UNIVERSITATEA
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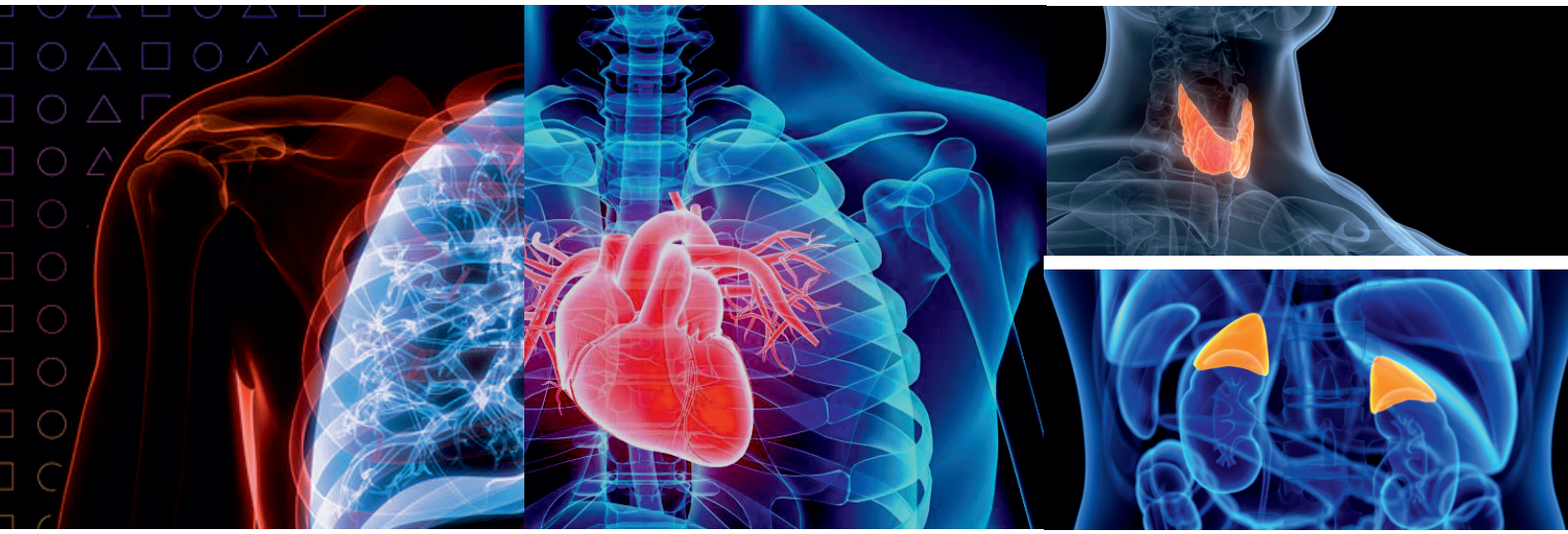
„VICTOR BABEȘ“ DIN TIMIȘOARA

PATHOPHYSIOLOGY

1 LECTURE NOTES FOR MEDICAL STUDENTS



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FOREWORD

Medicine, a continuously evolving science, is characterised by the symbiosis between clinical practice and scientific research, which allows the permanent optimisation of the diagnostic methods and therapeutic regimens for the patient benefit.

Pathophysiology is a basic subject at the interface between preclinical and clinical disciplines which studies disease as the alteration of body's physiological functions and has continuously benefited from the information explosion in medicine.

The study of pathophysiology offers the knowledge necessary to understand the: causes (*etiology*), mechanisms (*pathogenesis*) that initiate and contribute to the evolution of a disease, and consequences (*clinical manifestations*) resulting from the impairment of the physiological functions. The present work is purported to provide the 3rd year medical students with the knowledge needed for the understanding the etiopathogenesis of diseases whose clinical manifestations and therapeutics will be simultaneously studied at Medical Semiology and Pharmacology, respectively. The present content, originally published initially as the *Pathophysiology of the Respiratory and Cardiovascular Systems - A Manual for Medical Students,* has been updated and revised. New chapters have been included in order to match the published manual for the Romanian section, in line with the Pathophysiology syllabus for the 1st semester of the 3rd year of the Faculty of Medicine. To facilitate students' learning and preparation for the MCQ exam, information was concisely formulated and several notions were included in summative tables. Also, a brief overview of the main aspects taught in the first 2 years during the subjects that are curriculum prerequisites (anatomy, physiology, biochemistry, cell and molecular biology, biophysics, immunology) was introduced in the beginning of the chapter whenever considered useful. Also, when appropriate, both classic and novel pharmacological agents were mentioned in order to highlight the importance of correlating the mechanisms presented (Pathophysioloy) with the rational of therapeutics of the most frequent diseases (Pharmacology).

We trust that this first volume of lecture notes printed as e-book and made freely available in the purest academic spirit to medical students, residents and early-careers doctors, will complement the traditional classroom lecture courses and/or will be used as a self-guided study tool in order to gain a contemporary understanding of the pathophysiology of common diseases.

We will be grateful for any comments on the selection of material or any factual errors and remain receptive to constructive opinions that can be used to improve the next edition.

The Authors

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1. PATHOPHYSIOLOGY OF INFLAMMATION

OVERVIEW OF HUMAN DEFENCE MECHANISMS - BRIEF MICROBIOLOGY REVISION

DEFINITION: Human defence colectively refers to the multilevel, interactive systems and processes that protect the body against a wide variety of **infectious** (bacteria, viruses, fungi, parasites) or **traumatic agents** (physical, mechanical, chemical, including atmospheric pollutants etc.) responsible for tissue injury/destruction.

CLASSIFICATION:

I. NON-SPECIFIC defence

II. SPECIFIC defence (IMMUNITY) - 2 types:

A. INNATE (INBORN) immunity

B. ADAPTIVE (ACQUIRED) immunity

The main characteristics of the human defence mechanisms are summarised in Table 1.1.

Table 1.1. Summative of the non-specific and specific defence mechanisms.

NON-SPECIFIC Defence	**SPECIFIC Defence**	
	INNATE immunity	**ADAPTIVE immunity**
– **1st line of body defence** – **no specificity** = does not differentiate "self" from "non-self" – **immediate response** to aggression (tissue injury, infection etc.) – **moderate efficacy** – **no immune memory**	– **2nd line of defence** – **low specificity** = differentiates 'self' from 'non-self' but is **not specific** for a particular etiological agent – **immediate response** to aggression and **identical** after each exposure – **high efficacy** – **no immune memory**	– **3rd line of defence** – **high specificity** = differentiates "self" from "non-self" and is directed against **a specific etiological agent** – the response is triggered: = with *latency* (weeks) upon the first contact with the antigen - in the **primary immune response** (**IR)** = *immediately, rapidly and more effectively* (days) in case of subsequent exposures to the same antigen – in the **secondary IR** – **very high** efficacy – **with immune memory**

The components of the human defence systems are shown in Table 1.2.

Table 1.2. The main components of defence systems.

NON-SPECIFIC Defence	**SPECIFIC Defence**	
	INNATE immunity	**ADAPTIVE immunity**
1. Epithelial barriers (skin, mucous membranes): - Physical - Chemical **2. Saprophytic flora** **3. Expulsion of the foreign agents by:** coughing, sneezing, vomiting, diarrhoea **4. FEVER**	**1. Cells:** – Phagocytes: micro-/macrophages – Natural killer (NK) lymphocytes **2. Chemical substances:** – Mediators of **ACUTE INFLAMMATION:** ✓ *Cell-derived* mediators ✓ *Plasma-derived* mediators	**1. Antigens (Ag)** **2. Cells:** ▪ **Ag-presenting cells (APC):** - Tissue macrophages - Dendritic cells ▪ **Immune cells** - T lymphocytes - B lymphocytes **3. Humoral active molecules:** - Cytokines - Immunoglobulins (Ig)

INFLAMMATION is the the most common response of the body to injury. However, it should be stated from the very beginning that **acute inflammation** is a **defence reaction** while **chronic inflammation** is always a **pathological process**.
The **low-grade chronic inflammation** is currently considered as **central pathomechanism** of *most* **chronic non-communicable diseases** and **ageing**.

Observations:
The *subacute inflammation* is sometimes used to define the transformational period from acute to chronic which usually lasts from 2 to 6 weeks.
Diseases in which acute or chronic inflammation are central to the pathophysiology have the suffix *"-itis."* However, nowadays the low-grade inflammation is widely acknowledged as pathomechanim in most chronic diseases that do not have this suffix.

ACUTE INFLAMMATION

DEFINITION: a **defence reaction** *of the living, vascularized tissues* adjacent to an area of *tissue injury or necrosis* that: i) is *rapidly* activated (minutes) after damage, ii) *occurs according to the similar pattern* regardless of the type of etiological agent (non-specific), and iii) is dependent on the *release/activation* of *cell-* and *plasma-derived mediators,* with subsequent vascular and cellular responses.

Observation:
The controlled *acute inflammation* is beneficial but it can become detrimental if uncontrolled or excessively activated, e.g. in septic shock.

ETIOLOGY:

a) **NON-SPECIFIC agents:**
   - **biological:** *bacteria, viruses, fungi, parasites*
   - **chemical:** *caustic substances, insect or snake venoms, endogenous crystals*
   - **physical:** *ionizing radiation, extreme temperatures, electricity*
   - **mechanical:** *surgery, trauma, foreign bodies*

b) **SPECIFIC (immune) agents:**
   - **hypersensitivity (HS) reactions** that induce inflammation through:
     - ✓ mast cell degranulation - type I HS
     - ✓ complement activation - type II and III HS
     - ✓ release of lymphokines by activated T lymphocytes - type IV (delayed) HS
   - **autoimmune diseases**

GENERAL FEATURES:

- ✓ **Role: to defend the body** and **prevent the extension of injury** towards the healthy neighboring tissues, which is achieved via the:
  - destruction/elimination of the pathogenic agents and/or inhibition of their multiplication
  - neutralization of the toxins
  - removal of dead cells and cellular debris
  - allowing the tissue repair/healing process

- ✓ **Duration**: hours to days, usually, less than 2 weeks
- ✓ **Main characteristics:**
  - **predomination of the VASCULAR CHANGES** with an **abundant INFLAMMATORY EXUDATE**
  - the **CELLULAR INFILTRATE** is **rich** in **polymorphonuclear neutrophils (PMNs)** which are **microphages**
- ✓ **Tissue injury**: usually, **SELF-LIMITED**

MANIFESTATIONS:

a) LOCAL signs: 5 cardinal signs: *rubor, calor, tumor, dolor*, i.e., redness, heat, swelling and pain – the classic 4 signs (described in the 1st century AD by Celsus) and ***functio laesa*** (the 5th sign - loss of function, added by Virchow in the 19th century).

b) SYSTEMIC signs - the ***acute phase reaction*** characterized by:
- **fever –** caused by the release of endogenous pyrogens from phagocytes (IL-1, IL-6, IFN)
- **leukocytosis** and **left shift,** the latter being defined as an increase in the number of ***immature leucocytes***, namely of the ***neutrophil-precursor band cells*** (referred as bandemia) in acute inflammations of *infectious* etiology
- **increased erythrocyte sedimentation rate (ESR)** - caused by increased plasma levels of the *acute phase reactants*, proteins synthesized by mainly by the liver (but also the inflammatory cells): fibrinogen, C-reactive protein (CRP), serum amyloid A (SAA)
- **dysproteinemia –** electrophoresis characterized by: - decreased albumins
  - increased α1- and α2-globulins

MAINS STAGES:

I. **Release and/or activation of the inflammatory mediators**
II. **Vascular reaction** leading to the formation of the **inflammatory *exudate***
III. **Cellular reaction** leading to the formation of the **inflammatory cellular *infiltrate***
IV. **Tissue repair and healing**

I. RELEASE and/or ACTIVATION of the INFLAMMATORY MEDIATORS

- **Role**: to trigger and modulate the acute inflammation
- **Classification** – according to their *origin:*
  - **A. CELLULAR mediators**: released by the inflammatory *cells*
  - **B. PLASMA mediators** – 3 systems of *circulating proteins*: the *complement*, *clotting* and *kinin* systems whose components circulate in inactive forms (proenzymes) and are activated during acute inflammation

A. CELLULAR mediators – 2 types:

a) **PREFORMED** - stored in the granules of the cells participating to the inflammation
b) **NEWLY-FORMED** - synthesized *de novo* by the cells activated during inflammation or as metabolites of the membrane lipids released during cellular injury/destruction

a) The PREFORMED cellular mediators – are released by *degranulation* of the:
- mast cells (and basophils): **histamine** and **chemotactic factors for neutrophils** (NCF, Neutrophil Chemotactic Factor) and **eosinophils** (ECF, Eosinophil Chemotactic Factor)
- phagocytes: **lysosomal enzymes**

1. HISTAMINE:
- sources: **mast cells/basophils**
- effects:
  - ✓ vasodilation
  - ✓ increased vascular permeability
  - ✓ contraction of bronchiolar and intestinal smooth muscles
  - ✓ chemotaxis for neutrophils and eosinophils
  - ✓ itching (pruritus)

Observations: The effects are mediated through binding to histamine receptors (4 types: H1, H2, H3, H4, in the order of their discovery), with a major role for H1 and H4 receptors in the pathogenesis of the allergic inflammation. Nowadays, *H1 receptor blockers (antihistamines)* are used for the treatment of allergies with 3 generations of drugs being available: 1st generation – e.g., cyproheptadine, 2nd generation – e.g., loratadine, and 3rd generation – e.g., desloratadine (developed in order to reduce the side effects of the previous). Currently, several H4 receptor blockers are investigated in preclinical models of inflammation.

2. CHEMOTACTIC FACTORS for NEUTROPHILS (NCF) and EOSINOPHILS (ECF):
- sources: **mast cells/basophils**
- effects: attract the corresponding leukocytes into the inflammatory site:
  - neutrophils (microphages) are *early* attracted at the inflammation site, in the first 6-12 hours after its onset
  - eosinophils serve as the primary defence against *parasites* and contribute to the *allergic* inflammations

3. LYSOSOMAL ENZYMES:
- sources: **phagocytes** (micro- and macrophages) and **eosinophils**
- the enzymes are released:
  a) intracellularly – at the level of phagolysosome with role in *phagocytosis*
  b) extracellularly (through exocytosis of lysosomes) with a:
  - *physiological role* when released in small amounts, signaling the immune response and control of energy metabolism
  - *pathological role* when released in massive amounts through the destruction of phagocytic cells and they elicit direct and indirect deleterious effects
- effects:
  - *direct*, intra- and extracellular, with:
    - ✓ collagen lysis – *collagenase*
    - ✓ elastin lysis – *elastase*
    - ✓ lysis of extracellular matrix components (eg, proteoglycans) – *cathepsins*
  - *indirect*, extracellular, with:
    - ✓ activation of the complement system
    - ✓ activation of kinin system
    - ✓ activation of fibrinolysis via the transformation of plasminogen into plasmin

- the enzymes are rapidly inactivated extracellularly by the *inhibitors or antiproteases*: *α1-antitrypsin, α1-antichymotrypsin, α2-macroglobulin*, present in serum and interstitial fluid

b) The NEWLY-FORMED cellular mediators – are synthesized *de novo* under the action of the etiological factors:

1. **Arachidonic acid metabolites**
2. **Platelet Activating Factor (PAF)**
3. **Cytokines**

1. ARACHIDONIC ACID metabolites

Tissue damage and/or the etiological agents activate *phospholipase A2* that releases **arachidonic acid** from cell membrane phospholipids, which is further metabolized via 2 major pathways: the **cyclooxygenase (COX)** and **lipoxygenase (LOX)** pathways, respectively.

Two COX isoforms have been identified so far: **COX-1**, which is constitutively expressed in most cells and **COX-2**, which is the inducible isoform in the setting of acute/chronic inflammation.

The arachidonic acid is the precursor of: i) **prostaglandins, prostacyclins, thromboxanes** via the **cyclooxygenase** pathway and ii) **leukotrienes** via the **lipoxygenase** pathway.

- **Prostaglandins (PG)**, e.g. **PG D, E, F** induce:
  - vasodilation
  - increase in vascular permeability
  - contraction of bronchiolar smooth muscle (PG D_2)
  - pain
  - fever: PGE_2 is the *central (hypothalamic) mediator* of fever
- **Prostacyclins** (**PG I_2**) are a subtype of PG that induce:
  - vasodilation
  - inhibition of platelet adhesion and aggregation
- **Thromboxanes,** e.g. **Tx A_1, A_2** induce:
  - vasoconstriction
  - stimulation of platelet adhesion and aggregation
- **Leukotrienes,** e.g. **LT B, C, D, E** induce:
  - increase in vascular permeability
  - chemotactic effect for neutrophils – **LTB_4**
  - contraction of bronchiolar and gastrointestinal smooth muscles – **LT C, D** and **E**.

  LT C_4, D_4 and **E_4** have a **central role in the pathogenesis of asthma**, since they elicit severe bronchoconstriction, eosinophils recruitment, and promote chronic inflammation.

Observations:

1. Corticosteroids are broad-spectrum anti-inflammatory agents that reduce transcription of genes encoding *phospholipase A2* and *COX-2*.

2. Non-steroidal anti-inflammatory (NSAID) *drugs* are:

- *cyclooxygenase (COX) inhibitors*: i) *non-selective* - inactivate both COX-1 and COX-2, e.g., aspirin, diclofenac, indomethacin, ibuprofen, naproxen etc. and ii) *selective* COX-2 inhibitors – more potent in blocking COX-2 than COX-1, e.g. celecoxib
- *lipoxygenase (LOX) inhibitors*: e.g., zileuton.

3. Lipoxins (LX) are lipid mediators generated from arachidonic acid via the LOX pathway during in various cells, which exert ***anti-inflammatory effects***, being categorized as members of the *specialized pro-resolving mediators* family that serve to promote the *resolution* of acute inflammatory responses.

2. PLATELET ACTIVATING FACTOR (PAF)

- source: breakdown of membrane phospholipids under the action of *phospholipase A2* in several cells: platelets, neutrophils, monocytes/macrophages, and endothelial cells
- effects:
  - platelet activation and aggregation
  - increase in vascular permeability
  - chemotaxis and activation of neutrophils
  - contraction of the bronchiolar smooth muscle with severe bronchoconstriction

3. CYTOKINES

Cytokines are polypeptides synthesized and released by a wide range of cells: neutrophils/microphages, monocytes/macrophages, lymphocytes, fibroblasts, endothelial cells, etc., which comprise several types: interleukins (IL), interferons (IFN), lymphokines, monokines, tumor necrosis factors (TNF), growth factors (Transforming Growth Factors, TGF), colony stimulating factors (CSF).

To data, approx. 200 cytokines have been described with ***pro-inflammatory***, e.g., **IL-1, IL-6, IL-8, IL-17, TNF-α** or ***anti-inflammatory effects***, e.g., **IL-10, IL-11, TGF-β**.

Observation: The major role of the massive plasma release of *pro-inflammatory cytokines* or the so-called *"cytokine storm"* was described in the setting of the exacerbated acute inflammation or *"hyperinflammation"* – responsible for the unfavorable evolution of patients with severe forms of COVID-19 disease.

Interleukins IL-1, IL-6 and **TNF-α** elicit several effects, such as:

- increased **synthesis and expression of adhesion molecules on the surface of endothelial cells** in order to attract leukocytes at the inflammatory site by means of the sequential processes: pavementing, rolling, adhesion and migration into the interstitium
- trigger the **acute phase reaction**, by acting on:
  - ✓ ***hepatocytes***, especially **IL-6**, to **increase synthesis of acute phase proteins**: C-reactive protein, fibrinogen, serum amyloid A, lysosomal antiproteases (α1-antitrypsin, α1-antichymotrypsin, α2-macroglobulin), transporter/binding proteins (ceruloplasmin, haptoglobin, hemopexin), complement components (C3, C4, C5, C9);
  - ✓ ***hypothalamus,*** to induce **fever**, being called **endogenous pyrogens**
  - ✓ ***bone marrow,*** to cause **leukocytosis with neutrophilia** both by releasing the preformed leucocytes (PMNs) and inducing the proliferation of the granulocyte precursors.
- **proliferation of fibroblasts** with **collagen synthesis** to support the healing process.

Interferons (IFN) are cytokines with a **major role in the antiviral defence** – 3 main types:

- ✓ **type I, include IFN-α** and **IFN-β** – released by the **virally infected** *leukocytes, fibroblasts, macrophages/dendritic cells*, with the role of increasing the production of molecules capable of preventing viral replication in these cells as well as in the neighboring healthy cells (autocrine and paracrine effects);

- ✓ **type II, include IFN-γ** – produced by **immune cells**, *Natural Killer (NK) lymphocytes* and *T lymphocytes*, with the role of increasing the activity of macrophages and cytotoxic T lymphocytes, inducing a Th1-mediated immune response;
- ✓ **type III, include IFN-λ** – produced by **epithelial cells** with a role in local antiviral defence within the digestive tract, but also with antibacterial and antifungal properties.

