast growth factor).

Endocrine theory postulates, that ageing process is regulated via biologic clock and they are controlled by hormones. Molecule, which contributes to this regulation is IGF-1 (insulin-like growth factor 1). **Metabolic-toxic theories** explain ageing by accumulation of molecules with potentially cytotoxic properties, such as oxygen radicals, lipofuscin, calcium, cholesterol, amyloid and so on.

Changes in organism affected by ageing

Cardiovascular system – myocardium is affected by hypertrophy and fibrotisation of cardiomyocytes, there are degenerative changes on valves in progress, such as fibrotisation, sclerotisation and calcification; there is also steady decrease of cardiac output. Peripheral vascular resistance increases due to increased rigidity of vessels and progression of atherosclerosis. Typically, there is an increase of diastolic blood pressure.

In **respiratory system**, the compliance of chest decreases with age and reduction of vital lung capacity can be observed in increase of residual volume. There is no actual decrease of volumes and capacities, but it is a result of inability of respiratory muscles to perform manoeuvres in spirometry testing; the PEF value is reduced as well. In seniors, we also observe decrease of function of defensive reflexes of the airways and reduction of efficacy of mucocilliary transport and cough leads to more frequent viral/bacterial infections of respiratory tract. Thickening of alveolocapillary membrane can contribute to occurrence of oxygen gradients between alveoli and arterial blood.

In **uropoetic system,** decrease of number of functioning glomeruli, renal blood flow and glomerular filtration rate can be observed. In women, the presence of stress incontinence coupled with repeated infections of urogenital tract can be observed. Typical change in males is benign prostatic hyperplasia coupled with urine retention.

Gastrointestinal system decreases its activity, which manifests as dysphagia, diaphragmatic hernias, large intestine diverticulosis motility of gastrointestinal system decreases and the ability of digestion and resorption of nutrients is limited. Metabolism is decreased, as well as heat production in organism.

In endocrine system, the concentration of STH decreases, glucose tolerance is limited. There are also changes in sex hormone production (menopause and andropause).

In general, **mobility of seniors** is decreased due to degenerative changes of joints with limited regeneration of joint cartilage and skeletal muscles, which atrophy. There is also a decrease in bone matrix (osteoporosis), which predisposes to occurrence of pathologic fractures (spontaneous or after minimal trauma). **Striated muscles atrophy,** which manifests by decreased strength and endurance and increased exhaustion in physical activity. **Body height** decreases as well as overall physical appearance of elderly person (slouching of posture). **Skin** atrophies, wrinkles occur due to decrease of elastic fibres; due to decrease of melamine production **hair turn grey** and hair follicles atrophy. Seniors often have anaemia caused by decreased resorption of iron, rigidity of red blood cells increases, their lifespan shortens; the reactivity of white blood cells and platelet adhesive properties decrease which predisposes to thrombotic complications.

Central and peripheral nervous system undergo degenerative changes as well, most commonly vascular origin of degeneration – due to atherosclerosis of cerebral arteries. Atrophy of neurons is responsible for increased occurrence of neurologic and psychiatric disorders in older age, e.g. depressions, dementias, sleep disturbances, disturbances of short-term memory with long-term memory being intact. **Changes of mood and behaviour** (quarrelsomeness, weepy moods) are typical in seniors as well. Velocity of conduction decreases in peripheral nervous system. The **senses** are weakened as well.

Terminal stages

Ageing of organism ends with biologic death of an individual, as well as chronic progressive diseases and acute pathologic processes irreconcilable with life result in death of an individual. Death is preceded by terminal stages. **Thanatology** is science discipline focusing on death and mechanism of dying. **Death** is defined as termination of existence of an individual as bio – psycho – social entity, whereas **dying** is unclearly limited period of time and its last phase is called **terminal stages.**

Pathophysiology of processes leading to death of an individual is influenced by characteristics of disease which leads to death – course is different in acute conditions (acute myocardial infarction, massive pulmonary embolism, polytrauma, …) when individual dies from seemingly "full health" and different in chronic irreversible diseases (cancer, chronic renal failure, chronic respiratory insufficiency, muscle dystrophies and so on). In case of chronic diseases, patient undergoes not only somatic, but psychic changes as well, which change the course of underlying disease mostly by **chronic stress reaction –** distress. Patient goes through phases of **negation** (patient denies that he suffers from incurable disease), **aggression** (anger aimed towards doctors, other personnel, relatives and himself), **negotiation** (mobilization of reserves – if possible; to finish some unfinished activities) and through phase of **depression** the phase of **acceptance.** These phases are not clearly limited and their perception is individual.

Approximately **1 month prior to death** following changes occur: decrease of appetite, because organism does not need high amount of energy and regulatory mechanisms lead to death not survival of organism; patient is somnolent, not very active (neither physically nor mentally). Approx. **1-2 weeks prior to death** there is quantitative decrease of consciousness – patient is more and more somnolent, has decreased sensitivity, perception and ability to focus. From somatic changes, we can mention decreased body temperature, low

blood pressure, irregular pulse, increased sweating, hypoperfusion which leads to colour changes on acral parts of the body and breathing irregularities.

In some patients, so-called **lucid interval** will occur – after weeks of somnolence the clinical manifestation of patient seems to improve – he regains consciousness, appetite increases, has euphoric mood (endorphins), wants to meet relatives and so on. This lucid interval is caused by "final" **release of corticosteroids and endorphins.** Presence of lucid interval is a sign of imminent death. It is followed by **terminal stage**, which is divided into preagonal and agonal stage.