B. PLASMA mediators

Are represented by 3 plasma proteins systems present in an *inactive state* in the circulation and sequentially *activated* in the setting of acute inflammation:

1. **The COMPLEMENT system**
2. **The COAGULATION system**
3. **The KININ system**

1. The COMPLEMENT system:

- consists of a large number of proteins (10% of total circulating serum proteins) activated by 3 pathways: **classical**, **alternative and lectin pathway**
- effects: i) activation of the inflammation via: *anaphylatoxins*, *chemotactic factors* and *opsonins* and ii) direct lytic via the *membrane attack complex*.
  - **C_{3a}** and **C_{5a} are anaphylatoxins** and cause rapid degranulation of mast cells and the histamin release that elicits: vasodilation, increased vascular permeability and contraction of bronchiolar and intestinal smooth muscles
  - **C_{5a}** is also a **chemotactic factor**
  - **C_{3b}** is an **opsonin** that coats the surface of bacteria and thus increases phagocytosis
  - **C_{5b-9}** is called the **membrane attack complex (MAC),** which is assembled on the cells and bacteria surfaces and creates pores in the membrane that make them permeable for water and ions, resulting in ***osmotic lysis*** of the target cells.

2. The COAGULATION and FIBRINOLYSIS systems:

- together with fibrinolysis, coagulation regulate the hemostatic response and vascular repair by producing and breaking down fibrin, respectively
- aside from their role in hemostasis, the components of the clotting and fibrinolytic systems are important mediators of the chronic inflammation associated with the non-communicable diseases such as: atherosclerosis, asthma, cancer etc.
- tissue injury and/or vascular leak/rupture result in the activation of zymogens (clotting factors precursors) driving coagulation/fibrinolysis and acute inflammation/reparative pathways
- the inappropriate coagulation-mediated activation of inflammation can be harmful to tissue repair, i.e. excessive or insufficient fibrin deposition can lead to early convalescence complications such as: bleeding or thrombosis, the systemic inflammatory response syndrome syndrome, or even multiorgan dysfunction syndrome
- similarly, inadequate fibrin removal causes impaired tissue repair or tissue degeneration.

3. The KININ system

- comprises a family of plasma proteins, which closely interact with coagulation since both systems are activated by the clotting factor XII (Hageman factor)
- the main kinin is **bradykinin** that is generated from an inactive precursor, *kininogen* under the action of activated factor XII
- effects:
  - ✓ vasodilation
  - ✓ increased vascular permeability
  - ✓ contraction of bronchiolar and intestinal smooth muscles
  - ✓ pain

II. The VASCULAR REACTION

- **Role:** leads to the formation of the **inflammatory EXUDATE**
- **Comprises 3 processes:**
  - **a) Vasodilation**
  - **b) Increased vascular permeability**
  - **c) Changes in blood flow velocity**
- **Consequences:** the **metabolic changes** at the site of inflammation

a) Vasodilation:

- ***Cause****:* the release of histamine, bradykinin, anaphylatoxins, prostaglandins
- ***Consequencs:*** *increased local blood flow* or *hyperemia*, responsible for 2 cardinal signs:
  - local redness or **RUBOR**
  - local rise in temperature or **CALOR**

b) Increased vascular permeability:

- ***Cause:*** widening of the junctions between endothelial cells (contraction of the periendothelial muscle cells) elicited by the release of the above mentioned mediators and endothelial ccells injury
- ***Consequences:*** *leakage of fluid and proteins (albumins) from the vascular lumen into the interstitium at the site of injury* with the **formation of the inflammatory exudate** characterised by **high protein concentration > 3 g/dL** plus the presence of **cellular debris**, which elicits the 3rd cardinal sign **– edema / local swelling or TUMOR.**

c) Changes in blood flow velocity – initial **hyperemia,** followed by subsequent **blood stasis**

- ***Causes:***
  - vasodilation
  - local edema that compresses the vessels
  - increased blood viscosity with hemoconcentration due to fluid leak into the interstitium
  - microthrombi formation triggered by platelet adhesion and aggregation
- ***Consequences:*** *cellular hypoxia***,** responsible for **metabolic changes** and **endothelial damage**, which contribute to the worsening of vascular hyperpermeabilization

METABOLIC CHANGES at the inflammation site:

- **Causes: vascular stasis** and **cellular hypoxia** at the site of injury
- **The metabolic changes** consist of:

- **anaerobic glycolysis** and local **lactic acidosis**
- **decreased cellular energogenesis** with **decreased ATP synthesis** due to:
  - ✓ low yield of anaerobic glycolysis
  - ✓ mitochondrial damage with the uncoupling of oxidative phosphorylation
- **impairment of water and ion distribution** with:
  - ✓ ***inflammatory edema:*** accumulation of water into the interstitium due to the increased capillary permeabiliy
  - ✓ ***transmineralisation:*** K^+ outflow and Na^+ entry into the cells
- **breakdown of membrane phospholipids** with the release of arachidonic acid and increased synthesis of its metabolites
- **increased protein catabolism** due to the release of the phagolysosome content (lysosomal proteases) into the extracellular space, which occurs especially if phagocytes encounter materials that cannot be easily ingested
- **accumulation of algesic factors**: *bradykinin, prostaglandins (PGE_2), H^+*, which along with *the edema* compressing the nerve endings are responsible for the 4th local cardinal sign: pain or **DOLOR.**

ADVANTAGES of the inflammatory exudate formation are as follows:

- **water efflux** with the **dilution of bacterial toxins** and **cellular debris**
- **proteins efflux,** such as:
  - **Ig (antibodies)** with **local defence** role
  - **fibrinogen** with local generation of fibrin that **limits the propagation of the inflammatory response** and also, brings together the wound edges, allowing the **initiation of healing and tissue repair**
- **increased lymphatic drainage** allowing the **microbial antigens** to reach the **lymph nodes where they encounter lymphocytes with the activation of the acquired immunity,** BUT there is also a DISADVANTAGE, namely the *risk of spreading the infection*.

III. The CELLULAR REACTION

- **Role:** leads to the formation of the **inflammatory CELLULAR INFILTRATE**
- **Includes 5 stages:**

a) **Margination/Pavementig** is the **loss of the central position of leukocytes in the bloodstream and gather along the endothelium** (like the bricks paving a road), being favoured by blood stasis.

b) **Rolling and adhesion of leukocytes to the endothelium** is an active process mediated by **adhesion molecules** (e.g., selectins, integrins, cadherins) and **chemokines.**

c) **Migration across the vessel wall into the interstitium** - in the first **6-24 hours, neutrophils** leave the vessels and act as **microphages** but they are short-lived, and are followed by **monocytes** in the next **24-48 hours**, which act as **macrophages**, survive longer and can proliferate in tissues, being the dominant cells in chronic inflammation.

d) **Chemotaxis** is the **directed migration of leukocytes towards the inflammatory site** under the action of several **chemoattractants:**

- bacterial toxins

- anaphylatoxin C_{5a}
- leukotriene B_4
- IL-8 (chemokine)
- chemotactic factors: NCF, ECF

e) <u>Phagocytosis</u> involves:

- **adhesion** to foreign particles - favoured by their opsonization with IgG antibodies and the C_{3b} component of the complement system
- **endocytosis** - foreign particle engulfment and the formation of an intracellular phagocytic vacuole or **phagosome**
- **formation of the phagolysosome** - lysosomes fuse with the phagosome and within the phagolysosome where the destruction of the phagocytosed material occurs (with no damage to the rest of the cell since the content is sequestered from the cell cytoplasm) by **2 mechanisms**:
  - **oxygen-dependent killing** mechanisms: bactericidal and cytolytic action mediated by the formation of toxic **reactive oxygen species (ROS)**, mainly via the activation of NADPH oxidase and myeloperoxidase
  - **oxygen-independent** mechanisms: **lysosomal enzymes** (acidic hydrolases, collagenase, elastase), **bactericidal proteins** (eg, lysozyme), **lactoferrin** (that binds iron and thus inhibits the bacterial growth).

Observation: In acute inflammation, neutrophils also produce *neutrophil extracellular traps (NETs)*, which are extracellular fibrillar networks that trap microbes at sites of infection, thus helping to prevent their spread.

IV. TISSUE REPAIR and HEALING

There are 3 possible outcomes of acute inflammation:

a) Complete resolution: is the ideal type of healing that occurs with *little tissue destruction*, allowing removal of cellular debris and/or microbes by macrophages, resorption of edema and regeneration of damaged cells (via cell proliferation of differentiated cells that still retain the capacity to proliferate, e.g. liver cells).

b) Scarring & fibrosis: is healing by connective tissue replacement that occurs after *substantial tissue destruction* when the damaged tissue cannot regenerate.

c) Progression to chronic inflammation: occurs when the acute inflammatory response cannot be resolved due to persistence of injurious agent or other interference with the normal healing process.

CLASSIFICATION:

- **PRIMARY wound healing ("per primam intentionem")** - in **minimal** tissue injuries, e.g., aseptic wounds where wound edges are in close vicinity, such as *surgical incisions* closed with stiches or staples;
- **SECONDARY wound healing ("per secundam intentionem")** - in **severe** tissue injuries resulting in a **large amount of tissue loss**, such as an *ulcer* or an *abscess* (that cannot be stiched) – the stages of scarring are the same, but requires a greater amount of reparative tissue and takes longer.

Observation: The morphologic patterns of acute inflammation and abnormalities in tissue repair (deficient scar formation, excessive scarring and fibrosis, contracture etc.) are detailed at Morphopathology.

CHRONIC INFLAMMATION

DEFINITION: a **PATHOLOGICAL process lasting several days, weeks or months** characterised by the **coexistence** of varying degrees of **inflammation**, **tissue destruction** and **tissue repair** as the prolonged host reponse to persistent stimuli.

GENERAL FEATURES:

- ✓ **Duration**: days to months or years in case of chronic low-grade inflammation
- ✓ **Main characteristics:**
  - **VASCULAR CHANGES are REDUCED or ABSENT** (minimal edema)
  - **CELLULAR INFILTRATE** is dense and rich in **mononuclears,** which are macrophages - the main cells involved and **lymphocytes**
- ✓ **Tissue DESTRUCTION** (due to the persistence of the damaging agent and continuous recruitment of inflammatory cells) **is <u>coexisting</u> with tissue REPAIR** with:
  - **local angiogenesis**
  - **deposition and remodeling of connective tissue**
- **Tissue injury**: **EXTENSIVE**, with **scarring** and **fibrosis.**

CLASSIFICATION:

a) **Chronic inflammation *secondary to acute inflammation***, when the etiological agent was not be completely destroyed by the defence reaction.

b) **Chronic *primary* inflammation**, in case of:
   - ***infections with microorganisms with intracellular localization***, e.g. bacteria (in tuberculosis, brucellosis), fungi (in histoplasmosis), parasites (in toxoplasmosis, leishmaniasis) responsible for the chronic inflammation from *type IV hypersensitivity reaction* (cell-mediated or delayed type);
   - ***excessive activation of the immune response***, responsible for the chronic inflammation from *autoimmune diseases*, e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis;
   - ***chronic exposure to an exogenous damaging agent,*** e.g., in the lungs, chronic inhalation/deposition of silicon dioxide causes chronic inflammation from **silicosis** or ***to an endogenous agent***, e.g., in the vascular walls, cholesterol deposition causes chronic inflammation from **atherosclerosis;**
   - ***prolonged presence of physical irritants***, e.g. suture material, talcum powder, foreign bodies (wood splinter, glass, dirt) causes **chronic granulomatous inflammation** in the attempt of the body to isolate and wall-off that area.

The classic lesion is the **granuloma,** which consists of a:

- **Central core** made up of: i) **epitheloid cells,** which are activated macrophages specialized to phagocyte cellular debris and small particles, and ii) **multinucleated giant cells** called **Langhans cells**, which are formed by the fusion of epitheloid cells in order to engulf larger particles

- **Surrounding collar** of **lymphocytes**
- **Capsule of fibroblasts** secreting **collagen** and leading to **fibrosis** (and sometimes, calcification).

PATHOGENESIS:

Activated macrophages play the central role in **chronic inflammation**. Their activation is achieved by **non-immune** (*infectious/toxic*) or **immune** mechanism (*cytokines* - e.g. *IFN-*γ released by NK lymphocytes and T lymphocytes) and is responsible for 2 simultaneous processes:

i) **persistence of inflammation** and **tissue destruction** via increased release of ***pro-inflammatory cytokines****: IL-1, IL-12, IL-23 and TNF-*α and ***toxic mediators****:* reactive oxygen and nitrogen species (with oxidative and nitrogen stress)

ii) **activation of healing processes** with **fibrosis, angiogenesis and tissue remodelling** via the release of ***anti-inflammatory cytokines****: growth factors* – e.g. TGF-β , Transforming Growth Factor-β and *proangiogenic factors* – e.g. FGF, Fibroblast Growth Factor.

Currently **2 subpopulations of macrophages** have been described (Table 1.3).

Table 1.3. Macrophages subtypes in chronic inflammation.

	Classically activated (M1)	**Alternatively activated (M2)**
Induced by	- microbial products, e.g. endotoxin - cytokines, e.g. IL-2, IFN-γ secreted by T helper 1 (Th1) lymphocytes	- cytokines, e.g., IL-4, IL-5, IL-13 secreted by T helper 2 (Th2) lymphocytes
Secrete	- IL-1, IL-12, IL-23, TNF-α - reactive oxygen species	- IL-10, TGF-β
Functions	- microbicidal efect - inflammatory effect	- tissue repair, fibrosis - anti-inflammatory effects

Observation: Nowadays it is well known that the **intracellular signaling during the inflammatory reaction** has as a **central event the formation** in the cytosol of large oligomeric multiprotein structures called **inflammasomes**. Inflammasomes function as intracellular alarm sensors that activate signaling cascades responsible for the: i) secretion of pro-inflammatory cytokines and ii) release of caspases, enzymes triggering apoptosis (non-inflammatory programmed cell death) or pyroptosis (pro-inflammatory programmed cell death). Adequate activation of the inflammasome within a wide array of cells (neutrophils, macrophages, lymphocytes, dendritic cells, epithelial cells, neurons, osteoblasts etc.) allows the body to cope with pathogens or tissue damage, but its **aberrant activity** is involved in **chronic inflammation** from autoimmune, neurodegenerative, cardiometabolic diseases and various forms of cancer.

In the last two decades, the most studied inflammasome has been the ***NLRP3*** (Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3) ***inflammasome***, a multiprotein complex with a central role in inflammatory signaling and the innate immune system regulation. Its *dysfunction* and/or *pathological activation* has been implicated in the pathogenesis of cardiovascular diseases, metabolic syndrome, type 2 diabetes, Alzheimer's disease, chronic kidney disease etc., and represents currently one of the most investigated therapeutic targets.

PARTICULAR TYPES OF INFLAMMATION

1. CHRONIC LOW-GRADE INFLAMMATION is considered to be the ***common pathogenic mechanism of asthma, cardiac diseases, autoimmune disorders, neurodegenerative diseases (such as Alzheimer's disease),*** as well as ***metabolic diseases*** (obesity/metabolic syndrome, diabetes, non-alcoholic fatty liver disease) – for the latter condition, the term **META-INFLAMMATION** ("metabolic inflammation") being also in use.

2. AGE-RELATED CHRONIC INFLAMMATION, also referred to as **INFLAMM-AGEING**, is defined as the age-related increase in the levels of pro-inflammatory markers in blood and tissues. It is a strong risk factor for several diseases highly prevalent in elderly, e.g.: cardiovascular diseases, type 2 diabetes mellitus, chronic kidney disease, sarcopenia, anemia, dementia and cancer leading to a vicious cycle that exacerbates the decline in cellular functions further promoting ageing.

3. INFLAMMATION TRIGGERED BY the infection with the SARS-CoV2 virus is a widely recognized central pathophysiological mechanism in the evolution of COVID-19 disease, being described at least 3 types of inflammation:
1) Fulminant acute inflammation or **HYPER-INFLAMMATION**, characterized by the massive release of cytokines (the so-called "cytokine storm") responsible for: i) early lung damage through diffuse injury to the alveolar epithelium, ii) pan-vascular endotheliitis (at the micro and macrocirculation level) and systemic endothelial dysfunction underlying life-threatening acute complications: hypercoagulability/thrombosis and multiorgan dysfunction syndrome;
2) Multisystem Inflammatory Syndrome (MIS), described in adults (MIS-A, Adults) and children (MIS-C, Children) in the first 12 weeks post-COVID in patients with severe forms of COVID and which involves multiple organ inflammatory impairment (heart, brain, kidney, liver, eyes, skin) and requires hospitalization and systemic anti-inflammatory therapy;
3) Persistent chronic inflammation in the "long-COVID" syndrome, described in adults after 12 weeks post-infection and associated with asthenia, dyspnea or chest pain that can persist for several months or even years, in the presence or absence of inflammatory markers.

All the above mentioned conditions, including ageing, have been systematically associated with **mitochondrial dysfunction** characterized by: increased ROS production, reduced ATP, impaired signalling and increased extracellular release of mitochondrial components (e.g., cell-free mitochondrial DNA) with critical role in perpetuatingf chronic inflammation.

Observation: Uncontrolled or excessive acute tissue inflammation can lead to chronic inflammation that enhances tissue destruction, thus amplifying most chronic pathologies. The resolution of inflammation has emerged in the past decade as an important endogenous process, which protects the host tissues from prolonged or excessive inflammation that may become chronic. Several mediators known as *"**specialized pro-resolving mediators**" or **SPMs*** regulate resolution via anti-inflammatory effects: limitation of neutrophil tissue infiltration, stimulation of macrophage-mediated clearance of dead PMN neutrophils, cellular debris, and microbes, and counter-regulatory effects for the arachidonic acid-derived mediators and cytokines. The SPMs are bioactive metabolites of fatty acids and encompasses 4 classes: lipoxins, resolvins, protectins, and maresins. These molecules and related signaling pathways are currently highly investigated as novel therapeutic approaches for a variety of diseases associated with chronic inflammation, infections, organ protection during trauma in order to strengthen the body's innate resistance to adversity within the so-called ***resolution medicine***.

2. PATHOPHYSIOLOGY OF FEVER. DISORDERS OF TEMPERATURE REGULATION

OVERVIEW OF THERMOREGULATION - BRIEF PHYSIOLOGY REVISION

The body's core temperature is maintained constant within the narrow range of 37±0.5°C in order for the metabolic processes to occur properly. Thermoregulation is mainly under the control of hypothalamus (specifically, the thermoregulatory center in the preoptic area of the anterior hypothalamis), which acts as a thermostat that keeps the 'set point' of the body within the above mentioned values. Variations beyond this range are detected by the peripheral (skin) and central (visceral) thermoreceptors that inform the thermoregulatory center, which will return body temperature to the baseline via complex thermoregulatory mechanisms of heat production (thermogenesis), heat conservation or heat loss (thermolysis) that are summarized in Table 2.1. Heat is distributed from the central core towards body's surface by the circulatory system.

Table 2.1 Mechanisms of heat production (thermogenesis) and heat loss (thermolysis).

Mechanisms of THERMOGENESIS	Mechanisms of THERMOLYSIS
1. Chemical metabolic reactions, which occur at rest, mainly in the liver during the metabolism of ingested food (basal matabolism).	**1. Radiation**, which is heat loss in form of infrared rays radiated from the body when the body temperature exceeds the surrounding temperature.
2. Chemical thermogenesis, defined as increased basal metabolism via the: i) release of hormones: thyroxine, epinephrine, which are transiently increase heat production & conservation and ii) involvement of brown adipose tissue (rich in uncoupling proteins responsible leakage of hydrogen ions from the electron transport chain, which will dissipate as heat instead of producing ATP) mainly in newborns (and markedly decreases in adults).	**2. Convection,** which is heat loss in form of air currents; the warmer air at body's surface is exchanged with the cooler air in surrounding space.
3. Skeletal muscle contraction, which occurs as: - rapid involuntary contractions (shivering) - a gradual increase in the muscle tone	**3. Conduction,** which is heat loss via the direct contact with a solid object; the warmer surface transfer heat to the cooler surface.
4. Vasoconstriction in response to sympathetic stimulation, to prevent the diversion of the core-warmed blood to the skin surface, thus diminishing the heat transfer to the surrounding environment (heat conservation).	**4. Evaporation** of the: i) body water at the skin skin (trans-epithelial) and respiratory tract, known as *insensible perspiration* and ii) sweat, which is the *major mechanism of heat loss in warmer surroundings* (increased sweating).
5. Behavioral changes to allow heat conservation when body temperature decreases: adding clothing, increased voluntary movements, adopting a closed body position (bundle up) to reduce the body surface area available for heat loss, and increased appetite.	**5. Vasodilation** in response to parasympathetic stimulation, to stimulate the diversion of core-warmed blood to the skin surface, thus increasing the heat transfer to the surrounding environment (heat loss)
	6. A gradual decrease in skeletal muscle tone, perceived as exhaustion in a hot environment
	7. Behavioral changes to allow heat loss when body temperature increases: removing clothing, reduced voluntary movements, adopting an open body position (stretching out) to decrease the body surface area available for heat loss, and reduced appetite.