Preagonal stage

In preagonal stage, there is a clash of processes of opposite directions which influence each other. On one side, there is **pathologic process (acidosis, hypoxia, hypoperfusion)** which directs towards disintegration and death of an organism and on the other side there are **compensatory mechanisms (tachypnoea, tachycardia, vasoconstriction, hypertension reaction)** which have tendency to maintain organism survival – these two types of processes exclude each other. In failure of compensatory mechanisms following changes occur: **preterminal apnoea, atrioventricular blocks of 3rd grade with preatutomatic pause, tissue hypoperfusion and hypotension.**

Agonal stage

Agonal stage is characterized by chaotic and uncoordinated function of organ systems. Subcortical and reflexoric mechanisms, which drive certain functions, are dominant. In patient, we observe breathing irregularities, which is often interpreted as rattling (due to congestion – left heart failure) and decreased mucus elimination; later followed by **gasping**, **Adams-Stokes syndrome (asystole, unconsciousness, cramps)** caused by absence of cardiac output.

Stage of clinical death

Agonal stage turns to stage of clinical death. Absence of spontaneous breathing and heart action is called clinical death and in certain condition can be reversed by cardiopulmonary resuscitation which restores breathing and heart action. If it is not possible, irreversible pathologic changes occur depending on organ sensitivity to oxygen – **biologic death** of an individual occurs.

Nowadays, when it is possible to technically replace ventilation (artificial ventilation) and pharmacologic support of cardiovascular system, it was necessary to determine so-called brain death for needs of intensive care medicine and transplant medicine. Most important clinical signs are **absence of spontaneous breathing for 15 minutes, absence of voluntary and involuntary movement, loss of cerebral reflexes (spinal reflexes might be present), extreme mydriasis with unreactive pupils.** This condition is repeatedly confirmed by complex examination with absence of cortical and brainstem evoked potentials (isoelectric EEG), absence of brain perfusion, increased intracranial pressure and decrease of arteriovenous oxygen difference in cerebral circulation.

Chapter 32

REFERENCE BIOCHEMICAL VALUES

Serum

Basic metabolites and enzymes

Abbreviation	Name	G	Age from	Age to	Normal from	Normal to	Unit
ALP	ALP	F	0	1M	0,80	6,77	µkat/l
ALP	ALP	F	1M	1	2,10	5,70	µkat/l
ALP	ALP	F	1	3	1,80	5,25	µkat/l
ALP	ALP	F	3	7	1,60	4,95	µkat/l
ALP	ALP	F	7	9	1,15	5,42	µkat/l
ALP	ALP	F	9	12	0,85	5,53	µkat/l
ALP	ALP	F	12	15	0,85	2,70	µkat/l
ALP	ALP	F	15	18	0,78	2,00	µkat/l
ALP	ALP	M	0	1M	1,25	5,27	µkat/l
ALP	ALP	M	1M	1	1,37	6,38	µkat/l
ALP	ALP	M	1	3	1,73	5,75	µkat/l
ALP	ALP	M	3	7	1,55	5,15	µkat/l
ALP	ALP	M	7	9	1,43	5,25	µkat/l
ALP	ALP	M	9	12	0,70	6,00	µkat/l
ALP	ALP	M	12	15	1,25	6,50	µkat/l
ALP	ALP	M	15	18	0,87	2,85	µkat/l
ALP	ALP	U	18	150	0,50	2,00	µkat/l
ALT	ALT	F	1	150	0,10	0,60	µkat/l
ALT	ALT	M	1	150	0,10	0,85	µkat/l
ALT	ALT	U	0	1	0,22	0,75	µkat/l
AMS	Amylase	U	0	150	0,46	1,66	µkat/l
AMSP	AMS pancreatic	U	0	100	0,00	0,88	µkat/l
AST	AST	F	1	150	0,10	0,60	µkat/l
AST	AST	M	1	150	0,10	0,85	µkat/l
AST	AST	U	0	6T	0,42	1,25	µkat/l
AST	AST	U	6T	1	0,25	1,00	µkat/l
CK	CK	F	6	12	0,00	2,57	µkat/l
CK	CK	F	12	17	0,00	2,05	µkat/l
CK	CK	F	17	150	0,00	2,42	µkat/l
CK	CK	M	6	12	0,00	4,12	µkat/l
CK	CK	M	12	17	0,00	4,50	µkat/l
CK	CK	M	17	150	0,00	2,85	µkat/l
CK	CK	U	0	1D	0,00	11,90	µkat/l
CK	CK	U	1D	5D	0,00	10,90	µkat/l