PATHOPHYSIOLOGY OF FEVER

DEFINITION: a **systemic, non-specific defence reaction** triggered by various **external** and **internal agents** called **exogenous and endogenous pyrogens** and characterised by the **elevation of the core body temperature due to an increase in the 'set-point'** of the hypothalamic thermoregulatory center.

Observation: The most common causes of fever in clinical setting are: **sepsis** (accounts for up to 75% of cases in hospitalized patients), malignancy, tissue ischemia, and drug reactions (which account for most of the remainder of the fevers seen in the hospitalized setting). Major body trauma with damage to the central nervous system, major surgery, severe burns are responsible for "central fever", which does not induce sweating and is resistant to antipyrethic therapy.

PATHOPHYSIOLOGY:

1. EXOGENOUS pyrogens - are:

- **Pathogens** in **infections: bacteria** and their toxins - ***endotoxins*** produced by *Gram (–) bacteria (e.g., lipopolysaccharide) or* ***exotoxins*** produced by *Gram (+) bacteria (e.g., peptidoglycans),* **viruses, fungi, parasites**
- **Antigen-antibody complexes** in the **autoimmune diseases**
- **Drugs-induced fever** is associated with the administration of a drug and disappears when the drug is discontinued. Pharmacological agents may cause fever by several pathophysiological mechanisms that include: interference with the physiological mechanisms of pseripheral heat loss, interference with central temperature regulation, direct damage to tissues, drug pyrogenic property or stimulation of immune response (e.g., penicillin that induces a hypersensitivity reaction accompanied by fever)
- **Chemicals toxins**

Effects - fever is induced both:

- ✓ **directly** via the hypothalamic synthesis of prostaglandin E_2 (PGE_2) from arachidonic acid by means of COX2 induction by pyrogens
- ✓ **indirectly** via the release of **ENDOGENOUS pyrogens** from the **phagocytic cells**

2. ENDOGENOUS pyrogens - are:

- Cytokines released into circulation by the
  - **Inflammatory cells: micro-/macrophages, lymphocytes** in inflammations, infections including sepsis:
    - **IL-1 and TNF-α** - **the most potent endogenous pyrogens**
    - **IFN (α,γ)**
    - **IL-6 -** the weakest pyrogen, but with persistent effect
  - **Tumor cells** in leukemias, lymphomas, advanced cancers

Effects - 2 types:

a. CENTRAL effects:

- induce the **synthesis of PGE_2**, which is the **central mediator of fever,** in endothelial cells of vessels supplying the anterior hypothalamus (preoptic area)
- **PGE_2** binds to **receptors on the surface of neurons** in the of the hypothalamic preoptic area and raises **the thermostatic 'set point'** via cAMP synthesis

Role: to induce fever by temporary **upward "resetting" the hypothalamic thermostat**.

b. PERIPHERAL effects:

- **FAVOURABLE effects - in short term:**
  - increased liver synthesis of *acute phase proteins* - mainly the effect of IL-6 ⇒ elevation of their serum level (CRP is currently measured marker)
  - increased synthesis of mediators of lipid origin (PGE_2, Tx, PAF) ⇒ triggering the *acute inflammation* (defence reaction)
  - induce leukocyte mobilization from the bone marrow ⇒ *leukocytosis*
  - increase expression of adhesion molecules (selectins, integrins) in the vascular endothelium ⇒ *margination of leukocytes*
  - increased synthesis of IL-8 (chemotactic factor for neutrophils and monocytes) ⇒ *phagocytes recruitment at the inflammation site*
  - increased release of lysosomal enzymes ⇒ *enhanced phagocytosis*
  - increased production of *antiviral interferons*
  - *activation of NK cells, B and T lymphocytes*
  - *decreased serum levels of iron, zinc and copper*, oligoelements necessary for bacterial multiplication

  Role: to increase the defence capacity of the body

- **ADVERSE effects - in long term:**
  - acceleration of muscle catabolism & negative nitrogen balance ⇒ weight loss in prolonged febrile states
  - synergistic toxic effects ⇒ risk of *toxic shock* when released in large amounts/over a long period of time

EVOLUTIVE STAGES – 4 phases have been described:

1. The prodromal or onset phase is characterised by:

- non-specific symptoms (asthenia, myalgia, headache) caused by the release of endogenous pyrogens into circulation
- the 'set point' of the hypothalamic thermoregulatory center is **unchanged**

2. The temperature rise or effervescence phase is characterised by:

- **elevation of the thermoregulatory center 'set point'** (upward resetting)
- **mechanisms that promote heat production/conservation and prevent heat loss** are activated:
  - **increased thermogenesis** by means of: increased skeletal muscle tone, shivering reflex and increased metabolism
  - **decreased thermolysis** through: cutaneous vasoconstriction (perceived as a 'cold sensation') and decreased sweating

3. The febrile or flush phase is characterized by:

- **equilibrium between thermolysis - thermogenesis** at a **higher** temperature
- **cutaneous vasodilation** (patient "feels warm")

4. The temperature decrease or defervescence phase is characterised by:
- **the thermoregulatory center 'set point' returns to normal**
- **mechanisms that promote heat loss and prevent heat production/conservation** are activated:
  - **increased thermolysis** through: cutaneous vasodilation and increased sweating
  - **decreased thermogenesis** by decreasing the skeletal muscle tone

FEVER EFFECTS:

I. FAVOURABLE effects: increased body defence capacity **against infections through *bactericidal/bacteriostatic & antiviral effects*** via the:
- peripheral effects of endogenous pyrogens (listed above) with the *stimulation of the inflammatory response*
- lysosomal breakdown and autodestruction of infected cells with the *prevention of bacterial multiplication and viral replication*
- induction of heat shock proteins synthesis with *increased lymphocyte response to microbial antigens and stimulation of immune response*

II. UNFAVOURABLE effects:
- temperature increase requires the augmentation of cellular O_2 consumption, which in turn triggers the acceleration of metabolism with deleterious effects in patients with:
  - cardiovascular pathologies by overloading the heart
  - cerebral pathologies through the impairment of mental activity (delirium and stupor)
- children before the age of 5 are at risk of *febrile seizures*
- in pregnant women, in the first trimester of pregnancy, one febrile episode with a temperature ≥ 37°C doubles the risk of *fetal neural tube defects*

MANIFESTATIONS:

1. CARDIOVASCULAR manifestations:
- **Heart rate (HR):**
  - increases parallel to temperature increase (by 10-15 b/min for every 1°C)
- **Cardiac output (CO):**
  - decreases during the chill phase (due to vasoconstriction)
  - increases in the flush phase due to increased O_2 consumption ⇒ marked increase in CO and O_2 requirements are **precipitating factors for the decompensation of pre-existing heart failure**

2. RESPIRATORY manifestations:

Causes:
- **increased temperature of the blood supplying the respiratory control center**
- **accumulation of CO_2 at the level of respiratory center** due to decreased cerebral blood flow during shivering

Effects:
- **increased respiratory rate** (but tidal volume is low) in order to **accelerate thermolysis by insensible perspiration**
- **rapid and shallow breathing (polypnea)** leads to mild PaO_2 decrease and marked $PaCO_2$ decrease, the latter being responsible for **respiratory alkalosis**

3. DIGESTIVE manifestations:

- **decreased motility and secretory function of digestive tract glands** with **inappetence,** which together with:
  - **increased cell catabolism**
  - **fluid loss** through excessive/profuse sweating

which explain the *weight loss* in prolonged febrile states

4. NEUROLOGIC & COGNITIVE manifestations:

- **aggravation of an cerebral edema**
- **decreased seizure threshold** with decompensation of patients with mental disorders
- **benign (minor) febrile seizures** in healthy children and more severe seizures in children with neurological disorders

5. METABOLIC AND HUMORAL changes:

- **increased energy metabolism** (by 15% for each 1°C > 37°C)
- **increased catabolism of muscle proteins with the release of aminoacids** that are:
  - used for hepatic synthesis of acute phase reactants with **dysproteinemia and increased ESR**
  - used as substrate for neoglucogenesis with **hyperglycemia**
  - excreted through urine with **aminoaciduria**
- **increased bone catabolism** with **calciuria**
- **alteration of water and electrolytes metabolism** due to water loss greater than sodium loss (sweat fluid is hypotonic) with *hypertonic extracellular dehydration,* which causes compensatory water efflux from cells leading to *intracellular dehydration responsible for the thirst sensation*, and finally, **global extra- and intracellular dehydration.**

DISORDERS OF TEMPERATURE REGULATION

Acclimatisation to high temperatures consists of:

- **Increased thermolysis** by:
  - **sweating,** which is **the most effective mechanism of thermolysis when the atmospheric humidity is low** (when the air is saturated with moisture, sweat evaporation is limited)
  - **cutaneous vasodilation** to promote heat loss
- **Decreased thermogenesis** by:
  - **decrease in skeletal muscle tone**
- **Behavioral changes:** removing clothing, reduced voluntary movements, adopting an open body position (stretching out), and reduced appetite.

When these adaptative mechanisms are surpassed the progressive increase of the body core temperature occurs with the installation of **HYPERTHERMIA.**

HYPERTHERMIA

DEFINITION: pathological conditions characterized by the **elevation of the body core temperature**, but **without an increase in the hypothalamic thermostatic set-point** (which remains unchanged).

CLASSIFICATION (CLINICAL FORMS):

A. EXOGENOUS hyperthermia - the increase in body temperature is caused by **exposure to a hot environment**

I. Heat cramps
II. Heat exhaustion
III. Heat syncope
IV. Heatstroke

B. ENDOGENOUS hyperthermia - the increase in body temperature occurs at a **normal ambient temperature**

V. Malignant hyperthermia

I. HEAT CRAMPS

Cause: strenuous work effort in hot climates, especially in persons not acustomed with heat
Clinical manifestations: spasmodic cramps of the skeletal muscles in the extremities or abdominal cramps, tachycardia and premature atrial/ventricular contractions
Laboratory findings:

- hypovolemia/hemoconcentration ± ionic imbalances, e.g., sodium loss

II. HEAT EXHAUSTION - the most common type of hyperthermia in practice

Cause: prolonged exposure to or effort in a very warm environment, particularly in *elderly treated with diuretics* (and exposed to high temperatures), which are at risk of severe dehydration due to increased diuresis and excessive sweating responsible
Clinical manifestations: weakness, headache and dizziness, nausea and fainting, prostration, delirium
Related tests & findings:

- hypotension and decreased cardiac output due to profound vasodilation and sweating
- hypovolemia/hemoconcentration ± ionic imbalances
- **core temperature < 40°C and <u>sweating is present</u>** (the skin is moist at variance from the heatstroke where the skin is dry)

III. HEAT SYNCOPE

Cause: intense effort or prolonged exposure to a very warm environment, which leads to a **sudden loss of consciousness**
Related tests & findings:

- severe hypotension (SBP < 100 mmHg) and decreased cardiac output
- hypovolemia/hemoconcentration ± ionic imbalances
- **core temperature < 40°C and <u>sweating is present</u>** (the skin is moist at variance from the heatstroke where the skin is dry)

IV. HEATSTROKE - the most severe type of hyperthermia

Definition: a potential lethal condition characterized by:

- a core body **temperature > 40°C**
- **absence of sweating** (as a result of an overstressed thermoregulatory center): the skin is *hot and dry* initially (but it becomes cold upon the onset of vascular collapse)
- **central nervous system abnormalities:** delirium, convulsions, coma
- a **systemic inflammatory response** that may lead to **multiorgan dysfunction** syndrome, manifested primarily with encephalopathy

Classification:

1. CLASSIC (NON-EXERTIONAL) heatstroke:

- occurs in the elderly and people with comorbidities: obesity, diabetes, chronic heart or kidney disease, alcoholism with chronic liver disease, dementia who are immobilized, alone or unable to hydrate themselves adequately when exposed to very warm environment

2. EXERTIONAL heatstroke:

- occurs in outdoor workers, athletes, soldiers performing strenuous physical activities in hot environments

Pathogenesis: multifactorial, due to the **association** of the:

i) direct harmful effects of heat on body cells

ii) excessive release of endogenous pyrogens with an initial protective role against cellular damage but who leads to an *exaggerated acute phase reaction*

iii) acute thermoregulatory failure

Evolutive stages:

a) Hemodynamic changes, evolving in two stages:

Initial stage:

- cutaneous vasodilation → decrease in peripheral vascular resistance
- increased cardiac output
- normal blood pressure (BP) or divergent arterial hypertension (increased systolic BP and decreased diastolic BP)

Advanced stage:

- decreased cardiac output and BP

b) Acute circulatory failure (shock) with tissue ischemia responsible for the occurrence of complications:

- rhabdomyolysis
- disseminated intravascular coagulation (DIC)
- **multiorgan dysfunction syndrome**, a life-threatening condition with **organ failure affecting ≥ 2 organs** (e.g., acute respiratory failure and acute renal failure)

Clinical manifestations: nausea, vomiting, marked asthenia, tachycardia, headache, dizziness, confusion, delirium, convulsions, coma

Laboratory findings and related tests:

- ionic imbalances: hyponatremia, hypocalcemia, hyperkalemia, hyperphosphatemia in case of rhabdomyolysis (+ myoglobinuria)
- coagulation abnormalities

- increased blood creatinine and urea due to kidney damage (renal tubular necrosis)
- increased ASAT, ALAT due to hepatic failure
- ECG changes due to heart damage
- $PaCO_2$ up to < 20 mmHg due to hyperventilation

V. MALIGNANT HYPERTHERMIA

Definition: potential lethal complication of a rare hereditary disorder of skeletal muscle characterized by a **rapid increase in the core temperature , under conditions of a normal ambient temperature, due to excessive thermogenesis** triggered by:

- inhalation halogenated anesthetics (halothane, ether)
- depolarizing muscle relaxants (succinylcholine)

Pathogenesis:

A mutation of the gene encoding for the **ryanodine receptor, the calcium channel of the sarcoplasmic reticulum (SR)** is responsible for the **calcium storage defect responsible for the uncontrolled release of calcium from the skeletal muscle SR elicited by exposure to the above mentioned drugs.**

An abrupt and major increase in intracellular calcium concentration causes:

- *sustained muscle contraction* resulting in adenosine triphosphate (ATP) depletion
- *activation of the calcium pump (SERCA) at the level of SR* with increased ATP consumption
- *a hypermetabolic state* in the attempt to produce ATP with the: i) activation of anaerobic glycolysis with hyperproduction of lactate and ii) increased mitochondrial oxygen consumption with heat generation
- ultimately, *depletion of ATP stores* that leads to membrane integrity failure and cell content leakage responsible for potassium, creatinine kinase, and myoglobin increase into the circulation. *Hyperkalemia* is associated with *the risk of ventricular arrhythmias* and *precipitation of myoglobin* in the kidney may result in acute tubular necrosis with *oligo-anuria.*

Clinical manifestations: tachycardia, tachypnea, hypercapnia, metabolic and respiratoryacidosis, hypotension, skeletal muscle rigidity (muscle spasm) in the presence of rapid elevation of body temperature, which occur during the intraoperative and postoperative periods, mostly in children and adolescents.

Observation: the treatment of malignant hyperthermia is immediate discontinuation of all triggering agents, i.v. administration of dantrolene, and cooling measures.

Acclimatisation to low temperatures consists of:

- **Increased thermogenesis** by:
  - **shivering and increased skeletal muscle tone**
  - **increased basal metabolism** (chemical thermogenesis triggered by hormones: thyroxine, epinephrine, mainly in the liver)
- **Decreased thermolysis** by:
  - **cutaneous vasoconstriction** to promote heat conservation

- **Behavioral changes** to allow heat conservation: adding clothing, increased voluntary movements, adopting a closed body position (bundle up or curl up into a ball) to reduce the body surface area available for heat loss, and increased appetite.

When these adaptive mechanisms are surpassed, a progressive decrease of the core temperature occurs with the installation of **HYPOTHERMIA**.

HYPOTHERMIA

DEFINITION: decrease in body core temperature ≤ 35°C.

CLASSIFICATION

Based on the core temperature drop, 3 degrees of severity are defined:

- **Mild hypothermia: 32-35°C**
- **Moderate hypothermia: 28-32°C**
- **Severe hypothermia: < 28°C**

Observation: The term **profound hypothermia** is used to define a core temperature **< 24°C.**

CAUSES

1. **Prolonged cold exposure** in case of:
   – extreme ages (elderly living alone in unheated homes in the cold season or neonates and infants in which the themoregulatory mechanisms are easily exhaustible)
   – trauma patients
   – mentally ill persons
   – drug or alcohol abusers
   – homeless people in the cold season
2. **Impaired thermoregulation** due to:
   – cerebrovascular accidents
   – spinal cord injuries
   – neurodegenerative disorders
   – peripheral neuropathies
   – skin disorders and severe burns
   – endocrine disorders: hypothyroidism, hypopituitarism, diabetes
   – decreased metabolic rates in: malnourshment/malnutrition, hypoglycemia
   – drug misuse (sedative medication)

PATHOGENESIS:

Excessive heat loss (increased thermolysis) caused by:

- **accidental exposure to the cold environment:** e.g., immersion hypothermia
- **increased blood flow at the skin level:** e.g., burns

Impaired heat production (decreased thermogenesis) caused by:

- **decrease basal metabolism** in: malnutrition, hypothyroidism, liver failure, hypoglycemia – all are causes of endogenous hypothermia

- **alteration of thermoregulation control** in: brain lesions, septic or toxic states: uremia, diabetic ketoacidosis that induce hypothalamic dysfunction
- **drug-induced**: phenothiazines, barbiturates, opiates, benzodiazepines in overdose

PARTICULAR FORM:

IMMERSION HYPOTHERMIA

- **Causes** – appears in:
  - persons accidentally immersed in cold water
  - swimmers in case of prolonged exposure to cold water
- **Pathogenesis** – 3 evolutive phases:
  1. Excitation phase: the core temperature drops to 35°C
  → **increased thermogenesis** through: voluntary movements and shivering
  → **decreased thermolysis** through peripheral vasoconstriction

  2. Inhibition phase: the core temperature drops between 34-30°C
  → **inhibition of CNS activity:** sluggish thinking, depressed coordination
  → **reduction of voluntary movements**
  → **shivering** is replaced by **muscle rigidity**

  3. Critical phase: the core temperature drops < 30°C
  → **stupor:** decreased respiratory rate, heart rate and cardiac output
  → **metabolic rate falls, acidosis**
  → risk for **ventricular arrhythmias and asystole**

II. ENDOGENOUS HYPOTHERMIA

- **Definition:** hypothermia that occurs at a ***normal ambient temperature*** due to:
  - decreased thermogenesis associated or not with
  - decreased heat conservation capacity
- **Pathogenesis: acute thermoregulation failure** caused by the **lack of shivering reflex**
- **Favoring factors:**
  - the presence of comorbidities: hypothyroidism, hypopituitarism, diabetes, congestive heart failure
  - the presence of conditions that alter thermoregulation control: brain injuries, septic or toxic states: uremia, diabetic ketoacidosis (all induce hypothalamic dysfunction)

Observation: Therapeutic hypothermia is used to slow metabolism and preserve ischemic tissue following neurological injury, during surgery (e.g., limb re-implantation), postcardiac arrest (e.g., management of patients presenting with ventricular fibrillation or tachycardia).

THE LOCAL EFFECTS OF COLD:

1. DIRECT effects:

- Affect the ***cells and extracellular fluid***
- They consist of:
  - **crystallization of extracellular water with physical dislocation of cells** → increased tissue destruction in dense tissues and less pronounced in loose tissues

- **the appearance of areas with increased ionic concentration** → with irreversible denaturation of cell membranes

2. INDIRECT effects:

- Affect the ***blood vessels***
- They consist of:
  - **capillary injury with microcirculation damage** → ischemia and cellular hypoxia
  - **release of vasoactive mediators** (e.g., histamine):
    - hyperpermeabilization of capillaries with water efflux into the interstitium
    - increased adhesion & aggregation of platelets due to hemoconcentration with irreversible occlusion of small vessels and extensive tissue necrosis

3. PATHOPHYSIOLOGY OF HYPERSENSITIVITY REACTIONS

The PATHOLOGICAL immune response (IR) comprises the:

A. **EXAGGERATED immune response** – which elicits tissue damage via an:
   - *excessive increase in the intensity and/or duration of the IR* towards *foreign antigens* with the occurrence of the **hypersensitivity (HS) reactions.**
   - *IR directed* against *self antigens* with the occurrence of **autoimmune diseases**

B. **DEFICIENT immune response** – which is due to either **primary** (B, T lymphocyte or mixed disorders) or **secondary** (e.g., AIDS) **immune deficiencies.**

The HS reactions are central pathomechanisms for the occurrence and/or progression of several acute and chronic diseases and are further detailed.

THE HYPERSENSITIVITY REACTIONS

DEFINITION: pathological immune responses (increased intensity and/or duration), **antigen-specific** (antigen-directed) and capable to **induce tissue injury.**

CLASSIFICATION:

According to the mechanisms resposible for the tissue damage, Gell & Coombs (1963) described **4 major types of hypersensitivity reactions** – Table 3.1.:

- **Type I**: **ANAPHYLACTIC reaction**
- **Type II**: **CYTOTOXIC reaction**
- **Type III**: **IMMUNE COMPLEX-MEDIATED reaction**
- **Type IV**: **CELL-MEDIATED reaction** or **DELAYED-TYPE HS**

Table 3.1. Main types of hypersensitivity reactions and their characteristics.

	Name	*Onset*	*Type of antibody*	*Main cells involved*	*Activation of the COMPLEMENT*
I	**ANAPHYLACTIC HS reaction**	Immediate	IgE	Mast cells (+ *Eosinophils*)	**-**
II	**CYTOTOXIC HS reaction**	Immediate	IgG, IgM	Macrophages (+ *Neutrophils*)	Frequent
III	**IMMUNE COMPLEX-MEDIATED reaction**	Immediate	IgG, IgM	Neutrophils (+ *Macrophages*)	Yes
IV	**CELL-MEDIATED HS reaction**	Late	**-**	Lymphocytes, Macrophages	**-**

- The ***first 3 types*** belong to the **immediate-type HS reactions,** which**:**
  - are triggered within *minutes-hours* after re-exposure to the sensitising antigen
  - are mediated by the **humoral immunity**
- The ***4th type*** is known as **delayed-type HS,** which**:**
  - is triggered *several hours-days* after re-exposure to the antigen
  - is mediated by the **cellular immunity**

Observations:

- HS reactions can occur *simultaneously* or *sequentially* (2 or even 3 mechanisms combined) in the pathogenesis of a single disease.
- all HS reactions have a *common characteristic***:** require prior *sensitization* of the body during the *primary immune response,* while symptoms are typically present during the *secondary immune response.*

Type I HS – the ANAPHYLACTIC reaction

GENERAL FEATURES

- is **triggered** by various antigens called **allergens (Ag),** capable of producing a variety of manifestations, either: i) ***localized****,* called **allergic reactions** (often at the level of *mucous membranes*) or ii) **systemic** (anaphylactic shock)
- is **mediated by IgE class antibodies (Ab)** synthesized by *plasma cells* within the **humoral IR** which is amplified by T helper type 2 **(Th2)** lymphocytes via secretion of IL-4 and IL-13
- occurs in **atopic individuals,** i.e. persons with **a hereditary predisposition for allergic manifestations** (if one parent is atopic the incidence is 40%, if both parents are atopic the incidence increases to 80%)
- **atopic individuals** have: i) **elevated serum IgE levels**, ii) **hypereosinophilia**, and iii) **positive skin tests** for many allergens

ETIOLOGY

- Allergic reactions are induced by **allergens** introduced into the body via several pathways:
  - **inhalatory** – pollen, house dust (containing mites), mould, animal products (hair, feathers, saliva, urine), tobacco/cigarette smoke, chemicals (toxic fumes, room deodorants, scented sticks)
  - **digestive** – eggs, milk, hazelnuts/peanuts, almonds, fish, shellfish and seafood, peaches, strawberries, food preservatives, medicines (antibiotics, analgesics)
  - **injectable** – insect bites, medicines (antibiotics - penicillin, local anaesthetics - xylin), vaccines, contrast media
  - **dermal** – at the injection site (subcutaneous/intradermal) or in contact with plant (pollen) or animal products (hair, saliva, urine), latex (elicits both type I and IV HS reactions)

PATHOGENESIS

- **Type I HS** develops in **2 stages:**
  1. The **SENSITIZATION** stage
  2. The **SYMPTOMATIC** stage with 2 phases: **early** and **late**

1. The **SENSITIZATION stage:**

- occurs upon the **<u>first contact</u> with the allergen**, which is:
  - recognized by the *B lymphocytes* via specific receptors *and/or*
  - uptaken, processed by the antigen-presenting cells (APCs) - macrophages & dendritic cells in lymph nodes - and presented to *naive T lymphocytes*, which will differentiate into **Th2 lymphocytes**
- **Th2** lymphocytes **<u>amplify the humoral IR</u>** by releasing **cytokines,** such as:

- **IL-4** and **IL-13** which cause **proliferation** of the **B lymphocyte clone** that is specific for the allergen that triggered the immune response (*clonal selection and expansion*) and its transformation into **plasma cells that synthesize IgE class antibodies**
- **IL-5** which **stimulates the maturation and release of eosinophils** into the blood (from the bone marrow) with **hypereosinophilia** and the **attraction and activation of these cells at tissue level**

- **IgE** also called **reagins** (*reagieren – to react*, German) are **cytophilic** antibodies that bind to the receptors for the Fc fragment of IgE found on the surface of **mast cells and basophils** (which will increase the lifespan of IgE from a few days to several months).

2. The **SYMPTOMATIC stage:**

- occurs upon **second (and subsequent) contacts** with the allergen
- has a **biphasic evolution** with an **early** and a **late** phase
- the allergen binds to IgEs bound to the mast cell membrane and the ***FREE antigen - BOUND antibody*** reaction induces **mast cell degranulation** and **release of mediators of the inflammatory reaction:**

i) PRIMARY mediators - ***pre-formed***:

- **histamine**
- **lysosomal proteases**
- **chemotactic factors** for eosinophils (ECF) and neutrophils (NCF)

ii) SECONDARY mediators - ***newly formed*** from membrane phospholipids under the action of phospholipase A2:

- **arachidonic acid metabolites**: prostaglandins, e.g., PGD2, leukotrienes, e.g., LT B4, C4, D4, E4
- **Platelet Activating Factor** (PAF)

a) The EARLY phase of an allergy is characterized by:

- **rapid onset**: 5-30 minutes after the *second exposure to the allergen* and persists for several hours
- is the consequence of **the release of *primary* mediators** (mast cell degranulation), a major role being attributed to **HISTAMINE** which, through its action on ***H1 receptors,*** is responsible for:
  - vasodilation and increased vascular permeability with *tissue edema / angioedema*
  - contraction of airway smooth muscles with *laryngospasm, bronchospasm*
  - contraction of intestinal smooth muscles with *intestinal hypermotility (cramps, diarrhea)*
  - *mucus hypersecretion*
  - *itching sensation*
- **acute inflammation** with ***moderate*** cellular infiltrate, predominantly containing **mast cells and neutrophil PMNs (microphages)**

b) The LATE phase of an allergy is characterized by:

- **late onset**: recurrence of symptoms 2-8 hours after exposure, may persist 1-2 days, and if allergen exposure is frequent or continuous, leads to **chronic inflammation**

- is the consequence of **the synthesis of <u>secondary</u> mediators** – mainly, the **arachidonic acid metabolites** with the following effects:
  = *bronchoconstriction* - **leukotrienes C_4 , D_4 , E_4**
  = *chemoattractant* - **leukotriene B_4**
- **acute inflammation** with ***<u>abundant</u>*** cellular infiltrate**,** predominantly containing **eosinophils and mononuclear cells: monocytes/macrophages and lymphocytes**

CLINICAL FORMS

Depending on the site of the antigen-antibody (Ag-Ab) reaction, **2 forms** of type I HS occur:

a) LOCAL forms – Ag-Ab reaction occurs at **TISSUE** level**:**
- **Allergic rhinitis** – Ag-Ab reaction in *nasal* mucosa leads to vascular hyperpermeabilization, exudation at the level of the mucosal surface and local congestion with: *watery rhinorrhea, sneezing*, *stuffy nose sensation*
- **Allergic or extrinsic asthma** – Ag-Ab reaction in *bronchial mucosa* causes bronchial narrowing through the triad: bronchospasm, mucosal edema and hypersecretion of viscous mucus, with: *expiratory dyspnea, wheezing*, *coughing and expectoration*
- **Atopic dermatitis (eczema)** – Ag-Ab reaction at the *skin* level causes: *erythema, induration, burning sensation and local itching*
- **Allergic gastroenteritis** – Ag-Ab reaction at the level of the *gastrointestinal mucosa* causes: *abdominal cramps, vomiting, diarrhea*

b) SYSTEMIC forms – Ag-Ab reaction occurs at **INTRAVASCULAR** level**:**
- **Angioedema** – *subcutaneous edema* (eyelids, lips etc.), *dyspnea, intestinal colic*
- **Urticaria (hives)** - *skin erythema, itching*
- **Anaphylactic shock** – intense vasodilation with *vascular collapse and hypotension* & risk of death by *glottic edema with asphyxia* (it is a medical emergency!)

Type II HS – CYTOTOXIC reaction

GENERAL FEATURES
- is an **exaggerated humoral immune response** directed against **cell/tissue**, **endogenous or exogenous <u>antigens bound to the cells</u>** (eg, drugs bound to the surface of erythrocytes and/or platelets)
- has tissue/organ specificity

PATHOGENESIS
- is characterized by the **formation of IgG or IgM class antibodies** directed against **antigens present on the target cell membrane**
- the ***FREE antibody (Ab) - BOUND antigen (Ag)*** reaction will cause *cell destruction* or *their functional alteration* through **3 main mechanisms:**

a) CYTOLYSIS mediated by COMPLEMENT ACTIVATION
- the complement system is activated via the *classical* (fast) *pathway* by Ag-Ab complexes of the IgG or IgM classes

- complement activation leads to the formation of the **C5b-C9 membrane attack complex (MAC)**, which is assembled on the cell membranes surface and forms **transmembrane pores** that allow the bidirectional flow of ions and micromolecules, water entry and **osmotic cytolysis**

b) PHAGOCYTOSIS of the Ag-bearing CELLS (so-called sensitized cells)

- following the Ag - Ab (IgG) reaction, target cells are uptaken by splenic and hepatic macrophages, which have receptors for the Fc fragment of IgG (but not for IgM), the process being favoured by opsonins, such as C3b

c) FUNCTIONAL ALTERATIONS (MALFUNCTION) of the Ag-bearing CELLS

- binding of antibodies to surface receptors of target cells is the mechanism underlying some autoimmune diseases, through**:**
  - **stimulation of cell function** - e.g., antibodies against TSH receptors *stimulate thyroid hormone production* and induce *hyperthyroidism* in **Basedow-Graves disease**
  - **receptor function blocking** - e.g., antibodies against acetylcholine (ACh) receptors block the transmission of excitation at the level of the motor plate in **myasthenia gravis**

CLINICAL FORMS

A. The <u>first 2 mechanisms</u> - COMPLEMENT ACTIVATION and PHAGOCYTOSIS are involved in the pathogenesis of the following diseases:

- **Post-transfusion accidents** duet o incompatible transfusions in the AB0 system
  - *IgM class antibodies of the transfusion recipient* (alpha or beta agglutinins) *react with antigens* (A or B agglutinogens) *on the surface of donor red blood cells* and produce rapid intravascular haemolysis through complement activation
- **Idiopathic/immune thrombocytopenic purpura or Werlhof disease**
  - autoimmune disease characterized by the presence of serum *anti-platelet auto-antibodies of the IgG class* that bind the complement
  - sensitized platelets through IgG and C3 (opsonin role) binding are phagocytosed by splenic and hepatic macrophages $\Rightarrow$ thrombocytopenia
- **Goodpasture syndrome:** acute glomerulonephritis (GN) caused by formation of *IgG class auto-Ab directed against intrinsic Ag in the glomerular basement membrane (BM)*
  - local activation of the complement system and phagocytosis is responsible for the enzymatic destruction of the glomerular BM and the release of new Ag into the circulation with the appearance of a vicious circle of amplification of the formation of autoAb
  - the auto-Ab can cross-react with structurally similar Ag from the *alveolar BM* causing **pulmonary hemorrhage** *(with risk of respiratory failure and death by asphyxia)* in some patients with GN
- **Immune hemolytic anemias**
  - consist of the production of *anti-erythrocyte IgG* (in *'warm'* Ab immunohemolytic anemias) and *IgM Ab* (in *'cold'* Ab immunohemolytic anemias) reacting with Ag from the erythrocyte membrane $\Rightarrow$ erythrocytes are sensitized via Ab binding and are *phagocytosed* by *splenic and hepatic macrophages* or lysed via complement activation
  - they can be: **primary** (idiopathic) or **secondary** (to leukemias, lymphomas, SLE)

- **Drug-induced hemolytic anemias**
  - penicillin binding (hapten role) on the erythrocyte membrane induces IgG synthesis against the erythrocyte-drug complex
  - sensitized erythrocytes via IgG binding undergo splenic erythrophagocytosis and complement activation-mediated cytolysis
- **Erythroblastosis fetalis (hemolytic disease of the newborn)**
  - occurs in case of Rh incompatibility, with **Rh (-) mother** and **Rh (+) fetus**
  - in the first pregnancy, during birth, the fetus' red blood cells carrying the Rh antigen on their surface come into contact with the Rh (-) mother's immune system, which will induce sensitization of the maternal body (*primary* immune response with synthesis of anti-Rh IgM class antibodies)
  - in subsequent pregnancies with persisting incompatibility, the triggering of the *secondary* immune response in the mother is responsible for the *synthesis of anti-Rh IgG Ab that cross the placenta and pass into the fetal circulation,* inducing lysis of fetal red blood cells. The foetus is born with *hemolytic anemia* and is *at risk of kernicterus* if indirect bilirubin values exceed 20 mg% (with deposition of this toxic compound in the basal ganglia with variable neurological sequelae).

B. The <u>third mechanism</u> - FUNCTIONAL CELL ALTERATIONS - is found in:

- **Basedow-Graves disease**
  - production of autoAb with *stimulatory effect* that act by binding to TSH receptors in the thyroid tissue, being responsible for **hyperthyroidism**
- **Myasthenia gravis**
  - production of *autoAb againstthe acetylcholine receptors* at the level of the postsynaptic membrane of the neuromotor plate triggers bouts of **hypotonia/severe muscle fatigue**
- **Pernicious anemia (Biermer anemia)**
  - is an autoimmune disease characterized by an **impaired intestinal absorption of vitamin B_{12}** due to **the absence of intrinsic factor** caused by *anti-parietal cell autoAb* (gastric parietal cells produce HCl and intrinsic factor) and *anti-intrinsic factor autoAb*
  - besides type II HS, type IV HS is responsible for the chronic infiltration with cytotoxic T lymphocytes in the lamina propria of the gastric mucosa, resulting in **gastric mucosa atrophy**

Type III HS: IMMUNE COMPLEX-MEDIATED reaction

GENERAL FEATURES

- **the antigens** that make up the immune complexes can be **external** and **internal** and are **<u>SOLUBLE</u>, <u>FREE</u> in the serum**
- **antibodies** are of the **IgG and IgM** class (less frequently IgA) and bind to circulating Ag with the formation of **immune complexes (IC)** that produce tissue damage by **diffuse deposition** (at variance from type II HS, where there is tissue specificity)
- tissue damage occurs as a result of **IC formation and deposition**

- **the site of choice for IC deposition** is represented by **the basement membranes (BM)** throughout the body: *vascular, glomerular, synovial BMs*

ETIOLOGY

a) EXTERNAL (EXOGENOUS) antigens:

- *microbial and viral antigens* are responsible for: poststreptococcal glomerulonephritis (GN), GN from bacterial endocarditis and infectious diseases (typhoid fever, syphilis, infectious mononucleosis), GN and arthritis from hepatitis B
- *drugs* (e.g., quinine, quinidine, phenacetin) or *hormones* are responsible for: immune hemolytic anemia and thrombocytopenia
- *antitoxic serums* (antitetanus, antidiphtheria) are responsible for serum sickness

b) INTERNAL (ENDOGENOUS) antigens:

- *intrinsic* antigens responsible for autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis and autoimmune thyroiditis
- *tumor* antigens responsible for: GN that complicate colon, bronchogenic, renal cancers

PATHOGENESIS

The sequence of injury in type III HS occurs in the following steps:

1. **Formation and deposition of IC** in body tissues with different consequences:
   - *Small* ICs are eliminated by the kidneys without pathological consequences
   - *Large* ICs are uptaken from the circulation by tissue macrophages
   - *Intermediate* ICs are deposited at tissue level and produce lesions
2. **Complement activation** has a **CENTRAL role in pathogenesis** through the release of anaphylatoxins (C3a and C5a), chemoattractant (C5a) and opsonin (C3b) and explains the **LOW serum complement level** in these diseases
3. **Triggering of an inflammatory reaction** with **neutrophil-rich** cellular infiltrate
4. **Activation of neutrophils with release of lysosomal enzymes at tissue level** leading to glomerular, capillary and synovial BM injury with: **glomerulonephritis, vasculitis** and **arthritis**
5. Binding of immune complexes to Fc receptors on the platelet membrane **triggers platelet adhesion and aggregation** with **local microthrombi formation** that exacerbates the lesions through **ischemia secondary to vessel obstruction.**

Observation! *The heterogeneity of immune complexes, whose rate of formation and composition varies during the course of the disease, explains both the complex symptomatology as well as the unpredictable evolution with periods of exacerbation and remission of type III HS - mediated diseases.*

CLINICAL FORMS

Depending on the site of IC formation, 2 forms of type III HS occurs:

a) SYSTEMIC forms, when the IC are present in the circulation and their deposition affects one or more tissues or organs, as happens in the following pathologies:

- **Serum sickness**
- **Schonlein-Henoch anaphylactoid purpura**
- **Drug-induced vasculitis** (most frequently, by antibiotics)

- **Poststreptococcal glomerulonephritis**
- **Autoimmune diseases:** SLE, rheumatoid arthritis

b) LOCAL forms, when IC form at the site of antigen penetration under conditions of chronic exposure and are responsible for the:
- **Arthus reaction** (the experimental type III HS)
- **Extrinsic allergic alveolitis**

- **Serum sickness:**
  - was originally described as a complication arising after the therapeutic administration to humans of **animal antitoxic serum** (e.g., antitetanus serum - Ig - prepared from horses) that induced the synthesis of specific Ab directed against animal protein (horse Ig being foreign proteins, and therefore antigenic to humans)
  - in the beginning the relative excess of antigens causes generalized lesions (vasculitis, arthritis, glomerulonephritis) which reach a maximum at approx. 10 - 14 days; subsequently, symptoms progressively decline as the concentration of Ab increases and the resulting large IC will be rapidly phagocytosed and eliminated from the circulation
  - currently, HS reactions of the serum sickness type are associated with **vasculitis** from:
    i) ***repeated i.v. administration of drugs, especially antibiotics***
    ii) ***autoimmune diseases***

  A particular form of serum sickness is the ***Raynaud's phenomenon*** characterised by the **formation of immune complexes in the capillaries of the peripheral circulation, which precipitate at low temperatures** (cryoglobulins) in the extremities (fingers, toes, tip of nose, ears) and cause symptoms such as alternating pallor-cyanosis-hyperemia up to gangrene-like complications in severe forms.

- **Schonlein-Henoch anaphylactoid purpura:**
  - is an **allergic immune vasculitis,** i.e. an acute inflammatory reaction in the capillaries and sometimes, in the glomerular mesangial tissue, triggered 2-3 weeks after an infection with the beta-haemolytic streptococcus, mainly in children/young people
  - clinically, a characteristic symptomatic triad occurs: *cutaneous symmetrical purpura, arthritis* (transient arthralgias of the large joints) and *digestive hemorrhages* (hematemesis/melena + abdominal pain)
  - some cases may be complicated by *acute glomerulonephritis,* which may lead to acute kidney injury

- **Poststreptococcal glomerulonephritis:**
  - occurs following streptococcal pharyngitis and is caused by deposition of immune complexes at the glomerular basement membrane with local complement activation and lesions responsible for proteinuria and haematuria.

- **Arthus reaction:**
  - is the typical *localized* form of ***type III HS*** that occurs after:
    i) injection of antigens, e.g. extracts used in intradermal testing
    ii) ingestion of antigens, e.g. gluten from cereals in gluten enteropathy (celiac disease)
    iii) inhalation of antigens, e.g. extrinsic allergic alveolitis

Observation!
This *localized* form of type III HS has been firstly described by Arthus at an experimental level, as follows:
- *in phase I*: immunisation of experimental animals (rabbits) by repeated intradermal administration of *small* doses of Ag resulted in increased circulating IgG level
- *in phase II*: subsequent local administration of a *high* dose of Ag resulted in local activation of complement with neutrophil-rich inflammatory infiltrate at the injection site and the onset of *necrotizing vasculitis* through destruction of the vascular BM.