CK	CK	U	5D	6M	0,00	4,92	µkat/l
CK	CK	U	6M	1	0,00	3,38	µkat/l
CK	CK	U	1	3	0,00	3,80	µkat/l
CK	CK	U	3	6	0,00	2,48	µkat/l
GMT	GMT	F	0	6M	0,25	2,20	µkat/l
GMT	GMT	F	6M	1	0,02	0,65	µkat/l
GMT	GMT	F	1	12	0,07	0,37	µkat/l
GMT	GMT	F	12	18	0,07	0,40	µkat/l
GMT	GMT	F	18	150	0,07	0,63	µkat/l
GMT	GMT	M	0	6M	0,20	2,03	µkat/l
GMT	GMT	M	6M	1	0,02	0,65	µkat/l
GMT	GMT	M	1	12	0,05	0,37	µkat/l
GMT	GMT	M	12	18	0,03	0,70	µkat/l
GMT	GMT	M	18	150	0,03	0,92	µkat/l
CHS	Cholinesterase	F	0	150	65,00	180,00	µkat/l
CHS	Cholinesterase	M	0	150	77,00	192,00	µkat/l
LD	LD	U	0	4D	4,83	12,92	µkat/l
LD	LD	U	4D	10D	9,10	33,30	µkat/l
LD	LD	U	10D	2	3,00	7,20	µkat/l
LD	LD	U	2	15	1,83	4,92	µkat/l
LD	LD	U	15	150	1,83	4,12	µkat/l
LPS	Lipase	U	0	150	0,22	1,00	µkat/l
ALB	Albumin	U	0	4D	28,00	44,00	g/l
ALB	Albumin	U	4D	150	35,00	52,00	g/l
TBIL	Bilirubin total	U	0	1D	24,00	149,00	µmol/l
TBIL	Bilirubin total	U	1D	2D	58,00	197,00	µmol/l
TBIL	Bilirubin total	U	2D	5D	26,00	205,00	µmol/l
TBIL	Bilirubin total	U	5D	15	5,00	21,00	µmol/l
TBIL	Bilirubin total	U	15	150	5,00	21,00	µmol/l
BILk	Bilirubin conjugated	U	0	150	0,10	3,40	µmol/l
TP	Total protein	U	0	1M	41,00	63,00	g/l
TP	Total protein	U	1M	18	57,00	80,00	g/l
TP	Total protein	U	18	150	66,00	83,00	g/l
GLU	Glucose	U	0	15	3,30	5,60	mmol/l
GLU	Glucose	U	15	150	4,10	5,90	mmol/l
KRE	Creatinine	F	15	150	58,00	96,00	µmol/l
KRE	Creatinine	M	15	50	74,00	110,00	µmol/l
KRE	Creatinine	M	50	150	72,00	127,00	µmol/l
KRE	Creatinine	U	0	4D	45,00	105,00	µmol/l
KRE	Creatinine	U	4D	1	35,00	62,00	µmol/l
KRE	Creatinine	U	1	15	45,00	105,00	µmol/l
KMOC	Uric acid	F	0	1M	101,00	303,00	µmol/l
KMOC	Uric acid	F	1M	15	190,00	363,00	µmol/l
KMOC	Uric acid	F	15	150	155,00	357,00	µmol/l
KMOC	Uric acid	M	0	1M	131,00	340,00	µmol/l

KMOC	Uric acid	M	1M	15	190,00	440,00	µmol/l
KMOC	Uric acid	M	15	150	208,00	428,00	µmol/l
UREA	Urea	U	0	6T	1,40	4,30	mmol/l
UREA	Urea	U	6T	15	1,80	6,40	mmol/l
UREA	Urea	U	15	150	2,80	7,20	mmol/l

Electrolytes

K	Potassium	U	1M	1	4,00	7,00	mmol/l
K	Potassium	U	1	150	3,50	5,10	mmol/l
P	Phosphorus	U	0	15	1,29	2,26	mmol/l
P	Phosphorus	U	15	150	0,81	1,45	mmol/l
Mg	Magnesium	F	0	150	0,77	1,03	mmol/l
Mg	Magnesium	M	0	150	0,73	1,06	mmol/l
Cl	Chlorides	U	0	150	101,00	109,00	mmol/l
Clpo	Chlorides in sweat	U	0	15	5,00	35,00	mmol/l
Clpo	Chlorides in sweat	U	15	150	0,00	39,00	mmol/l
Li	Lithium	U	18	150	1,00	1,20	mmol/l
Cu	Copper	F	15	150	11,60	19,20	µmol/l
Cu	Copper	M	15	150	12,40	20,60	µmol/l
Cu	Copper	U	0	6T	3,00	10,00	µmol/l
Cu	Copper	U	6T	15	10,30	21,40	µmol/l
OSM	Osmolality	U	0	15	285,00	295,00	mmol/kg
OSM	Osmolality	U	15	60	275,00	295,00	mmol/kg
OSM	Osmolality	U	60	150	280,00	300,00	mmol/kg
Na	Sodium	U	0	1M	130,00	145,00	mmol/l
Na	Sodium	U	1M	15	132,00	144,00	mmol/l
Ca	Calcium	U	0	1T	1,90	2,60	mmol/l
Ca	Calcium	U	1T	2	2,25	2,75	mmol/l
Ca	Calcium	U	2	15	2,20	2,75	mmol/l
Ca	Calcium	U	15	150	2,20	2,65	mmol/l
CaI	Calcium ionized	U	0	15	1,05	1,45	mmol/l
CaI	Calcium ionized	U	15	150	1,13	1,32	mmol/l
Fe	Iron	F	12	150	10,70	32,20	µmol/l
Fe	Iron	M	12	150	12,50	32,20	µmol/l
Fe	Iron	U	0	1M	17,90	44,80	µmol/l
Fe	Iron	U	1M	2	7,20	17,90	µmol/l
Fe	Iron	U	2	12	9,00	21,50	µmol/l

Proteins

Al1A	Alfa-1-antitrypsin	U	0	150	0,89	2,05	g/l
AL1G	Alfa-1-kyslý glycoprotein	F	0	150	0,40	1,20	g/l
AL1G	Alfa-1-kyslý glycoprotein	M	0	150	0,50	1,30	g/l
ASLO	ASLO	U	0	15	0,00	150,00	U/ml
BETA	Beta-2-mikroglobulin	U	0	150	0,80	1,80	mg/l

C1IN	C1 - inhibitor	U	0	150	0,23	0,41	g/l
CPL	Ceruloplasmin	U	0	150	220,00	610,00	mg/l
C3	C3-komplement	U	0	150	0,90	1,80	g/l
C4	C4-komplement	U	0	150	0,10	0,40	g/l
IgG	IgG	F	2	150	5,52	16,31	g/l
IgG	IgG	M	2	150	5,40	18,22	g/l
IgG	IgG	U	0	1M	3,97	17,65	g/l
IgG	IgG	U	1M	1	2,05	9,48	g/l
IgG	IgG	U	1	2	4,75	12,10	g/l
IgA	IgA	F	12	60	0,65	4,21	g/l
IgA	IgA	F	60	150	0,69	5,17	g/l
IgA	IgA	M	12	60	0,63	4,84	g/l
IgA	IgA	M	60	150	1,01	6,45	g/l
IgA	IgA	U	0	3M	0,01	0,34	g/l
IgA	IgA	U	3M	1	0,08	0,91	g/l
IgA	IgA	U	1	12	0,21	2,91	g/l
IgM	IgM	F	1	12	0,47	2,40	g/l
IgM	IgM	F	12	150	0,33	2,93	g/l
IgM	IgM	M	1	12	0,41	1,83	g/l
IgM	IgM	M	12	150	0,22	2,40	g/l
IgM	IgM	U	0	3M	0,06	0,21	g/l
IgM	IgM	U	3M	1	0,17	1,43	g/l
IgE	IgE	U	0	1	0,00	25,00	IU/ml
IgE	IgE	U	1	5	0,00	60,00	IU/ml
IgE	IgE	U	5	9	0,00	90,00	IU/ml
IgE	IgE	U	9	15	0,00	200,00	IU/ml
IgE	IgE	U	15	150	0,00	100,00	IU/ml
HPT	Haptoglobin	U	18	150	0,32	2,05	g/l
Kapa.vol.s	Kappa free chains serum	U	0	150	3,30	19,40	mg/l
Lamb.vol.s	Lambda free chains serum	U	0	150	5,71	26,30	mg/l
PK/L	Ratio Kappa/Lambda	U	0	150	0,26	1,65	
CRP	CRP	U	0	1M	0,00	1,60	mg/l
CRP	CRP	U	1M	150	0,00	5,00	mg/l
PRES	Presepsine	U	0	150	0,00	337,00	pg/ml
PROC	Procalcitonine	U	0	150	0,00	0,50	ng/ml
RF	Rheumatoid factor	U	0	150	0,00	15,00	U/ml
TRF	Transferrin	U	0	150	2,00	3,60	g/l
FERI	Ferritin	F	18	50	15,00	150,00	ng/ml
FERI	Ferritin	F	50	150	30,00	400,00	ng/ml
FERI	Ferritin	M	18	150	30,00	400,00	ng/ml
FERI	Ferritin	U	0	18	15,00	150,00	ng/ml

Lipids

CHOL	Cholesterol	U	0	4T	0,00	4,40	mmol/l
CHOL	Cholesterol	U	4T	15	0,00	4,40	mmol/l

CHOL	Cholesterol	U	15	150	0,00	5,17	mmol/l
HDLC	Cholesterol HDL	F	15	100	1,20	2,20	mmol/l
HDLC	Cholesterol HDL	M	15	100	1,03	2,00	mmol/l
HDLC	Cholesterol HDL	U	0	6T	0,73	1,17	mmol/l
HDLC	Cholesterol HDL	U	6T	1	0,94	1,26	mmol/l
HDLC	Cholesterol HDL	U	1	10	1,11	1,83	mmol/l
HDLC	Cholesterol HDL	U	10	15	1,27	1,71	mmol/l
LDLV	Cholesterol LDL-calc.	U	0	150	0,00	3,88	mmol/l
TRG	Triacylglyceroles	F	15	150	0,40	1,70	mmol/l
TRG	Triacylglyceroles	M	15	150	0,40	1,70	mmol/l
TRG	Triacylglyceroles	U	0	6	0,32	0,95	mmol/l
TRG	Triacylglyceroles	U	6	10	0,35	1,14	mmol/l
TRG	Triacylglyceroles	U	10	15	0,10	1,64	mmol/l

Electrophoresis

Ealb	Elfo alfa1	U	0	150	1,20	3,30	%
EA1	Elfo albumin	U	0	150	54,30	65,50	%
EA2	Elfo alfa1	U	0	150	1,20	3,30	%
EB	Elfo alfa2	U	0	150	8,30	15,00	%
EB2	Elfo beta1	U	0	150	6,50	11,50	%
EGAM	Elfo beta2	U	0	150	2,50	7,20	%
HBA	Elfo gamma	U	0	150	7,10	19,50	%
HBF	Haemoglobin A	U	0	150	96,50	100,00	%
HEA2	Haemoglobin F	U	0	150	1,00	2,00	%
	Haemoglobin A2	U	0	150	0,00	3,50	%