- **Extrinsic allergic alveolitis (hypersensitivity pneumonitis):**
  - *causes:* inhalation of organic antigens leading initially to *acute haemorrhagic inflammation of the pulmonary alveoli* and in long-term exposure, *chronic granulomatous inflammation with diffuse interstitial fibrosis,* in the production of which a dual mechanism is involved, type III and IV HS
  - *clinical forms:* **farmer's lung** (Ag from moldy hay or straw, e.g. thermophilic actinomycetes), **bird breeder's lung** (Ag from bird droppings, e.g. pigeons)

Type IV HS: CELL-MEDIATED hypersensitivity or DELAYED HS

GENERAL FEATURES

- is the **delayed-type HS** reaction that:
  - is mediated by the **following effector cell types:**
    i) **cytotoxic T lymphocytes,** which are responsible for the *destruction of target cells*
    ii) **Th1 and Th17 lymphocytes,** which *amplify the cellular IR* by secreting cytokines (*lymphokines*)
    ii) **macrophages,** responsible for *triggering the chronic inflammation* (eg, granulomatous)
- **does NOT** involve **antibodies**

PATHOGENESIS

Type IV HS develops in **2 stages:** *sensitization* and *symptomatic stage,* respectively

1. The **SENSITIZATION stage:**
- upon first contact, the antigen is recognised by **cytotoxic T lymphocytes (cTL)**
- the antigen is uptaken, processed by the APC (macrophages/dendritic cells from the lymph nodes) and presented to **naive T lymphocytes** which will differentiate into **Th1 and Th17 lymphocyte** subpopulations that secrete **lymphokines**
- absence of symptoms

2. The **SYMPTOMATIC stage:**
- upon the 2nd contact, symptoms are triggered within **24-72 hours** (and can last up to 14 days)
- sensitized **cytotoxic T lymphocytes (cTL)** will **act directly on target cells by releasing cytotoxic proteins, e.g., perforin**, which is structurally and functionally similar to the complement membrane attack complex (perforin, upon insertion into the target cell membrane, causes the formation of transmembrane pores leading to electrolyte loss, water entry, swelling and cell lysis)

- sensitized **Th1 lymphocytes** will amplify the lesions by secreting:
  - **lymphokines with chemotactic effect: IL-8**
  - **lymphokines that activate cytotoxic T lymphocytes: IL-2**
  - **lymphokines that activate macrophages**: **IFN-γ, MIF** (Macrophage Migration Inhibiting Factor), **MFF** (Macrophage Fusion Factor)

CLINICAL FORMS

a) SYSTEMIC forms

- Delayed-type reaction is involved in the production of **lesions** from:
  - **chronic intracellular bacterial infections**: tuberculosis, leprosy and brucellosis
  - **fungal infections**: histoplasmosis and blastomycosis
  - **viral infections**: herpes, epidemic parotitis, viral hepatitis
  - **autoimmune diseases** with: **i) multi-organ involvement:** e.g., SLE, rheumatoid arthritis or **ii) organ specificity:** e.g., type I diabetes mellitus, Hashimoto thyroiditis, pernicious anaemia, chronic autoimmune hepatitis.

b) LOCAL forms

- **Contact dermatitis** is **the most common form of type IV HS** occurring in the **epidermis 1-2 days after a second exposure** to a sensitising antigen: e.g. cosmetics, metals (e.g., nickel), dyes, chemicals, oils of toxic plants (e.g., poison ivy, poison oak). A particular form of contact dermatitis is that induced by **chronic exposure to latex from surgical gloves** (in the case of doctors and nurses in operating theatres) - in association with type I HS.
- **Tuberculin intradermal reaction (IDR)** is the prototype of ***localized* type IV HS** in which administration of the purified protein derivative (PPD) to a *previously sensitised individual to the b. Koch* results in the appearance of an **indurated papule 48-72 hours after injection** due to the formation of an inflammatory cellular infiltrate with **Th1 lymphocytes and macrophages.**
- **Extrinsic allergic alveolitis** (or hypersensitivity pneumonitis) - in association with type III HS.

4. PATHOPHYSIOLOGY OF RESPIRATORY DISEASES

ASTHMA

DEFINITION: Asthma is one of the most frequent chronic respiratory diseases, with plurifactorial etiology and characterized by the **triad:**

1. **CHRONIC INFLAMMATION of the respiratory tract, mainly of the DISTAL airways** - small bronchi and bronchioles with a diameter of < 2 mm
2. **INTERMITTENT bronchial obstruction**
3. **bronchial HYPER-RESPONSIVENESS**

Bronchial hyper-responsiveness (BHR) is the **central pathogenic element** of the disease, defined as an *exaggerated bronchoconstrictor response* to a wide variety of *endogenous and exogenous stimuli* that DO NOT generate a pathological response of the airways in normal subjects.

GENERAL FEATURES

- **Clinical** – recurrent paroxysms manifested by the **clinical triad**:
  - *expiratory dyspnea*
  - *wheezing*
  - *cough (± expectoration)*
- **Functional** – episodes of **acute, variable, diffuse and REVERSIBLE bronchial obstruction** (at least partially), spontaneously or after treatment, which are associated with a **pathogenic triad:**
  - *bronchospam*
  - *mucosal edema*
  - *mucus hypersecretion*

CLASSIFICATIONS – 3 TYPES

a) ETIOLOGICAL classification:

1. EXTRINSIC (ALLERGIC) asthma

- **General features:**

– is the **most common** form of asthma, often with *onset in childhood*

– occurs with predilection in **children and young adults with atopy**, defined as the genetic predisposition to develop an exaggerated immune response mediated by IgE, which presents with:

- personal or family history of allergies: *allergic rhinitis, atopic dermatitis (eczema, urticaria), digestive or drug allergies*
- positive skin tests for allergens
- increased serum level of total and specific **IgE**
- increased number of **eosinophils** on sputum examination

– the asthma attack is induced by **specific triggers,** i.e. **inhaled allergens** of **2 types**:

- ***Outdoor allergens*** – responsible for ***seasonal*** allergies to:
  - pollens from trees, grasses, weeds (Ambrosia, Artemisia)

- ***Indoor allergens*** – responsible for ***perennial*** allergies**:**
  - house dust and feathers containing mites (Dermatophagoides pteronyssinus)
  - animal saliva, hair, dander (e.g., cats, dogs)
  - kitchen cockroaches
  - molds
  - houseplants (e.g., Ficus benjamina)

– favorable response to **inhaled corticosteroid therapy**

– the severity of the asthma attacks often **diminishes with age** (good prognosis)

- **Pathogenesis:**

Extrinsic asthma is a **type I hypersensitivity reaction** that evolves in **2 stages**:

1. **During the first contact with the allergen – the *SENSITIZATION contact,*** an **HUMORAL IMMUNE RESPONSE** is triggered, as follows:
   - dendritic cells (antigen presenting cells) in the airways capture and process the allergen, migrate into regional lymph nodes and present it to the **Th_0 (naïve) lymphocytes**, which differentiate into the **Th_2 lymphocyte subpopulation**
   - **Th2 lymphocytes** are main players within the humoral immunity and release specific cytokines, considered the ***immunological hallmark of allergic asthma*** and ***the target of modern biological therapies*** with *anti-cytokine monoclonal antibodies*:
     - **IL-4** and **IL-13** – stimulate the **differentiation** of **B lymphocytes** into **plasma cells** responsible for **secretion** of **IgE type antibodies (reagines)** specific for the allergen
     - **IL-5 –** stimulates **eosinophil maturation / release into circulation** (from the bone marrow) and **eosinophil migration / activation** at the level of the inflammatory site
   - **IgE** – are **cytophilic** immunoglobulins that bind to specific, **high-affinity** receptors on the surface of **basophils and mast cells** in the respiratory tract.

Observation: IgE were the first target of biological therapies with anti-IgE monoclonal antibodies that reduce their quantity at the circulatory level and implicitly, the binding to receptors, the drug being omalizumab (Xolair).

2. **During the following contacts with the same allergen – the *TRIGGERING contacts,*** a **RESPIRATORY TRACT INFLAMMATION** occurs, as follows**:**
   a. **<u>ACUTE</u> inflammation of the airways,** in which the reaction of **free antigen – <u>bound</u> antibody** to the **mast cell surface** induces **mast cell degranulation** through an ***IgE-dependent mechanism*,** with the release of **inflammatory mediators:** *preformed* (histamine, ECF, NCF) and *newly formed* (arachidonic acid metabolites: prostaglandins - PGD2, PGF2, thromboxanes - TxA_2 and especially, leukotrienes - LTC_4, LTD_4, LTE_4)

These mediators are responsible for the **EARLY reaction (IMMEDIATE response)**, respectively the **asthma attack** characterized by the **pathogenic triad:**

- *bronchospasm* - mediated mainly by leukotrienes LT C, D, E
- *edema of the bronchial mucosa*
- *hypersecretion of mucus*

b. <u>CHRONIC</u> inflammation of the airways, in which **Th_2** lymphocytes, but also **respiratory epithelial cells**, release:
- **IL-5** – for further **recruitment** of **eosinophils** towards the airways
- **IL-33** - for the **persistence of mast cell and eosinophil activation** in the airways
- **Chemotactic factors** - for the **recruitment of eosinophils** and **phagocytes (neutrophils and macrophages)** to the airways

These cytokines are responsible for the **LATE reaction (DELAYED response)**, characterized by:
- initiation/maintenance of the ***chronic eosinophilic or neutrophilic inflammation***
- progressive worsening of ***bronchial hyper-responsiveness (BHR)***

2. INTRINSIC (NON-ALLERGIC, IDIOSYNCRATIC) asthma

- **General features:**
  - affects mainly ***adults with NO signs of atopy***
  - the asthma attack is induced by **<u>non-specific (non-allergic) triggers</u>** (Table 4.1)
  - most frequently, the onset of symptoms occurs a few days *after a* ***viral respiratory tract infection****,* consisting in paroxysms of *dyspnea, wheezing, cough and rhinorrhea/ expectation* that persist from several days up to a couple of months
  - the presence of ***neutrophils, eosinophils*** or a ***reduced number of inflammatory cells*** (*paucicellular asthma*) in the sputum examination
  - **reduced response** to ***inhaled corticosteroid therapy***
  - the severity of the asthma attacks may increase with age (worse prognosis and poorer response to standard therapy as compared to extrinsic asthma); **chronic obstructive pulmonary disease (COPD)** may develop in evolution.

- **Pathogenesis:**

a. EARLY reaction (IMMEDIATE response) - ***mast cell degranulation*** reaction through an ***IgE-independent mechanism***, possibly through the action of **IL-33**, a cytokine (alarmin type), released by **respiratory epithelial cells that were damaged/destroyed** under the action of non-specific "trigger" factors (infectious or irritant agents).

b. LATE reaction (DELAYED response) - ***chronic inflammation (eosinophilic or neutrophilic)*** of the airways and worsening of BHR, under the action of **leukotrienes** (**LTC4, D4 and E4**), mainly released by eosinophils.

Observations:

Mast cell degranulation is a process prevented by *sodium cromoglycate and sodium nedocromil drugs,* currently less indicated in intercritical periods in asthma due to their lower efficiency compared to inhaled corticosteroids.

LTC4, D4 and E4 are cysteinyl leukotrienes (LTCys) with a *central role in the pathogenesis of asthma* – through the triple effect of *bronchoconstriction, recruitment of eosinophils and promotion of chronic inflammation* via binding to LTCys1 and LTCys2 receptors. LTCys1 leukotriene receptor antagonists in clinical use are the drugs called *montelukast* and *zafirlukast.*

Table 4.1. NON-SPECIFIC triggers of intrinsic asthma.

Type of trigger	Particularities
1. VIRAL stimuli ▪ *In children:* respiratory syncytial virus, parainfluenza virus ▪ *In adults:* rhinoviruses, influenza virus	▪ Are responsible for inducing the ***cough-varaint asthma***, manifested by chronic, dry, non-productive cough, frequently when obesity is present, but also for episodes of exacerbation of allergic asthma.
2. INHALATION irritants ▪ *Occupational factors* (metal salts, detergents, paints, vegetable dusts, animal secretions etc.)	▪ Are responsible for inducing the clinical form of ***occupational asthma***, characterized by relief of symptoms on non-working days and aggravation at work (they appear at the end of working hours and may persist after leaving the environment).
▪ *Cigarette smoke* ▪ *Air pollutants: ozone, nitrogen dioxide, sulfur dioxide* ▪ *Strong fragrances*	▪ Contribute to the triggering of asthma attacks by ***direct or reflex stimulation of the airways***.
▪ *Gastro-esophageal reflux*	▪ Is responsible for the ***nocturnal asthma.***
3. Intense exercise in a COLD ATMOSPHERE	▪ Is responsible for the clinical form of ***exercise-induced asthma*** - significant loss of heat and water at the airways level during effort (in order to heat up the cold air inhaled) induces *hyperemia* and *congestion* of the bronchial walls responsible for post-exercise bronchial obstruction.
4. PSYCHOLOGICAL stress	▪ Is responsible for an ***increase in airway reactivity*** to other bronchoconstrictors.
5. PHARMACOLOGICAL stimuli ▪ *Aspirin and other nonsteroidal anti-inflammatory drugs (NSAID)*	▪ Administration of aspirin/NSAID causes inhibition of cyclooxygenase (COX) which favors the metabolism of arachidonic acid via the ***lipoxygenase*** pathway, leading to an increased release of *leukotrienes* which are potent *bronchoconstrictors**.*** *Aspirin-induced asthma* begins with symptoms of *nasal congestion* and may be associated with *nasal polyposis* within the *Widal-Samter triad* (*asthma, aspirin sensitivity and nasal polyposis*). Recently, *hyperplastic sinusitis* has been added to this, the condition being currently known as *NSAID-exacerbated respiratory disease.*
▪ *β-blockers (e.g., propranolol)*	▪ Are responsible for the ***sympathetic inhibition*** (sympathetic stimulation elicits bronchodilation).
6. Obesity	▪ It has a **direct** effect on **pulmonary mechanics** and an **indirect** effect, by **maintaining the low-grade chronic systemic inflammation**.
7. Pregnancy	▪ During pregnancy, the disease can improve in 1/3 of cases (in case of mild forms), worsen in 1/3 of cases or remain unchanged in the remaining 1/3 of cases.

Observations:
The practical relevance of the etiopathogenic classification into allergic and non-allergic asthma has been called into question in recent decades because:
- an increased serum total IgE level has been demonstrated in patients who have been classified as having intrinsic asthma (on the basis of negative skin tests, the absence of atopy history and the absence of an increased level of specific IgE) without the significance of this increase being elucidated
- in patients with intrinsic asthma and elevated total IgE, the administration of omalizumab - anti-IgE monoclonal antibody was followed by improvement of symptoms and of long-term quality of life.

b) <u>PATHOPHYSIOLOGICAL</u> classification of both *allergic* and *non-allergic* asthma takes into account the **type of chronic inflammation,** with **2 major ENDOTYPES of asthma** being described**:**

1. Asthma "T2-high" – is the most frequent form, characterized by **chronic <u>eosinophilic</u> inflammation** or so-called **<u>type 2 inflammation</u>** of the airways:
- mediated by the **Th2 L subpopulation** and increased secretion of **IL-5, IL-4 and IL-13** (type 2 cytokines)
- accompanied by **eosinophilia** and the presence of an **increased number of eosinophils in the sputum**
- with **good response to inhaled corticosteroid therapy**
- **<u>WITH indication</u>** for **biological therapies** in **severe/corticosteroid-resistant forms** of the disease

Observations:

Modern therapy for **severe (multiple exacerbations) or refractory eosinophilic asthma** include **monoclonal antibodies**, which work by blocking specific molecules that trigger inflammation.
Six biologic drugs (or biologics) are currently approved by FDA: **anti-IgE antibody** - *omalizumab (Xolair),* **anti-IL-5 antibodies** - *mepolizumab (Nucala), reslizumab (Cinquaero)*, **anti-IL-5 receptor** - *benralizumab (Fasenra)*, **anti-IL-4 and IL-13 receptor antibody** - *dupilumab (Dupixent)* and **anti-TSLP antibody** - *tezepelumab (Tezpire)*. TSLP (Thymic Stromal Lymphopoietin) is an alarmin-type cytokine released by the epithelial cells of the airways whose increased serum level has been correlated with the severity of bronchial obstruction and corticosteroid resistance in all types of asthma.
Anti-cytokine therapies, e.g, anti-IL-33 – *itepekimab* and anti-ST2 receptor for IL-33 – *astegolimab* are under evaluation.

2. Asthma „T2-low" – is **rare** and characterized by **chronic <u>neutrophilic</u> inflammation** or so- called **<u>type 1 airway inflammation</u>**:
- mediated by **Th1 and Th17 L subpopulations** and increased secretion of: **IL-1, IFN-γ, TNF-α and IL-17** respectively
- accompanied by **neutrophilia** and the presence of an **increased number of neutrophils in the sputum** or a **reduced number of inflammatory cells, in the paucigranulocytic subtype**
- with ***low* response to inhaled corticosteroid therapy**
- **<u>WITH NO indication</u>** for **anti-IL-5, IL-4 and IL-13 biological therapies** in severe/corticosteroid-resistant forms of the disease

Observation:
The severe forms within this endotype have an incompletely elucidated pathogenesis. The latest monoclonal antibody, anti-TSLP - tezepelumab, has been proven effective in their case. Monoclonal antibodies directed against IL-33 may also be a therapeutic option for these patients.

c) PHENOTYPIC classification – according to the GINA (**G**lobal **IN**itiative for **A**sthma, 2023) report comprises:

1. **ALLERGIC asthma** - ***childhood onset*** phenotype (with increased eosinophils in sputum and good response to corticotherapy)
2. **NON-ALLERGIC asthma** - the phenotype found in ***adults*** (with neutrophils, eosinophils or paucigranulocytic and limited response to corticotherapy)
3. **ADULT asthma with LATE ONSET** - the phenotype with onset ***past 50 years*****,** frequently in **women** (it is non-allergic and the response to corticosteroid therapy is reduced - it requires high doses or becomes corticosteroid resistant)
4. **Asthma with PERSISTENT AIRFLOW LIMITATION** - the phenotype found in patients with ***old asthma*** (in which airway remodeling has occured, with fixed bronchial obstruction)
5. **Asthma associated with OBESITY** - the phenotype found in some ***obese*** patients (with reduced eosinophilic airway inflammation)

PATHOGENESIS

❑ **General features:**

- the existence of complex interactions between: **inflammatory cells** (mast cells, eosinophils, Th2 lymphocytes, neutrophils and macrophages), **epithelial cells** and **airway smooth muscle cells**
- the **CENTRAL** pathomechanism in asthma is the **activation/degranulation of MAST cells in the airways**, which is:
  - *IgE-dependent* in extrinsic asthma
  - *IgE-independent* in intrinsic asthma
- there are **2 consequences** of mast cells activation/degranulation (Table 4.2.):
  - an *early reaction* or the *immediate response*
  - a *late reaction* or the *delayed response*

Table 4.2. General pathogenesis of asthma.