Homeostasis

PO2	PO2	U	0	1M	7,60	9,20	kPa
PO2	PO2	U	1M	1	8,00	12,00	kPa
PO2	PO2	U	1	14	9,30	12,00	kPa
PO2	PO2	U	14	150	9,80	13,30	kPa
PCO2	PCO2	U	0	1M	4,00	6,30	kPa
PCO2	PCO2	U	1M	1	4,40	5,30	kPa
PCO2	PCO2	U	1	14	4,40	5,60	kPa
PCO2	PCO2	U	14	150	4,64	6,00	kPa
pH	pH	U	0	1M	7,22	7,44	
pH	pH	U	1M	1	7,32	7,44	
pH	pH	U	1	150	7,36	7,44	
BEB	BE(B)	U	0	1D	-7,50	-0,50	mmol/l
BEB	BE(B)	U	1D	3	-3,40	2,30	mmol/l
BEB	BE(B)	U	3	4	-3,00	2,50	mmol/l
BEB	BE(B)	U	4	150	-2,50	2,50	mmol/l
HCO3	HCO3 act	U	0	1M	18,50	24,00	mmol/l
HCO3	HCO3 act	U	1M	1	20,00	23,00	mmol/l
HCO3	HCO3 act	U	1	150	22,00	26,00	mmol/l

O2HB	Oxyhaemoglobin	U	0	6T	40,00	90,00	%
O2HB	Oxyhaemoglobin	U	6T	150	90,00	95,00	%
COHB	Carboxyhaemoglobin	U	0	150	0,50	2,50	%
MetH	Methaemoglobin	U	0	150	0,40	1,50	%

Oncomarcers

AFP	Alfa-1-fetopr. AFP	U	18	150	0,00	9,00	ng/ml
BHCG	Total beta HCG	F	18	150	0,00	2,90	mIU/ml
BHCG	Total beta HCG	M	18	150	0,00	2,67	mIU/ml
C724	CA 72-4	U	18	150	0,00	6,90	U/ml
C153	CA 15-3	U	18	150	0,00	31,30	U/ml
C125	CA 125	U	18	150	0,00	35,00	U/ml
C199	CA 19-9	U	18	150	0,00	35,00	U/ml
CY21	CYFRA 21-1	U	18	150	0,00	2,08	ng/ml
NSE	NSE	U	18	150	0,00	16,30	ng/ml
PSA	PSA	M	18	150	0,00	4,00	ng/ml
SCC	Antigen SCC	U	0	150	0,00	1,50	ng/ml
ChrgA	Chromogranin A	U	0	150	19,40	98,10	ng/ml
GAST	Gastrin	U	0	150	0,00	90,00	pg/ml
Thyr	Thyroglobulin	U	0	150	0,10	35,00	ng/ml

Medication

CSP	Cyclosporine	U	0	150	50,00	200,00	ng/ml
DIG	Digoxin	U	0	150	0,80	2,00	ng/ml
FENY	Phenytoin	U	0	150	10,00	20,00	µg/ml
KARB	Carbamazepine	U	0	150	5,00	12,00	µg/ml
VALP	Valproic acid	U	0	150	50,00	100,00	µg/ml
SIR	Sirolimus	U	0	150	3,00	10,00	ng/ml
TAC	Tacrolimus	U	0	150	3,00	15,00	ng/ml
TEOF	Theophylline	U	0	4T	5,00	10,00	µg/ml
TEOF	Theophylline	U	4T	150	10,00	20,00	µg/ml
VAN	Vancomycin	U	0	150	5,00	40,00	µg/ml
SALI	Salicylates	U	0	150	150,00	300,00	mg/l
PAR	Paracetamol	U	0	150	10,00	30,00	µg/ml

Toxicology

AMAN	Amanitin serum	U	0	150	0,00	1,50	ng/ml

Vitamins

VIDc	Vitamin D total	U	0	150	30,00	100,00	ng/ml
B12	Vitamin B12	U	0	150	180,00	914,00	pg/ml

Hormones

CPEP	C-peptide	U	0	150	0,78	5,19	ng/ml
ESTR	Estradiol	M	0	150	20,00	75,00	pg/ml

ESTR	Estradiol	F	0	150	cycle		pg/ml
hFSH	Follicle stimulating hormone	F	50	150	16,74	113,59	mIU/ml
hFSH	Follicle stimulating hormone	M	0	150	1,27	9,00	mIU/ml
INZ	Insulin	U	0	150	1,90	23,00	uIU/ml
KORT	Cortisol	U	0	150	185,00	624,00	nmol/l
hLH	Luteinizing hormone	M	0	150	1,24	8,62	mIU/ml
hLH	Luteinizing hormone	F	0	150	cycle		mIU/ml
PTH	Parathormone	U	0	150	12,00	88,00	pg/ml
PRL	Prolactin - PRL	F	0	50	3,34	26,72	ng/ml
PRL	Prolactin - PRL	F	50	150	2,74	16,64	ng/ml
PRL	Prolactin - PRL	F	0	150	2,64	13,13	ng/ml
PROG	Progesterone	M	0	150	0,10	0,84	ng/ml
PROG	Progesterone	F	0	150	cycle		ng/ml
hGH	hGH-Growth hormone	F	0	150	0,01	5,22	ng/ml
hGH	hGH-Growth hormone	M	0	150	0,01	5,22	ng/ml
FT3	FREE T3	U	0	1M	3,30	10,50	pmol/l
FT3	FREE T3	U	1M	18	3,90	6,70	pmol/l
FT3	FREE T3	U	18	150	3,80	6,00	pmol/l
FT4	FREE T4	U	0	2D	10,70	40,00	pmol/l
FT4	FREE T4	U	2D	1M	6,20	30,00	pmol/l
FT4	FREE T4	U	1M	18	7,86	17,00	pmol/l
FT4	FREE T4	U	18	150	7,86	14,41	pmol/l
TSTR	Testosterone	F	18	150	0,07	0,85	ng/ml
TSTR	Testosterone	M	18	150	3,00	12,00	ng/ml
TSTR	Testosterone	F	18	150	0,10	0,75	ng/ml
TSTR	Testosterone	M	18	150	1,75	7,81	ng/ml
TPOA	TPO Ab	U	0	150	0,00	9,00	IU/ml
TgAb	TgAb	U	0	150	0,00	4,00	IU/ml
TSH	TSH	U	0	3D	5,20	14,60	mIU/l
TSH	TSH	U	3D	4T	0,40	16,10	mIU/l
TSH	TSH	U	4T	12M	0,60	8,10	mIU/l
TSH	TSH	U	12M	4	0,50	4,50	mIU/l
TSH	TSH	U	4	11	0,70	4,10	mIU/l
TSH	TSH	U	11	19	0,50	3,60	mIU/l
TSH	TSH	U	19	150	0,34	3,60	mIU/l

Cardiovascular markers

CKMB	CK-isoenzyme MB	U	0	150	0,00	0,40	µkat/l
HOM	Homocysteine	U	18	150	5,00	20,00	µmol/l
MYOG	Myoglobin	U	0	150	0,00	70,00	µg/l
TRPI	Troponin I	U	0	150	0,00	0,02	ng/ml
NTBN	NT pro BNP	U	0	75	0,00	125,00	pg/ml
NTBN	NT pro BNP	U	75	150	0,00	450,00	pg/ml

Other examinations

HIOK	5-HIOK	U	0	150	10,40	31,20	umol/24 h
AMON	Ammonia	U	0	150	16,00	53,00	µmol/l
GlHh	Glycated haemoglobin - HbA1c	U	0	150	2,80	4,80	%
LAK	Lactate	U	0	4T	0,00	3,00	mmol/l
LAK	Lactate	U	4T	15	0,56	2,25	mmol/l
LAK	Lactate	U	15	150	0,50	2,20	mmol/l
KVMA	Vanillylmandelic acid	U	0	150	0,00	68,60	umol/24 h
Quantiferon	Quantiferon	U	0	150	negativeive	positive	

Serology

HIV	HIV 1/2	U	0	150	0,00	0,90	
AHCV	Anti.HCV	U	0	150	0,00	1,00	
HBsA	HBsAg	U	0	150	0,00	1,00	IU/ml
AHBC	Anti HBc	U	0	150	1,00	99,00	
EBNA	anti EBNA-IgG	U	0	150	0,00	20,00	RU/ml
TOXG	TOXO IgG	U	0	150	0,00	1,00	IU/ml
CMV	CMV IgG	U	0	150	0,00	1,00	
Syphilis	Syphilis	U	0	150	neg.	pos.	

Female hormones

LH	.	hLH	hFSH	mIU/ml
FSH	follicular phase	2.12-10.89	3.85-8.78	
	mid-cycle.	19.18-103.03	4.54-22.51	
	luteal phase	1.20-12.86	1.79-5.12	
	after menopause	10.87-58.64	16.74-113.59	

ESTRADIOL		ESTRADIOL	pg/ml
	follicular phase	24 - 114	
	periovulation ph.	62 - 534	
	luteal ph.	80 - 273	
	after menopause	20 - 88	

PROGESTERON			
		PROG	ng/ml
	follicular phase	0.31 - 1.52	
	luteal phase	5.16 - 18.56	
	after menopause	0.08 - 0.78	
	pregnant 1.trimester	4.73 - 50.74	
	pregnant 2.trimster	19.41 - 45.3	

HCG BETA

	Beta HCG - pregnant	mIU/ml
0.2 - 1 week	5 - 50	
. 1 - 2 weeks	50 - 500	
. 2 - 3 weeks	100 - 5000	
. 3 - 4 weeks	500 - 10000	
. 4 - 5 weeks	1000 - 50000	
. 5 - 6 weeks	10000 - 100000	
. 6 - 8 weeks	15000 - 200000	
. 8 - 12 weeks	10000 - 100000	

Abbreviations

Age
- D - day
- T - week
- M - month
- R - year

Gender
- P/G - gender
- F - female
- M - male
- U – male and female

Urine

Abbreviation	Name	G	Age from	Age to	Normal from	Normal to	Unit
fAMS	Amylase - waste	U	0	150	0,00	8,20	ukat/l
B2MG	Beta-2-mikrog. urine	U	18	150	0,00	0,50	mg/l
fKVP	Total protein - waste	U	0	150	0,00	0,15	g/d
fUK	Potassium-waste	U	0	1M	5,00	25,00	mmol/d
fUK	Potassium-waste	U	1M	1	15,00	40,00	mmol/d
fUK	Potassium-waste	U	1	5	20,00	60,00	mmol/d
fUK	Potassium-waste	U	5	15	40,00	90,00	mmol/d
fUK	Potassium-waste	U	15	150	25,00	125,00	mmol/d
fUP	Phosphorus-waste	U	0	150	12,90	42,00	mmol/d
	Glucose	U	0	150	0,1	0,8	mmol/l
Mg	Magnesium urine	U	0	150	0,00	4,11	mmol/l
fUMG	Magnesium-waste	U	0	1	0,80	1,60	mmol/d
fUMG	Magnesium-waste	U	1	150	3,00	5,00	mmol/d
fUCl	Chlorides-waste	U	0	1	2,00	10,00	mmol/d
fUCl	Chlorides-waste	U	1	7	22,00	73,00	mmol/d
fUCl	Chlorides-waste	U	7	15	110,00	250,00	mmol/d
fUNa	Natrium	U	0	150	40,00	220,00	mmol/d
fUCa	Calcium-waste	F	15	150	0,60	6,20	mmol/d
fUCa	Calcium-waste	M	15	150	0,60	7,50	mmol/d