Feature	The EARLY reaction	The LATE reaction
Temporal evolution	*Onset*: minutes *Maximum*: 10-20 minutes *Remission*: 30-90 minutes	*Onset*: 6-9 hours *Maximum*: 12-24 hours *Remission*: days/weeks → months/years
Major manifestation	▪ *Acute bronchial inflammation or the asthma attack* with: – bronchospasm – mucosal edema – hypersecretion & plugging of viscous, adherent mucus	▪ *Chronic bronchial inflammation* with: – damage/shedding of the bronchial epithelium – submucosal fibrosis – infiltration/thickening of bronchial mucosa – hypertrophy of smooth muscle cells – hypertrophy of mucous glands

Cells involved	▪ **Mast cells**	▪ **Eosinophils**, **T helper lymphocytes**, neutrophils and **macrophages,** airway epithelial cells
Consequences	▪ ***REVERSIBLE*** bronchial obstruction	▪ ***AGGRAVATED*** bronchial obstruction (prolongation and amplification of the acute reaction which trigger/ increase the severity of BHR) ▪ ***PERSISTENT*** bronchial obstruction via **airway remodeling**

❑ **Roles of MAST CELLS:**

- Mast cells are the **main cells** that mediate the ***EARLY reaction*** and they contribute *to initiation* of ***DELAYED reaction*** via the release of **3 groups of inflammatory mediators:**
  - ① **Mediators with BRONCHOCONSTRICTOR effect** – induce *the* ***asthma attack*** during the **early reaction:**
    - **histamine** – by acting on the *H1 receptors*
      The effect is inhibited by H1 antihistamines drugs, e.g. *loratadine (Claritine), desloratadine (Aerius), fexofenadine (Allegra, Telfast), levocetirizine (Xyzal)*.
    - **leukotrienes** – induce the **most potent bronchoconstriction** (100 - 1000 times higher as compared to histamine)
      The effect inhibited by leukotriene receptor antagonists, e.g., *montelukast (Singulair).*
  - ② **Mediators with CHEMOTACTIC effect** – are responsible for the ***local cellular infiltrate*** and ***chronic inflammation*** during **the late reaction**:
    - *chemoattractants for eosinophils*: ECF, IL-5
    - *chemoattractant for neutrophils*: NCF, LTB_4
  - ③ **Mediators with role in AIRWAYS REMODELING** – ***TNF***–α that has the following effects:
    - stimulates the *fibroblasts* activation/proliferation with *extracellular matrix* deposition
    - induces the hyperplasia of the goblet cells and increased mucus production

❑ **Roles of EOSINOPHILS:**

They are the **main cells of the LATE reaction,** responsible for the **BRONCHIAL HYPEREACTIVITY (BHR) and AGGRAVATED bronchial obstruction**, via release of the:

- ① **Granule proteins with cytotoxic effect** on **the airway epithelial cells** and BHR:
  - Major Basic Protein (MBP)
  - Eosinophil Cationic Protein (ECP)
  - Eosinophil Peroxidase (EPX)
  - Eosinophil-Derived Neurotoxin (EDN)
- ② **Growth factors** - **TGF-α** and **TGF-β** (Transforming Growth Factors) with aggravated bronchial obstruction via **hyperplasia/hypertrophy of smooth muscle** and **goblet cells**

Injury of the bronchial epithelium **triggers and maintains chronic NEUROGENIC inflammation** through an **AXON REFLEX** mediated by **C-type unmyelinated fibers** in the airway walls:

- the unmyelinated C fibers release **substance P** which:
  - triggers *bronchospasm* via mastocyte degranulation (with histamine release)
  - maintains the *local inflammation via* a vasodilator effect (mediated by bradykinin release)
- the desquamated epithelial cells within the bronchial lumen are eliminated as **Creola bodies** in the **sputum** of patients with asthma

❑ **Roles of <u>T helper LYMPHOCYTES</u>:**

- They are the cells that modulate ***TYPE I HYPERSENSITIVITY*** involved in the pathogenesis of the **extrinsic** asthma (via **Th_2 lymphocytes**) and they also contribute to the pathogenesis of the **intrinsic** asthma (via **Th_1 and Th_{17} lymphocytes**)

① **Th_2 subpopulation:**
- proliferate in response to *allergens* and *parasites*
- secrete *IL-4* and *IL-13* responsible for the differentiation of B lymphocytes into *plasma cells* that will further secrete IgE
- secrete *IL-5* responsible for the recruitment and activation of EOSINOPHILS $\Rightarrow$ **chronic eosinophilic inflammation (type 2)**

② **Th_1 subpopulation:**
- proliferate in response to *bacterial and viral antigens*
- secrete *TNF-*α responsible for activation of *neutrophils* and *fibroblasts* proliferation
- secrete *IFN-*γ responsible for the activation of *macrophages*

③ **Th_{17} subpopulation:**
- proliferate in response to *bacterial and fungal antigens*
- secrete *IL-17* responsible for the recruitment and activation of NEUTROPHILS $\Rightarrow$ **chronic neutrophilic inflammation (type 1)**

❑ **Roles of <u>MACROPHAGES:</u>**

- They are the **main cells of the CHRONIC INFLAMMATION**, being responsible for the **PERSISTENT bronchial obstruction and AIRWAY REMODELING** via the secretion of several **growth factors:**
  - TGF-α and TGF-β – mediate **bronchial remodeling**
  - Fibroblast Growth Factor (FGF) – induces the proliferation/activation of fibroblasts with colagen deposit and **subepithelial fibrosis**

FUNCTIONAL CHANGES

1) BRONCHIAL OBSTRUCTION

- **Definition:** the functional expression of the **increase in airflow resistance**
- **Pathophysiology:**
  - bronchospasm due to BHR
  - hypersecretion of viscous and adherent mucus with the formation of intraluminal plugs
  - edema of the bronchial mucosa

– remodeling of the bronchial walls

- **General features:**
  - ***during an asthma attack*** - bronchial obstruction is reversible *spontaneously* or after *bronchodilators* (FEV1 increases after administration of β2-adrenergic agonists)
  - ***between asthma attacks*** - bronchial obstruction is *absent* or *triggered by bronchoconstrictors* (FEV1 decreases after administration of methacholine)
  - ***in persistent asthma*** - *daily variability of the bronchial obstruction is increased* (PEFR ≥ 20% - see Lab)
- **Clinical manifestations:**

① **In the MILD/MODERATE asthma attacks,** the following occurs:
- *expiratory bradypnea (with prolonged exhalation)*
- moderate cough and wheezing
- obstructive ventilatory dysfunction (spirometry): **low FEV1/FVC, low FEV1, normal FVC**

② **In the SEVERE asthma attacks,** the following occurs:
- *tachypnea* (due to the use of the accessory respiratory muscles in order to increase the ventilatory drive)
- inefficient cough
- intense wheezing
- **obstructive ventilatory dysfunction with "air trapping"** (body plethysmography): **increased RV, low FVC, normal/slightly high TLC**

2) Alteration of the VENTILATION and PERFUSION distribution (V_A/Q ratio)

- **General features:**
  – the **diffuse and nonhomogenous** distribution of the bronchial obstruction is responsible for the **coexistence of hypo and compensatory normo/hyperventilated territories**
  – the increase in the **respiratory drive** (the usage of the accessory respiratory muscles) induces the increase of the **amplitude of the inspiration with pulmonary hyperinflation**
  – in severe asthma attacks the decreased filling of the left ventricle during inhalation (by hyperinflation and the bulging of the interventricular septum caused by the increased filling of the right ventricle) is responsible for the occurrence of the **paradoxical pulse** (Kussmaul) or tachycardia ≥ **110 b/min**.

Observation:
The **paradoxical pulse** is defined as the ***decrease of systolic BP*** (decrease in ventricular filling and systolic volume) by ***more than 10 mmHg during inspiration*** (normally, in inspiration systolic BP decreases by 6-10 mmHg) and ***increase in systolic BP during expiration*** (increase in ventricular filling and systolic volume).

3) Alteration of the PULMONARY GAS EXCHANGE

- **General features:**

– the coexistence of *hypo- and normo/hyperventilated territories* impairs **the ventilation/perfusion ratio (V_A/Q)** and pulmonary gas exchange leading to **respiratory failure**

① **In the MILD/MODERATE attacks** – obstruction DOES NOT occur in all pulmonary territories. In the mild attack blood gases are within normal limits but in the moderate one the alteration of ventilation distribution induces **partial respiratory failure** defined by**:**
- decreased PaO_2 (hypoxemia) with compensatory *hyperventilation* and *reflex pulmonary vasoconstriction*
- decreased $PaCO_2$ (hypocapnia) due to *reflex alveolar hyperventilation* with *respiratory alkalosis*

② **In the SEVERE attacks** – obstruction **occurs in ALL** pulmonary territories and the alteration of the ventilation distribution induces **global respiratory failure** defined by**:**
- decreased PaO_2 (hypoxemia) with *cyanosis* (the increase of the reduced Hb concentration)
- increased $PaCO_2$ (hypercapnia) due to global alveolar hypoventilation with *respiratory acidosis*

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

DEFINITION: a chronic disease with multifactorial etiology determined by exposure to irritants, mainly **smoking,** and characterized by the **triad**:

1. **Chronic LUNG INFLAMMATION**
2. **Association of varying degrees of PULMONARY EMPHYSEMA (extrinsic obstruction) and CHRONIC OBSTRUCTIVE BRONCHITIS (intrinsic obstruction)**
3. **Progressive, diffuse BRONCHIAL OBSTRUCTION, with <u>minimal reversibility</u>**

ETIOLOGY

1. <u>EXTERNAL</u> factors:

a) Chronic SMOKING - represents the **most important risk factor for COPD,** being responsible for approx. 90% of cases (minimum 20 packages/year, for 10-15 years).

Observation: In smokers, there is a decrease rate of FEV1 of approx. 50-60 ml/year (some even reaching values of 90-100 ml/year) while normally, FEV1 decreases by 15-30 ml/year.

b) Air POLLUTANTS in industrial environments (exacerbate the effects of smoking):
- steel industry (in foundries)
- extractive industry (coal, metals)
- chemical industry (SO_2, NO_2, chlorine, ammonia)
- textile industry (dyers using volatile solvents)
- rubber industry (tyre production)

c) Recurrent RESPIRATORY INFECTIONS

2. <u>INDIVIDUAL</u> factors:

a) Genetic deficiency of α_1-antitrypsin (AAT)

– AAT is the **main antiprotease** which inhibits the ***lysosomal enzymes***: trypsin, chymotrypsin, elastase, collagenase etc., released by **phagocytic cells** (micro-/macrophages) in the lungs in response to the aggression induced by **infectious agents** and/or **air pollutants**

– The genetic defects causes a decrease in the hepatic synthesis of AAT (less than 10% of normal in the homozygous defect), responsible for:
  - loss of the lung protection against the destructive action of lysosomal proteases
  - exacerbation of emphysematous lesions viathe destruction of pulmonary elastic fibers
  - accelerated decrease in FEV1

b) Severe asthma can progress towards COPD with *persistent* bronchial obstruction (and permanent dyspnea).

PATHOGENESIS

a) Chronic pulmonary INFLAMMATION - is triggered by chronic exposure to the components of cigarette smoke (more than 4000 volatile substances) and other inhalational noxious substances and is responsible for:
  - **Lesions of the *lung parenchyma*** in the case of ***pulmonary emphysema,*** secondary (at least in part) to the *protease-antiprotease imbalance*, mainly an AAT deficit (but also of alpha-2-macroglobulin and beta-1-anticollagenase)
  - **Lesions of the *bronchial walls*** in the case of ***chronic bronchitis,*** secondary (at least in part) to the *imbalance between pro-oxidant-antioxidant factors*, i.e., excess of pro-oxidant agents in the cigarette smoke and generated at the level of phagocytes

b) REMODELING of both airways and lungs - is triggered by the **repair processes** induced by chronic inflammation and is characterized by **structural changes of the bronchial walls and extracellular matrix,** listed below with their functional consequences:
  - **bronchial wall thickening and reduction of airway caliber** due to: increased deposition of extracellular matrix proteins, collagen deposition with fibrosis, hyperplasia/hypertrophy of airway smooth muscle cells, which together with hypertrophy of the mucous glands (in large airways) and goblet cells (in small airways) responsible for mucus hypersecretion determines: i) **increased resistance to flow in the airways, i.e. intrinsic bronchial obstruction** and ii) **mismatched distribution of ventilation and perfusion**, abnormal **V_A/Q ratio** $\Rightarrow$ **obstructive ventilatory dysfunction**
  - **loss of lung elastic fibers** due to neutrophil-mediated elastin lysis via elastase released in an environment of low AAT, and subsequent **decreased pulmonary elastic recoil**, determines: i) **distal bronchiolar collapse with extrinsic dynamic bronchial obstruction in forced expiration** and ii) **pulmonary hyperinflation** $\Rightarrow$ **increased TLC**
  - **loss of alveoli** due breakdown of the alveolar walls, and subsequent permanent enlargement of airspaces, i.e., bullae of emphysema, is responsible for the: i) **decreased alveolar-capillary exchange surface** and ii) **decline of gas exchange** $\Rightarrow$ **low DL_{CO}** (diffusion lung capacity of carbon monoxide)

CLINICAL FORMS

I. PULMONARY EMPHYSEMA or COPD type A

- **Definition: permanent enlargement of the alveolar spaces distal to the terminal bronchiole** associated with a **loss of the distal lung architecture.**

- **Pathophysiology: EXTRINSIC obstruction of the DISTAL airways** induced by the **decreased pulmonary elastic recoil,** which is due to the ***loss of the elastic and alveolar tissue*** with the tendency of *bronchioles to collapse during the forced expiration* and **pulmonary HYPERINFLATION**.

- **Classification:**

a) According to the ETIOLOGY:

① PRIMARY emphysema:

- **Cause** – **genetic deficiency of AAT**, mainly homozygous but also heterozygous
- **Consequences:**
  - **early destruction** of pulmonary **elastin** and **collagen** by the lysosomal enzymes: elastase, collagenase, proteases (which are normally inhibited by AAT)
  - the onset of the disease **< 40 years of age**, **independent of smoking**

② SECONDARY emphysema:

- **Causes:**
  - **smoking** – **main cause,** the components of the cigarette smoke inhibit the activity of AAT via a *double mechanism:* (i) *direct,* by decreasing AAT activity and (ii) *indirect*, by stimulating the formation of a *chronic infiltrate with inflammatory cells* which secrete proteolytic enzymes
  - air pollution (industrial pollutants including smog, toxic chemicals)
  - repeated respiratory infections
- **Consequences:**
  - **late** loss of elastic and alveolar tissue under the action of lysosomal proteases
  - delayed onset **> 50 years of age, in the presence of smoking**

Observation:

THE CONCEPT OF THE EQUAL PRESSURE POINT (EPP)

In the case of a forced expiration with open glottis, **the intrabronchial pressure** (i.e., the pressure that generates the airflow through the airways) is equal to the difference between the **alveolar pressure** (i.e., the sum between the positive pleural pressure, +30 mmHg, and the elastic pressure generated by the pulmonary recoil, +10 mmHg) and the **pressure from the mouth** (the atmospheric or the reference pressure, which is considered zero) (Fig.4.1).

Due to flow resistance, the intrabronchial pressure **progressively decreases** in the airways, **from the alveoli towards the mouth**, the loss of the pressure at a certain level being more important as the airflow increases. As a consequence, at a certain point within the airways, **the intrabronchial pressure will become equal to the peribronchial pressure**, namely to the positive pleural pressure during the forced expiration (+30 mmHg); this point is called **the equal pressure point (EPP)** and it splits the airways **in two zones**:

- **distal**, towards the **alveoli**, a zone where the *intrabronchial pressure is higher than the peribronchial pressure* and tends to **maintain the airways opened**
- **central**, towards the **trachea,** a zone were the *peribronchial pressure* is higher than the *intrabronchial pressure and tends* **to collapse the airways** (forced dynamic compression)

During the forced expiration, the **EPP is lowered from the trachea towards the distal airways**, due to the progressive decrease of the elastic recoil as a result of the lung air depletion. The EPP position **influences the expiratory airflow**, as follows:

- at the level of **large bronchi** (diameter > 2 mm and cartilage wall), the collapse of the airways is blocked by the presence of the cartilage

– at the level of **small bronchi** (diameter < 2 mm and muscle wall), the collapse of the airways is allowed by the absence of the cartilage

During the forced expiration, the **EPP is lowered from the trachea towards the distal airways**, due to the progressive decrease of the elastic recoil as a result of the lung air depletion. The EPP position **influences the expiratory airflow**, as follows:

– at the level of **large bronchi** (diameter > 2 mm and cartilage wall), the collapse of the airways is blocked by the presence of the cartilage
– at the level of **small bronchi** (diameter < 2 mm and muscle wall), the collapse of the airways is allowed by the absence of the cartilage

(the down-shift of the EPP is more pronounced as the elastic recoil is more decreased, as in emphysema)

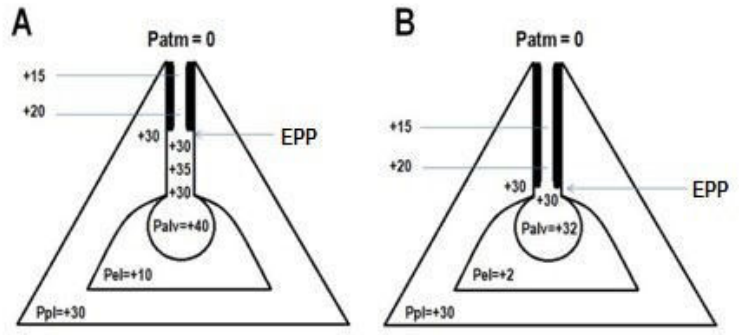

Figure 4.1. The EQUAL PRESSURE POINT (EPP): **A** – normal lung (normal pulmonary elastic recoil), **B** – emphysema (decreased pulmonary elastic recoil). P_{pl} = pleural pressure, P_{el} = elastic pressure, P_{alv} = alveolar pressure, P_{atm} = atmospheric pressure.

b) According to the <u>LOCATION of LESIONS</u>:

① CENTRIACINAR emphysema

– is the most frequent type in **smokers**
– is predominantly located in the **UPPER pulmonary lobes**
– destruction of the **central portion of the acinus**, i.e. its proximal part, only the **respiratory bronchioles**

② PANACINAR emphysema

– is the most frequent form in **patients** with **AAT deficiency and in elderly**
– is predominantly located in the **LOWER pulmonary lobes**
– destruction of **all parts of the acinus** – *respiratory bronchioles, alveolar ducts and alveoli*, with the formation of typical **bullae,** hence the term **bullous emphysema**

Observation:

In smokers there is a frequent *association* of *centriacinar emphysema in the upper lobes* and *panacinar emphysema in the lower lobes of the lungs.*

II. CHRONIC BRONCHITIS or COPD type B

- **Definition: chronic inflammation** of **DISTAL** and **PROXIMAL airways**, characterized by **productive cough lasting for <u>≥ 3 months a year</u>**, **<u>at least 2 consecutive years</u>**, in the presence of **<u>obstructive ventilatory dysfunction.</u>**
- **Pathophysiology: INTRINSIC bronchial obstruction** with the increase of **the airflow resistance** due to:

① **Lesions of chronic OBSTRUCTIVE BRONCHITIS** elicited via the:
- hypertrophy/hyperplasia of mucosal glands and goblet cells
- hypersecretion of viscous mucus with plugs
- thickened bronchial mucosa due to local edema

② **PERIBRONCHIOLAR fibrosis**

③ **CHRONIC BRONCHOSPASM**, which may be:
- *intermittent* - in chronic **asthmatic bronchitis** (bronchitis that occurs in patients with asthma, which demonstrates bronchial hyperreactivity and usually are smokers)
- *persistent, partially reversible/irreversible* - in **COPD**

FUNCTIONAL CHANGES

a) BRONCHIAL OBSTRUCTION

- **Definition**: is the functional expression of the *decrease in pulmonary elastic recoil* and the *increase in flow resistance in the airways*
- **Pathophysiology:** the association, to varying degrees, of ***lung emphysema*** lesions, which decrease in lung elastic recoil (extrinsic obstruction) with ***chronic obstructive bronchitis*** lesions, which increases the airflow resistance (intrinsic obstruction)
- **Characteristics:**
  - absence of BHR - *negative bronchoconstrictor tests*
  - partially reversible/irreversible obstruction - *negative bronchodilator tests*
  - daily variability of obstruction is low - *PEFR < 20%* (see Lab)
- **Manifestations:**
  - **obstructive** ventilatory dysfunction (forced spirometry): **low FEV1/FVC, low FEV1, normal FVC**
  - obstructive ventilatory dysfunction with **"lung hyperinflation"** (body plethysmography): **greatly increased RV, normal/low vital capacity, greatly increased TLC**

b) Alteration of the VENTILATION and PERFUSION DISTRIBUTION (V_A/Q ratio)

- **In pulmonary emphysema:**
  - the *uneven* decrease in the exchange of **O_2** (decreased **alveolar ventilation** by **extrinsic** obstruction) and **CO_2** (reduced **pulmonary perfusion** by reduced number of perialveolar capillaries) results in an *initial* increase in **$PaCO_2$** (hypercapnia) that **CAN** be **compensated** by *reflex hyperventilation*
  - the increase in ventilatory drive keeps blood gas pressures within the normal limits
  - changes in blood gas pressures characteristic of respiratory failure occur **late** in the course of the disease
- **In chronic bronchitis:**
  - the major decrease in **O_2** exchange (decreased **alveolar ventilation** due to **intrinsic** obstruction) translates into an *initial* decrease in **PaO_2** (hypoxemia) **that CANNOT be compensated** by *reflex hyperventilation*
  - the chronic severe hypoventilation causes **early changes in the blood gas pressures**:
    - hypoxemia and normo- or hypocapnia - in **partial respiratory failure**
    - hypoxemia and hypercapnia - in **global respiratory failure**

c) Alteration of PULMONARY GAS EXCHANGE

- **Characteristic** – the **decreased alveolo-capillary exchange surface** due to destruction of the alveolar walls in **emphysema** contributes to the pathogenesis of the **respiratory failure**

d) Alteration of PULMONARY CIRCULATION

- **Pathophysiology:**
  - **constriction of arterioles** – caused by:
    - early endothelial dysfunction in the pulmonary circulation (low nitric oxide NO / increased endothelin ET-1)
    - hypoxia secondary to the impaired gas exchange
  - **increase of blood viscosity** – due to ***polycythemia* secondary to hypoxia** (stimulates the release of erythropoietin and the activation of erythropoiesis)
- **Characteristics - HEMODYNAMIC changes:**
  - increased **resistance in the pulmonary circulation** with **PULMONARY HYPERTENSION (PH)**
  - chronic pressure overload of the **right ventricle** with **RIGHT HEART FAILURE** or ***cor pulmonale***

CLINICAL and FUNCTIONAL FEATURES – are presented in Table 4.3.