fUCa	Calcium-waste	U	0	1M	0,50	2,50	mmol/d
fUCa	Calcium-waste	U	1M	5	0,50	4,00	mmol/d
fUCa	Calcium-waste	U	5	15	0,60	5,50	mmol/d
Kapa.vol.m	Kappa free chains urine	U	0	150	0,01	32,71	mg/l
Lamb.vol.m	Lambda free chains urine	U	0	150	0,00	5,00	mg/l
fUKR	Creatinine-waste	U	0	1M	0,13	0,26	mmol/d
fUKR	Creatinine-waste	U	1M	1	0,70	0,92	mmol/d
fUKR	Creatinine-waste	U	1	5	2,24	4,08	mmol/d
fUKR	Creatinine-waste	U	5	10	3,50	6,38	mmol/d
fUKR	Creatinine-waste	U	10	15	6,09	11,09	mmol/d
fUKR	Creatinine-waste	U	15	150	4,40	18,00	mmol/d
fUKM	Uric acid - waste	U	0	150	1,48	4,46	mmol/d
MALB	Microalbuminuria	U	0	150	0,00	30,00	mg/d
fURE	Urea-waste	U	0	1T	2,50	3,30	mmol/d
fURE	Urea-waste	U	1T	2M	10,00	17,00	mmol/d
fURE	Urea-waste	U	2M	1	33,00	67,00	mmol/d
fURE	Urea-waste	U	1	15	67,00	333,00	mmol/d
fURE	Urea-waste	U	15	150	250,00	570,00	mmol/d
Lamb.vol.m	Lambda free chains urine	U	0	150	0,00	5,00	mg/l
Kapa.vol.m	Kappa free chains urine	U	0	150	0,01	32,71	mg/l
ERY	Erythrocytes	U	0	150	0,00	10,00	v 1µl
LEUK	Leukocytes	U	0	150	0,00	15,00	v 1µl
VALC	Cylinders	U	0	150	0,00	1,00	v 1µl
EPDL	Squamous epithelium	U	0	150	0,00	15,00	v 1µl
PH	pH urine	U	18	150	4,80	7,40	
ETAU	Ethanol - urine	U	0	150	0,00	0,00	mg/ml
AMAm	Amanitin urine	U	0	150	0,00	1,50	ng/ml

Drugs in urine

ETAU	Ethanol - urine	U	0	150	0,00	0,00	mg/ml
AMAm	Amanitin urine	U	0	150	0,00	1,50	mg/ml
THC	THC - tetrahydrocannabinol	U	0	150	negative	positive	
METF	Methamphetamine	U	0	150	negative	positive	
AMPH	Amphetamine	U	0	150	negative	positive	
MOR	Morfín	U	0	150	negative	positive	
KOKA	Cocaine	U	0	150	negative	positive	
EXT	Ecstasy (NMDA)	U	0	150	negative	positive	
BENZ	Benzodiazepines	U	0	150	negative	positive	
BARB	Barbiturates	U	0	150	negative	positive	

Osmolality of urine

OSM	Osmolality urine	U	18	20	0,00	970,00	mmol/kg
OSM	Osmolality urine	U	21	50	0,00	940,00	mmol/kg
OSM	Osmolality urine	U	51	60	0,00	830,00	mmol/kg

OSM	Osmolality urine	U	61	70	0,00	790,00	mmol/kg
OSM	Osmolality urine	U	71	150	0,00	780,00	mmol/kg

Reference values – gastric juices

BAO	BAO	F	18	150	1,00	3,00	mmol/h
BAO	BAO	M	18	150	2,00	5,00	mmol/h
MAO1	MAO 1	U	18	150	5,00	20,00	mmol/h
BAO1	BAO1	F	18	150	1,00	3,00	mmol/h
BAO1	BAO1	M	18	150	2,00	5,00	mmol/h
BAO2	BAO2	F	18	150	1,00	3,00	mmol/h
BAO2	BAO2	M	18	150	2,00	5,00	mmol/h
BAO3	BAO3	F	18	150	1,00	3,00	mmol/h
BAO3	BAO3	M	18	150	2,00	5,00	mmol/h
BAO4	BAO4	F	18	150	1,00	3,00	mmol/h
BAO4	BAO4	M	18	150	2,00	5,00	mmol/h

Elfo of urine

EGAM	Elfo gamma	U	0	150			%
EAM	Elfo albumin urine	U	0	150			%
EA1M	Elfo alfa1 urine	U	0	150			%
EA2M	Elfo alfa2 urine	U	0	150			%
EB1M	Elfo beta1 urine	U	0	150			%
EB2M	Elfo beta2 urine	U	0	150			%
EGM	Elfo gamma urine	U	0	150			%

Immunofixation

IEFMD	IFX in urine (IgD)	U	0	150	verbal evaluation		
IEFM	IFX in urine (IgA, IgG, IgM)	U	0	150	verbal evaluation		

Stool

FZTK	Lipid droplets	U	0	150	negative	positive	
FZSV	Muscle fibres	U	0	150	negative	positive	
FZŠZ	Starch grains	U	0	150	negative	positive	
FOK1	Faecal occult blood 1	U	0	150	negative	positive	
FOK2	Faecal occult blood 2	U	0	150	negative	positive	
FOK3	Faecal occult blood 3	U	0	150	negative	positive	

Reference values cerebrospinal fluid

Abbreviation	Name	G	Age from	Age to	Normal from	Normal to	Unit
ALB	Albumin CSF	U	0	150	0,09	0,21	g/l
PROT	Protein CSF	U	1M	3M	0,20	0,72	g/l
PROT	Protein CSF	U	3M	6M	0,15	0,50	g/l

PROT	Protein CSF	U	6M	12M	0,10	0,45	g/l
PROT	Protein CSF	U	1	2	0,10	0,40	g/l
PROT	Protein CSF	U	2	4	0,10	0,43	g/l
PROT	Protein CSF	U	4	15	0,10	0,45	g/l
EPAL	Elfo prealbumin CSF	U	0	150	1,85	4,50	%
EAL	Elfo albumin CSF	U	0	150	52,70	68,30	%
EA1L	Elfo alfa1 CSF	U	0	150	2,60	6,40	%
EA2L	Elfo alfa2 CSF	U	0	150	3,80	7,80	%
EB1L	Elfo beta1 CSF	U	0	150	9,20	16,00	%
EB2L	Elfo beta2 CSF	U	0	150	3,80	6,00	%
EGL	Elfo gamma CSF	U	0	150	5,60	11,40	%
GLU	Glucose CSF	U	0	16	1,80	4,60	mmol/l
GLU	Glucose CSF	U	16	150	2,66	4,36	mmol/l
Cl	Chlorides CSF	U	0	150	113,00	131,00	mmol/l
IgA.	IgA CSF	U	0	150	0,00	3,00	mg/l
IgG,	IgG CSF	U	0	150	0,00	34,00	mg/l
IgM,	IgM CSF	U	0	150	0,00	1,00	mg/l
LAKT	Lactate CSF	U	0	15	1,10	1,80	mmol/l
LAKT	Lactate CSF	U	15	50	1,50	2,10	mmol/l
LAKT	Lactate CSF	U	51	150	1,10	2,90	mmol/l
ERYL	Erythrocytes CSF	U	0	150	0,00	5,00	
SEGL	Segments CSF	U	0	150	0,00	1,00	
LYMF	Lymfocyty CSF	U	0	150	0,00	5,00	
SPEK	Spectrograph CSF	U	0	150	0,00	0,02	

Transudate

Abbreviation	Name	G	Age from	Age to	Normal from	Normal to	Unit
pPH	pH punctate transudate	U	0	150	7,25	7,54	
pGLU	Glucose punctate transudate	U	0	150	3,6	5,6	mmol/l
pBIE	Total protein transudate	U	0	150	0	15	g/l
pCHO	Cholesterol transudate	U	0	150	0	5,2	mmol/l
pLD	LD punctate transudate	U	0	150	0	3,3	µkat/l
pKM	Uric acid transudate	U	0	150	178	416	µmol/l
pAMS	AMS transudate	U	0	150	0	1,66	µkat/l
pERY	Erythrocytes transudate	U	0	150	0	1	v 1 µl
pLEU_	Leukocytes transudate	U	0	150	0	2000	v 1 µl
pRFt	Rheumatoid factor transudate	U	0	150	1,4	1,6	U/ml

Synovial fluid

Abbreviation	Name	G	Age from	Age to	Normal from	Normal to	Unit
ERY.	Erythrocytes	U	0	150	0	1	in 1 µl
LEU	Leukocytes	U	0	150	0	200	in 1 µl
RF	Rheumatoid factor	U	0	150	0	1	U/ml

C3ps	C3-komplement	U	0	150	0,9	1,8	mg/l
C4ps	C4-komplement	U	0	150	0,1	0,4	g/l
PROT	Total protein	U	0	150	11	22	g/l
GLUC	Glucose	U	0	150	3,3	5,3	mmol/l
KMp	Uric acid	U	0	150	178	416	µmol/l
LDp	LD	U	0	150	0	3,3	µkat/l

Exudate

Abbreviation	Name	G	Age from	Age to	Normal from	Normal to	Unit
pHe	pH exudate	U	0	150	6,85	7,41	
pGLUe	Glucose exudate	U	0	150	0	3,3	mmol/l
pCBe	Total protein exudate	U	0	150	30	60	g/l
pKMe	Uric acid exudate	U	0	150	178	416	mmol/l
pChe	Cholesterol exudate	U	0	150	0	5,2	mmol/l
pLDe	LD exudate	U	0	150	0	3,3	µkat/l
pAMSe	AMS exudate	U	0	150	0	1,66	µkat/l
pERYe	Erythrocytes exudate	U	0	150	0	1	v l µl
pLEUe	Leukocytes exudate	U	0	150	6000	40000	v l µl
pRFe	RF exudate	U	0	150	1,4	1,6	U/ml
pC3e	C3-komplement exudate	U	0	150	0,9	1,8	g/l
pC4e.	C4-komplement exudate	U	0	150	0,1	0,4	g/l

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