Table 4.3. The main clinical and functional features of COPD forms.

CLINICAL & FUNCTIONAL features	**Pulmonary emphysema (″pink puffers″) – type A**	**Chronic bronchitis (″blue bloaters″) – type B**
Smoker history	Yes	Yes
Onset	40-50 years of age	30-40 years of age
Productive cough	Late (in case of infection)	**Early, classical sign**
Dyspnea	**Frequent, classical sign**	Late in the evolution
Wheezing	Minimal	Intermittent
Barrel chest	**Frequent, classical sign**	Occasionally
Prolonged expiration	Always present	Always present
Cyanosis	Rare	**Frequent, classical sign**
Polycythemia	Late in the evolution	**Frequent**
Cor pulmonale	Late in the evolution	**Frequent**
Weight loss	Severe in advanced stages	Occasionally

a) PULMONARY EMPHYSEMA – type A COPD, the **"pink puffer"** clinical form

- **Main features:**
  - ***normal skin coloration ("pink")*** due to *compensatory (reflex) hyperventilation* which maintains normal arterial pressures of blood gases for a long period
  - ***important dyspnea and tachypnea ("puffer")*** due to *the increase of the respiratory drive* through reflex *alveolar* hyperventilation

- ***"barrel chest",*** i.e. the increase of the anteroposterior thorax diameter due to *pulmonary hyperinflation*
- ***prolonged pursed-lip expiration*** in order to *prevent the collapse of the airways during expiration*

b) OBSTRUCTIVE CHRONIC BRONCHITIS – type B COPD, the **"blue bloater"** clinical form

- **Main features:**
  - ***early occurrence*** *of* ***hypoxemia and cyanosis,*** i.e., the ***blue color of the teguments*** since *the arterial pressures of the blood gases CANNOT be maintained in normal limits by compensatory (reflex) hyperventilation*
  - ***absence of dyspnea and tachypnea*** due to *lack of* reflex *alveolar* hyperventilation
  - ***peripheral edema ("bloater")*** due to *right heart failure or cor pulmonale* caused by secondary pulmonary hypertension induced by reflex pulmonary vasoconstriction associated with chronic hypoxia
  - ***typical productive cough*** *– the hallmark of lesions of chronic bronchitis*

PULMONARY HYPERTENSION (PHT)

DEFINITION: heterogenous group of disorders that have as common feature **the increase in mean pulmonary artery pressure (mPAP) ≥ 20 mmHg** at rest measured by right heart catheterization (normal mPAP = 11 – 18 mmHg).

PATHOPHYSIOLOGY – 2 main mechanisms:

① **Increased RESISTANCE in the pulmonary circulation** via:
- pulmonary vasoconstriction due to chronic *hypoxemia*
- partial/total obstruction of the pulmonary vessels = the „obstructive" PHT
- increased left atrium pressure with retrograde transmission = the „passive" PHT
- the structural remodeling of the arteries/arterioles walls = the „stable" PHT

② **Increased BLOOD FLOW in the pulmonary circulation** in the case of the **left-to-right shunts** in congenital heart diseases.

Observation:
The pulmonary vasoconstriction triggered by *hypoxia* represents an **adaptive physiological response** of the pulmonary circulation in the areas with **alveolar hypoventilation** where blood will be *redistributed* towards the better ventilated regions. When a large part of the lung is hypoventilated, this **response becomes pathological** inducing *excessive increase of the pulmonary vascular resistance* with the occurrence of **PHT.**

CONSEQUENCES – in chronic forms:
- the prolonged pulmonary artery pressure increase is responsible for vascular *structural* changes - **media hypertrophy** and **intimal fibrosis** with PHT „*stabilization*"
- the PHT stabilization induces **right ventricle hypertrophy** due to chronic pressure overload and thus, the progression to **right heart failure** or **cor pulmonale**

CLINICAL FORMS

I. **PRIMARY or IDIOPATIC PHT** – unknown cause, unrelated to an identifiable disease
II. **SECONDARY PHT** – related to underlying diseases or known risk factors

I. PRIMARY PHT

- **Definition** – a rare form of **PHT** characterized by **media hypertrophy** and **concentric intimal fibrosis** with progressive obstruction of *pulmonary arteries* and *arterioles.*
- **Cause** – it is an *autosomal dominant transmission disorder* characterized by:
  - **decreased nitric oxide (NO) production** (NO effects: vasodilator and inhibitor of the vascular smooth muscle cells proliferation) and **increased endothelin 1 (ET-1) production** (ET-1 effects: vasoconstrictor and stimulator of the vascular smooth muscle cells proliferation)
  - **increased production of growth factors** (e.g., VEGF, PDGF) which stimulate the vascular smooth muscle cells proliferation
- **Conditions associated to primary PHT**:
  - collagen disorders (e.g., scleroderma)
  - persistent pulmonary hypertension in newborns
- **Evolution** – unfavorable, progressive to **right heart failure** and **respiratory failure.**

II. SECONDARY PHT

- **MAJOR causes:**

① **Chronic hypoxia** – is the major cause:
  - Advanced COPD
  - Severe obstructive sleep apnea syndrome

② **Obliteration/obstruction of the pulmonary vessels – „obstructive" PHT** in:
  - pulmonary interstitial disorders with severe fibrosis
  - recurrent pulmonary thromboembolism

③ **Increased pressure in the left atrium** with **retrograde transmission – „passive" PHT** in:
  - left heart failure
  - mitral stenosis

④ **Increase of the pulmonary blood flow in congenital cardiopathies with left-right shunt,** such as:
  - atrial/ventricular septal defect or patent arterial duct

Observation:

The current WHO classification includes 5 major groups of PHT:

1. Pulmonary ARTERIAL HT (PAH) – due to **increased pulmonary VASCULAR RESISTANCE** (rare):
1.1. Idiopathic PAH - primary PHT, historically more frequent in young females, currently increasing prevalence in elderly people and potentially less favorable response to therapy
1.2. Hereditary PAH - mutations of the *Bone Morphogenetic Protein Receptor 2* (BMPR2) gene (75% of cases), a receptor belonging to the TGF-β family, which stimulates the proliferation of endothelial and vascular smooth muscle cells (VSMCs) with: i) *intimal fibrosis,* ii) *hypertrophy of media*, and iii) *endothelial dysfunction* defined by *increased endothelin and decreased nitric oxide and prostacyclin*.
1.3. Drug-and toxin-induced PAH – amphetamines, appetite suppressants, dasatinib
1.4. PAH associated with various diseases: connective tissue diseases (scleroderma, SLE), congenital heart diseases with left-to-right shunt (atrial or ventricular septal defect), portal hypertension, HIV infection
Pathophysiology:
There are 4 aberrant pathways implicated in the development of PAH, which are currently targets for therapy (with drugs being given in combination or alternate):

- ✓ *Endothelin pathway*, responsible for persistent vasoconstriction – targeted by the drugs belonging to the class of endothelin-receptor antagonists (bosentan, ambrisentan)
- ✓ *Nitric oxide pathway*, responsible for decreased vasodilation (the NO dilator effect is mediated via the generation of cGMP whose level is maintained by inhibiting phosphodiesterase - the enzyme responsible for its degradation or activating guanylate cyclase - the enzyme responsible for its synthesis, thus the design of NO-cGMP enhancer drugs) – targeted by the drugs from the classes of phosphodiesterase 5 (PDE5) inhibitors (sildenafil, tadalafil and vardenafil) and soluble guanylate cyclase stimulators (riociguat)
- ✓ *Prostacyclin (PGI2) pathway*, responsible for decreased vasodilation – targeted by the class of prostacyclin analogs (iloprost, treprostinil, epoprostenol)
- ✓ BMPR2 pathway, responsible for remodelling of small pulmonary arteries walls – targeted by the most recent drug, sotatercept (which restores restore the balance between anti-proliferation and pro-proliferation signaling pathways) and is indicated in idiopatic and hereditary PAH

2. PHT caused by left heart disease – due to increased pulmonary VENOUS PRESSURE (most common cause - 75% of cases):

- **2.1. Heart failure with preserved ejection fraction (HFpEF)**
- **2.2. Heart failure with reduced ejection fraction (HFrEF)**
- **2.3. Valvular heart diseases** – most frequent, mitral stenosis

3. PHT caused by lung diseases and/or hypoxia (the 2nd most common cause)

- **3.1. COPD** (obstructive dysfunction)
- **3.2. Interstitial lung disease** (restrictive dysfunction)
- **3.3. Obstructive sleep apnea**
- **3.4. Alveolar hypoventilation disorders**

4. PHT caused by chronic thromboembolism – due to the occlusion of pulmonary arteries

5. PHT with multifactorial mechanisms

- **5.1. Hematologic disorders** – myeloproliferative disorders, chronic hemolytic anemia
- **5.2. Systemic disorders** – sarcoidosis
- **5.3. Metabolic disorders** – glycogen storage disease, thyroid disease
- **5.4. Chronic renal failure** on dialysis

SLEEP APNEA SYNDROME

DEFINITION: recurrent episodes of complete (apnea) or **partial collapse (hypopnea) of the upper airway** during the **sleep,** associated with:

- decreased oxygen saturation
- **cortical micro-awakenings** and/or **arousals from sleep,** resulting in **fragmented, nonrestorative sleep and diurnal somnolence**

TERMINOLOGY:

① **Apnea** – complete cutoff of the airflow at oropharyngeal level for periods lasting **more than 10 seconds** (most of the patients present apnea episodes lasting for 20-30 seconds up to 2-3 minutes)

② **Hypopnea** – airflow reduction at oropharyngeal level by at least **30%** for **periods** lasting **more than 10 seconds,** associated with the decrease by **3-4%** of the **peripheral oxygen saturation of hemoglobin** (SpO_2 measured by pulse oximetry) or with a **cortical micro-awakening**

③ **Apnea/hypopnea index (AHI)** – the ratio between the number of apnea/hypopnea episodes and the total sleep duration; it is suggestive for sleep apnea syndrome if **higher than 5/hour**:
- 5 - 14/hour – *mild form*
- 15 - 29/hour – *moderate form*
- > 30/hour – *severe form*

④ **Cortical micro-awakening** – the arousal reaction identified on the **EEG**, which appears as a consequence of ***hypoxemia, i.e.,*** **PaO_2 < 60 mmHg**, the patient being unaware of it.

CLASSIFICATION

I. OBSTRUCTIVE sleep apnea – the frequent form, characterized by episodes of partial or complete collapse of the airflow at oropharyngeal level with the persistence of the thoraco-abdominal respiratory movements (at polysomnography)

II. CENTRAL sleep apnea – the rare form, characterized by central impairment of the respiratory drive (the brain stem does not respond appropriately to changes in CO2 level) responsible for transient decreases and/or pauses in respiration with the interruption of the thoraco-abdominal respiratory movements (at polysomnography)

OBSTRUCTIVE SLEEP APNEA (OSA)

PATHOGENESIS

The OSA syndrome is characterized by the following sequence of events, which can be repeated tens/hundreds times during the night:

1. After the onset of sleep, **the collapse of oro-pharynx** induces the **episode of apnea / hypopnea.**
2. The onset of **hypoxemia (PaO_2 < 60 mmHg)** causes the **cortical microawakening** and/or the **sudden awakening from sleep.**
3. Restoration of the **oro-pharynx patency** and of the airflow is followed by **resumption of sleep,** after which the sequence repeats itself.

RISK factors

1. AGE and GENDER
- **between 30 and 60 years of age** – the prevalence of OSAS is higher in males than in females
- **after 60 years of age** – the prevalence of OSAS is equal in both genders *and it increases with age* due to the occurrence of the *oropharyngeal muscular hypotonia* (collapse of the oropharynx during sleep) and the *decreased sensitivity to hypoxemia of the peripheral chemoreceptors* (with microwakening suppression at the end of each apnea/hypopnea episode)

2. CENTRAL obesity (abdominal, android)
- is present in *more than 80% of the patients*
- it reduces *the upper airway caliber* via:
  - ✓ the increase of the fat deposits in the *soft pharyngeal tissue*

- ✓ the *pharyngeal compression* by the superficial fat mass from the neck

3. STRUCTURAL abnormalities of the UPPER AIRWAYS

- *nasal polyps, deviated nasal septum, tonsils hypertrophy, micro/retrognathia, and glossitis* are present especially in **children**, isolated or within genetic syndromes

4. FUNCTIONAL abnormalities of the UPPER AIRWAYS

- *neuromuscular disorders* that associate hypotonia of the pharyngeal musculature, exacerbated during REM sleep (e.g., amyotrophic lateral sclerosis, several polyneuropathies) leading to nocturnal hypoventilation, repeated episodes of apnea/hypopnea and sleep fragmentation

5. ENDOCRINE pathology

- *acromegaly*, *hypothyroidism, Cushing syndrome* induce *infiltrations* and *edema* of the neck/face soft tissues, which decrease the upper airways caliber

6. ALCOHOL and SEDATIVE drugs consumption

- *reduces the pharyngeal muscle tone* and *depresses the cortical micro-awakenings response* at the end of each apnea episode (it increases the prevalence/severity of the disease)

7. SMOKING

- determines the *irritation and edema of the pharyngeal walls leading to the reduction of the oro-pharinx caliber*

Factor FAVORING OSA:

- **SUPINE position during sleep** – exacerbates the reduction of the upper airways caliber due to the *effect of gravity on the tongue and pharyngeal soft tissues (uvula, soft palate)*

CLINICAL and FUNCTIONAL MANIFESTATIONS

1. CARDIAC and RESPIRATORY

- **Stimulation of the PERIPHERAL chemoreceptors by *hypoxemia* does NOT trigger the appropriate increase in ventilation** (due to oropharyngeal collapse), **but activates the sympatho-adrenergic *"alarm"* system** responsible for:
  - **Reflex changes in heart rate (HR): *bradycardia*** (< 50 b/min) during **apnea** and ***tachycardia*** (> 90 b/min) in the **airflow restoration phase,** with the possibility of:
    - ✓ *atrial arrhythmias:* atrial fibrillation
    - ✓ *ventricular arrhythmias:* premature ventricular contractions, ventricular tachycardia
    - ✓ *sudden cardiac death* due to ventricular arrhythmias at an AHI > 20/hour
  - **Systemic vasoconstriction** *due to increased sympathetic tone* with **secondary hypertension** responsible for **increased left ventricular afterload** and worsening of *left heart failure* in patients with preexisting heart disease
  - **Pulmonary vasoconstriction** *secondary to hypoxemia and increased sympathetic tone* with **chronic PHT** responsible for ***increased right ventricular afterload*** and worsening of *right heart failure* (cor pulmonale) in patients with COPD.

2. NEUROLOGICAL and BEHAVIORAL

- The **loss/fragmentation of sleep** and **cerebral hypoxia** – induce:
  - *excessive diurnal somnolence in passive situations* – initially during reading or watching TV and as the disease progresses, during all daily activities

- *attention, memory disorders* – the decrease of the professional performance
- *personality changes* – irritability, depression, anxiety crises
- *morning headache*
- *in children* – the decreased performance in school activities, aggressivity, parasomnias (e.g., sleep talking, night terror/pavor nocturnus, sleepwalking)

INTERSTITIAL LUNG DISEASES

DEFINITION: a group of chronic pulmonary disorders that **affect the interstitial space of the lungs** and are also called **diffuse parenchymal diseases**.

ETIOLOGY

- **Idiopathic** – **IDIOPATHIC PULMONARY FIBROSIS** (or cryptogenic fibrosing alveolitis) in over **50%** of cases
- **INHALATORY causes** – professional or environmental exposures to ***organic/inorganic powders, smoke*:**
  - *pneumoconioses* (e.g., sillicosis, asbestosis)
  - *extrinsic allergic alveolitis* (type III + IV HS reaction) - e.g., bird fancier's, farmer's lung
  - *pulmonary talcosis* (inhalation of talc, as in heroin users)
  - *tobacco smoking*
- **AUTOIMMUNE SYSTEMIC disorders:**
  - sarcoidosis
  - collagenosis (systemic lupus erythematosus - SLE, rheumatoid arthritis, scleroderma)
- **DRUG-RELATED causes:**
  - **amiodarone therapy** for long term (> 6 months)
  - **chemotherapy** - cytostatics (cyclophosphamide, busulfan, bleomycin), monoclonal antibodies (medication with the suffix "mab")
  - **thoracic radiotherapy**

PATHOPHYSIOLOGY

a. PATHOGENIC triad:

1. **Low-grade CHRONIC INFLAMMATION** of the **alveolar walls**
2. **Pulmonary FIBROSIS** which is **extensive and inhomogeneous**, characterized by:
   - coexistence of **injury** and **healing processes** that are neither uniform nor synchronous
   - **coexistence of extensive areas of fibrosis** alongside **relatively normal areas** with a typical **"*honeycomb*" appearance** at chest X-ray
   - **decreased lung compliance** and **increased pulmonary elastic recoil**
3. **Destruction of the LUNG PARENCHYMA** which is **progressive** and **irreversible**

b. FUNCTIONAL triad:

1. Decrease in **ALVEOLAR VENTILATION (V_A)**
2. Decrease in **CAPILLARY PERFUSION (Q)**
3. Decrease in **GAS EXCHANGES**

IDIOPATHIC PULMONARY FIBROSIS (IPF)

DEFINITION: a **chronic lung disease** characterized by **ABNORMAL HEALING** of **recurrent lesions** of the **alveolar epithelium**, caused by **chronic exposure** to an **unknown environmental factor** (irritant or toxic) in subjects with **favoring endogenous factors**:

- genetic predisposition (familial IPF)

- male gender
- age over 50 years

ETIOLOGY

a) ENVIRONMENTAL factors (suspected)

- **smoking** (> 20 packs per year)
- occupational factors - chronic exposure to organic/inorganic dusts and vapors (farmers, stone/metal workers)
- atmospheric pollutants
- recurrent viral infections

b) INDIVIDUAL factors

① **GENETIC factors - gene mutations** responsible for the existence of a **"vulnerable" alveolar epithelium** characterized by:

- decrease in the lifespan of type I alveolocytes in the structure of the alveolar epithelium ("early aging")
- decrease in the regeneration capacity of the damaged alveolar epithelium by type II alveolocytes
  - normally, in case of an alveolar injury they differentiate into type I alveolocytes
  - pathologically, in the case of an alveolar injury they differentiate into myofibroblasts

② **ASSOCIATED pathology** - gastroesophageal reflux disease (chronic irritant factor)

PATHOGENESIS

IPF is considered an **"epithelio-fibroblastic" disease** in which the recurrent action of an irritating/toxic environmental factor in a predisposed person, causes:

1. **Damage to the ALVEOLAR EPITHELIUM** → low grade chronic inflammation and inflammatory infiltrate rich in **MACROPHAGES**
2. **Differentiation of FIBROBLASTS** and **type II ALVEOLOCYTES** into **MYOFIBROBLASTS** → **PROLIFERATION OF MYOFIBROBLASTS** under the action of factors secreted by **macrophages:**
   - pro-inflammatory cytokines: e.g.,TNF-alpha
   - growth factors like **TGF-β** (transforming growth factor - β), **FGF** (fibroblast growth factor) and **PDGF** (platelet derived growth factor)
3. **Increased secretion of COLLAGEN and COMPONENTS OF THE EXTRACELLULAR MATRIX** by **myofibroblasts** with:
   - the occurence of **INTERSTITIAL FIBROSIS sites** - **the CENTRAL PATHOGENIC element of the disease**
   - **ABERRANT HEALING** with **progressive alveolar and bronchiolar destructions**

Observation:

Current disease therapy uses *anti-fibrotic agents* such as *nintedanib*, an inhibitor of FGF, PDGF receptors, and *pirfenidone* that interferes with the signaling pathway of TGF-β.

FUNCTIONAL CHANGES

a) Impairment of ALVEOLAR VENTILATION due to the:

- **Decrease of pulmonary compliance** and **increase of elastic recoil,** which are responsible for:
  - ***progressive dyspnea*** – initially, during exercise and later, at rest
  - ***superficial breathing*** **(tachypnea)** – the increase of the respiratory drive (reflex alveolar hyperventilation to maintain PaO_2 within normal limits in the blood from affected areas)
  - ***restrictive parenchymal ventilatory dysfunction*** defined by:
    - low FVC, low FEV1, normal FEV1/FVC (forced spirometry) and
    - low vital capacity, low RV and low TLC (body plethysmography)
- **Distortion of bronchial tree** responsible for *chronic, irritative (non-productive) cough*

b) Impairment of CAPILLARY PERFUSION due to:
- **Vascular obstruction**
- **Reduction of the pulmonary capillary bed**

which may lead to **secondary pulmonary hypertension** and **right ventricular failure (*cor pulmonale*)**

c) Impairment of PULMONARY GAS EXCHANGE due to:
- **Increased thickness of the alveolo-capillary membrane** causes a **decrease in O_2 diffusion,** identified by a **decrease in DL_{CO}** and is responsible for the occurrence of **hypoxemia ($PaO_2 < 60$ mmHg)**
  - **In the INITIAL stages of the disease:**
    - **hypoxemia** occurs only ***during physical exertion***
    - reflex alveolar hyperventilation will be responsible for: **normocapnia** (normal $PaCO_2$ = 35-45 mmHg) or **hypocapnia** (low $PaCO_2 < 35$ mmHg) $\rightarrow$ **partial respiratory failure**
  - **In the ADVANCED stages of the disease:**
    - **hypoxemia** is present ***at rest***
    - reflex alveolar hyperventilation cannot compensate any longer for the decrease in CO_2 diffusion
    - **hypoxemia is associated with hypercapnia (high $PaCO_2 > 45$ mmHg) $\rightarrow$ global respiratory failure**

RESPIRATORY FAILURE (RF)

DEFINITION: a **pathological condition** characterized by the **abnormal values of the pulmonary gas partial pressures in the arterial blood.**

CLASSIFICATION

a) According to the PATHOGENESIS and the RESPIRATORY GAS PRESSURES at rest:

1. PARTIAL, HYPOXEMIC RF or type I RF – only the O_2 change is affected **(oxygenation deficit)**
- $PaO_2 < 60$ mmHg – HYPOXEMIA
- $PaCO_2$ normal, 35-45 mmHg or decreased < 35 mmHg – NORMO/HYPOCAPNIA

2. GLOBAL, HYPERCAPNIC RF or type II RF – the **exchange for both O_2 and CO_2** is affected **(ventilation deficit)**

- PaO_2 < 60 mmHg – HYPOXEMIA
- $PaCO_2$ > 45 mmHg – HYPERCAPNIA

b) According to the EVOLUTION:

1. Acute RF (duration of hours/days) – decompensated respiratory acidosis: pH is very low, $PaCO_2$ is elevated, bicarbonate value is normal

2. Chronic RF (duration of months/years) – partially compensated respiratory acidosis (low pH, high $PaCO_2$, high bicarbonate) or compensated respiratory acidosis (pH = normal, high $PaCO_2$, very high bicarbonate)

A. HYPOXEMIA

DEFINITION: decreased PaO_2 < 60 mmHg

PATHOPHYSIOLOGY

- **In PARTIAL, HYPOXEMIC RF or type I RF**
  - **Hypoxemia** – is caused by the DIFFUSE and NON-UNIFORM lung injury due to:
    a) *Alteration of ventilation-perfusion ratio (V_A/Q)*
    b) *Alteration of gas diffusion through the alveolar-capillary membrane*
    c) *Presence of arterio-venous shunts*
    d) *Decrease of the O_2 pressure in the inhaled air*
  - **Normo/hypocapnia** – is caused by reflex alveolar hyperventilation in the unaffected areas
- **In GLOBAL, HYPERCAPNIC RF or type II RF**
  - **Hypoxemia** and **hypercapnia** – are caused by the DIFFUSE and UNIFORM lung injury due to:
    a) *Global alveolar hypoventilation*

a) Alteration of the V_A/Q RATIO – **<u>the most common pathogenic mechanism of RF</u>**

- **Etiology:**
  - Obstructive pulmonary diseases: mild COPD type B, *moderate* asthma attack
  - Acute CARDIOGENIC pulmonary edema due to acute left heart failure
  - Acute NON-CARDIOGENIC pulmonary edema due to Acute Respiratory Distress Syndrome (ARDS)
- **Pathogenesis:** the coexistence of **hypoventilated** and **normo-/HYPERventilated** alveolar territories

① **In the hypoventilated territories** (deficit of ventilation by comparison to perfusion):

- the gas pressures in the *arterial blood* **tend** towards the values in the *venous blood:*
  - PaO_2 = 40 mmHg
  - $PaCO_2$ = 46 mmHg
- the blood leaving the hypoventilated territories has a **low O_2 saturation** ($SatO_2 < 97\%$)

② **In the areas with compensatory HYPERventilation** (excess of ventilation compared to perfusion):

- the gas pressures in the *arterial blood* **tend** towards the values in the *atmospheric air*
  - PaO_2 = 130 mmHg
  - $PaCO_2$ = 0,23 mmHg
- the blood leaving the hyperventilated territories has **normal O_2 saturation** ($SatO_2 \geq$ 97%)

③ **In the arterial blood leaving the lungs**:
- $PaO_2 < 60$ mmHg
- $PaCO_2 \leq 40$ mmHg
- $SatO_2$ decreased $<$ 97%

Explanation:
- the ***„S"*** shape of the oxyhemoglobin dissociation curve DOES NOT allow the increase of the $SatO_2 > 100\%$, *even if the PaO_2 pressure rises above 100 mmHg* $\Rightarrow$ desaturation of the blood in O_2 in the ***hypoventilated*** *territories* ***CANNOT be compensated*** by an *O_2 „oversaturation"* of the blood in the **hyperventilated territories**
- *the linear relationship between the concentration of CO_2 (vol%) and $PaCO_2$* allows the accumulation of CO_2 from the **hypoventilated territories** to be compensated by the increased elimination of CO_2 in the **hyperventilated territories**

– O_2 administration will rapidly **correct hypoxemia** in ***RF caused by V_A/Q ratio alteration*** by **normalizing the $SatO_2$ in the hypoventilated territories** (NOT in hyperventilated ones) because the increase in the alveolar-capillary O_2 pressure gradient will force the O_2 diffusion through the alveolar-capillary membrane.

b) Alteration of GAS DIFFUSION at the ALVEOLAR-CAPILLARY MEMBRANE

- **Etiology:**

① **Decreased alveolar-capillary EXCHANGE SURFACE in**:
- Pulmonary resections
- Emphysema (bullous)

② **Increased alveolar-capillary membrane THICKNESS in**:
- Acute pulmonary edema
- Acute pulmonary inflammation: pneumonia, bronchopneumonia, ARDS
- Interstitial lung diseases with pulmonary fibrosis

- **Pathogenesis:**
  - the **exchange of O_2** is primarily impaired, while the exchange of **CO_2 remains unaffected for a long time** because the diffusion coefficient of CO_2 is **20 times higher** than that of O_2
  - administration of O_2 **corrects the hypoxemia** in ***RF caused by the altered alveolo-capillary DIFFUSION*** because the increase in the alveolo-arteriolar (A-a) pressure gradient of O_2 forces the diffusion of O_2 through the alveolo-capillary membrane in the **diseased lung areas**
  - the decrease in PaO_2 due to impaired alveolar-capillary diffusion is **exacerbated** by **breathing in an O_2-poor atmosphere** or by **physical exertion**

c) Presence of ARTERIO-VENOUS SHUNTS

- **Etiology:**
  ① **PULMONARY shunts** due *to impaired physiological pulmonary circulation* in:
  - vascular occlusion: e.g., pulmonary embolism
  - alveolar collapse: e.g., atelectasis, pneumothorax, massive pleurisy

  ② **EXTRAPULMONARY shunts** *due to pathological communication between the right and left heart chambers,* in*:*
  - congenital heart diseases with right-to-left shunt: e.g., tetralogy of Fallot
- **Pathogenesis:**
  - the passage of a fraction of *venous* (non-oxygenated) *blood* **directly** into the *systemic arterial circulation* is responsible for decreased **$PaO_2 < 60$ mmHg** and **$SaO_2 < 97\%$**
  - **hypoxemia** induces **reflex hyperventilation,** which compensates for the CO_2 excess brought by the shunted venous blood, thus **normo-/hypocapnia** ($PaCO_2 \leq 35$ mmHg) is present $\Rightarrow$ **partial, type I RF**
  - if the volume of the shunted venous blood represents an important fraction of the CO (rarely), **hypercapnia** ($PaCO_2 > 45$ mmHg) occurs $\Rightarrow$ **global**, **type II RF**
  - administration of O_2 **<u>does not</u> correct completely the hypoxemia in *RF caused by arterio-venous shunts*** because the increase in the alveolo-arteriolar (A-a) pressure gradient for O_2 **<u>cannot</u> force the diffusion of O_2 through the alveolo-capillary membrane from the diseased areas.**

d) Decreased O_2 PRESSURE in the INHALED AIR

- **Etiology:**
  - high altitude respiration (global RF appears at $PaO_2 < 30$ mmHg)
  - inhalation of toxic gases (chlorine, CO, H_2S) or vitiated air with reduced O_2 content

e) GLOBAL alveolar hypoventilation

- **Etiology:**
  ① **CENTRAL disorders,** which interfere with **respiration regulation** by **inhibiting the respiratory centers**:
  - *drug (morphine) or medication (barbiturates, opioids) overdose*
  - *central nervous system tumors or trauma*

  ② **PERIPHERAL disorders,** which interfere with **lung mechanics:**
  - *thoracic cage malformations:* kyphosis, scoliosis, accidents (e.g., crush syndrome)
  - *disorders of the nerves supplying the respiratory muscles:* spinal cord injuries
  - *disorders of the respiratory muscles:* miastenia gravis, muscular dystrophies
  - *pulmonary diseases:*
    i) chronic - most commonly, **COPD type B is consistently associated with type II RF**
    ii) acute - *severe* asthma attack, massive pneumothorax
- **Pathogenesis:**
  - **decreased alveolar ventilation in all lung areas** is responsible **for decreased $PaO_2 <$ 60 mmHg and increased $PaCO_2 > 50$ mmHg $\rightarrow$ global, type II RF**
  - **alveolar hypoxia** causes ***reflex pulmonary vasoconstriction,*** which when prolonged transforms a physiological mechanism (purported to restore the V_A/Q ratio back to 0.8)

into a ***pathological*** one responsible for increased pulmonary resistance with the occurrence of pulmonary HT, right ventricle hypertrophy and *cor pulmonale*

– administration of O_2 **corrects the hypoxemia from the *global RF*** because increased alveolar-arteriolar (A-a) pressure gradient for O_2 **can force the diffusion of O_2 across the alveolar-capillary membrane from the affected areas.**

CONSEQUENCES of HYPOXEMIA:

1. Activation of COMPENSATORY MECHANISMS (Table 4.4.)

Table 4.4. COMPENSATORY mechanisms in HYPOXEMIA.

Compensatory mechanisms	Causes	Consequences
1. Reflex hyperventilation (tachypnea)	Stimulation of peripheral aortic/carotid sinus chemoreceptors to correct the ***hypoxemia***	Tachypnea (high breathing rate due to hyperventilation) Hypocapnia (when CO_2 elimination is not altered)
2. Pulmonary vasoconstriction	Local effect of ***hypoxemia*** in an attempt to readjust the V_A/Q ratio	Acute right HF in *ac. hypoxemia* Chronic right HF in *chronic hypoxemia*
3. Stimulation of erythropoiesis	The increase of the renal release of erythropoietin to correct ***hypoxemia***	Secondary polyglobulia (polycythemia)
4. Shift to the *right* of the oxyHb dissociation curve	The "S" shape of oxyHb dissociation curve	The increase of the tissue O_2 release

2. MANIFESTATIONS - depend on the **severity of hypoxemia**:

a. **Cardio-vascular manifestations –** *due to the stimulation of the "alarm" sympatho-adrenergic system*
   - Early phase: tachycardia, hypertension, diaphoresis (cold and moist skin)
   - Late phase: bradycardia

b. **CNS manifestations –** *behavioral manifestations due to the damage of the most vulnerable tissue to hypoxia*:
   - Early phase: agitation/anxiety, confusion, delirium
   - Late phase: extreme agitation further replaced by obnubilation, stupor, coma

3. CYANOSIS

- **Definition: bluish coloration** of the **teguments and mucous membranes** induced by the **increased concentration of the reduced Hb > 5 g/dL** in the **capillary blood.**
- **General features:**
  - corresponds to a **SpO_2 < 90%** in the patient with *normal erythrocyte count*
  - depends on the **absolute value of reduced Hb** (g/dL):
    - *in **severe anemias*** – the cyanosis is **absent** even in the **presence of hypoxemia** (at a low level of total Hb, the value of 5 g/dL for reduced Hb cannot be achieved)

  - *in **polycythemias*** – the cyanosis can **occur** even in the **absence of hypoxemia** (at a high level of total Hb concentration, the value of 5 g/dL for reduced Hb can be easily achieved)
- is *favored* by the presence of **pathological hemoglobins** (e.g., methemoglobin)

- **Classification:**
  a) CENTRAL or ARTERIAL type cyanosis
  b) PERIPHERAL or VENOUS type cyanosis
  c) MIXED cyanosis

a) CENTRAL or ARTERIAL cyanosis

- **Definition:** the type of cyanosis induced by the **decrease of $SatO_2$% in the arterial blood** as a result of the decreased PaO_2
- **Etiopathogenesis** – severe decrease of blood oxygenation - **hypoxemia** (+ hypercapnia)
  - Severe chronic pulmonary disorders – e.g., COPD type B
  - Congenital cardiopathies with right-to-left shunt – e.g., Fallot tetralogy
- **General features:**
  - more evident at the level of *nose*, *lips* and *oral mucosa*
  - *warm,* due to cutaneous vasodilatation induced by *hypercapnia*
  - *ameliorated* by O_2 administration in chronic pulmonary disorders (but not completely in the presence of cardiac right-left shunts)
  - *accentuated by exercise* due to increased O_2 extraction at muscular level
  - associated with *clubbing fingers*

b) PERIPHERAL or VENOUS cyanosis

- **Definition:** type of cyanosis induced by the **decrease of $SatO_2$% from the venous blood** as a result of the increased O_2 extraction at tissue level (SaO_2% of arterial blood is normal)
- **Etiopathogenesis:**
  ① **Increased extraction of O_2 at tissue level by accentuated peripheral vasoconstriction** with **localized** cyanosis in:
    - Prolonged exposure to cold (hypothermia)
    - Peripheral arterial disease
  ② **Decreased tissue perfusion** by **marked decrease in cardiac output** with **generalized** cyanosis in:
    - Severe heart failure
    - Circulatory shock (exception, septic shock)
- **General features:**
  - more obvious at the *extremities (nail beds) at cold,* due to the decreased cutaneous blood flow
  - *persistent* after O_2 administration

c) MIXED cyanosis

- **Definition:** the association between the **decrease of $SatO_2$% in both arterial and venous blood**
- **Etiopathogenesis:**

① **Decreased *blood oxygenation at pulmonary level*** in **COPD**
② **Increased *O_2 tissue extraction*** **in right HF** due to:
- decreased cardiac output
- venous stasis (peripheral cardiac edema)

B. HYPERCAPNIA (HYPERCARBIA)

DEFINITION: increased **$PaCO_2$ > 45 mmHg**

ETIOLOGY – all causes of **global alveolar hypoventilation:**
- **CENTRAL causes** (which interfere with the regulation of respiration):
  – *inhibition of the respiratory centers* – drugs/medication, CNS tumors/traumatisms
- **PERIPHERAL causes:**
  – *thoracic cage malformations* – kyphosis, scoliosis, injuries(e.g., the crush syndrome)
  – *disorders of the nerves supplying the respiratory muscles* – spinal cord damage
  – *disorders of the respiratory muscles* – miastenia gravis, muscular dystrophies
  – *pulmonary diseases:*
    i) chronic - most commonly, **COPD type B is consistently associated with type II RF**
    ii) acute - SEVERE asthma attack, massive pneumothorax

CONSEQUENCES OF HYPERCAPNIA:

1. RESPIRATORY ACIDOSIS – increased $PaCO_2$, normal/increased HCO_3^-, low/normal pH

2. NEUROLOGICAL effects: decrease of the neuronal activity with **sedative, anesthetic and narcotic effect** proportional to the **severity of hypercapnia:**
- at $PaCO_2$ > 70 mmHg – disorientation, somnolence
- at $PaCO_2$ > 85 mmHg – narcosis, coma

3. VASODILATION:
- **cerebral** with headache, drowsiness, confusion, increased intracranial pressure and risk of papilledema
- **hyperemia** of the **skin and mucous membranes**

4. RESPIRATORY effects – variable:
① **According to the SEVERITY of hypercapnia:**
- when $PaCO_2$ = 60 – 70 mmHg – *dyspnea and tachypnea* due to the stimulation of the *central* chemoreceptors
- when $PaCO_2$ > 70 mmHg – *bradypnea* due to the depression of the respiratory centers; in this case ventilation is controlled by hypoxemia which stimulates the *peripheral* chemoreceptors.

② **According to the ONSET of hypercapnia:**
- **In ACUTE hypercapnia:**
  - stimulation of ventilation is *directly proportional* to **hypercapnia** (the $PaCO_2$ value) detected by the *central chemoreceptors* (since CO_2 crosses the blood-brain barrier)

- **In CHRONIC hypercapnia:**
  - stimulation of ventilation is *directly proportional* to **hypoxemia** (the PaO_2 value), detected by the **peripheral chemoreceptors**, which will take over the task of stimulating ventilation (since the central chemoreceptors undergo a *"reset"* at high $PaCO_2$ values)
  - O_2 administration in patients with **chronic hypercapnia** will correct the hypoxemia and thus, may abolish its stimulatory effect on ventilation, inducing **severe bradypnea** and **aggravation of hypercapnia**. Therefore, in order to correct *hypoxemia* in patients with *hypoxemia and chronic hypercapnia*, **O_2** is administered to achieve an **SpO_2 between 88-92% (not between 94-98%).**

THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

DEFINITION: ARDS (Acute Respiratory Distress Syndrome) or "*the shock lung*" is a **fulminant form** of **acute RF** induced by a **severe acute pulmonary inflammation** responsible for:
- **diffuse damage of the alveolar-capillary membrane**
- **acute non-cardiogenic pulmonary edema**

ETIOLOGY
- **DIRECT lesions of the alveolar epithelium:**
  - ***COVID-19***
  - ***severe pulmonary infections: pneumonia***
  - ***aspiration of acidic gastric content in the airways,*** *e.g., in comatous patients*
  - water aspiration in the airways (drowning)
  - inhalation of toxic gasses (smoke, ammonia) or drugs (cocaine)
  - thoracic polytrauma (lung contusions)
- **INDIRECT pulmonary lesions:**
  - ***septicemia***
  - ***polytrauma with shock***
  - ***prolonged cardiopulmonary by-pass***
  - severe burns
  - acute pancreatitis
  - DIC (disseminated intravascular coagulation)
  - medication (barbiturates) or drug (heroin) overdose

PATHOGENESIS – the condition progresses in **3 stages:**

1. The EXUDATIVE stage
- **Characteristics:**
  a) Begins in the **first 1-3 days after the injury**
  b) The hallmark is the presence of **acute inflammatory reaction** with:
  - **Vascular changes** - responsible for the formation of **inflammatory exudate** via the:
    - *release of* ***primary (preformed) cell-derived mediators****:* histamine, lysosomal enzymes

- *synthesis of* ***secondary (newly formed) cell-derived mediators****:* metabolites of arachidonic acid, pro-inflammatory cytokines (TNF-α, IL-1, IL-6)
- *activation of* ***plasma-derived mediators****:* the complement system, kinins, the coagulation cascade with the formation of intravascular thrombi
- *increased microcirculation capillary membrane permeability* with:
  - ***interstitial edema*** - inflammatory exudate
  - ***alveolar edema*** - *hemorrhagic* inflammatory exudate, rich in platelets and fibrin, which *inactivates the surfactant*

– **Cellular changes** - responsible for the formation of the **cellular infiltrate**, mainly composed of **NEUTROPHILS** as dominant cells

– **DIFFUSE injury to type I alveolocytes** with:
- *denudation of the alveolar epithelium* and *accumulation of intra-alveolar cellular debris*

- **Consequences:**
  a) **NON-CARDIOGENIC acute pulmonary edema**
  – alveolar edema decreases *pulmonary compliance and causes alveolar hypoventilation*
  – *alveolar hypoventilation in the affected areas* results in hypoxemia
  – *hypoxemia in affected areas* induces *reflex alveolar hyperventilation in unaffected areas*
  b) **Partial, HYPOXEMIC or type I respiratory failure is <u>triggered</u>** by: the ***decrease in alveolar-capillary diffusion***

2. The PROLIFERATIVE stage
- **Characteristics:**
  a) Begins **1-2 weeks after the lung injury**
  b) **Type II alveolocyte damage** causes a **decrease in surfactant production**, and the hemorrhagic alveolar exudate contributes to *surfactant inactivation*. Decreased production and inactivation of surfactant results in **alveolar collapse** with the appearance of **areas of atelectasis $\Rightarrow$ intrapulmonary arterio-venous shunts**
  c) **Excessive alveolar fluid** causes **alveolar hypoventilation** in affected areas, with ***hypoxemia*** causing reflex alveolar hyperventilation in unaffected areas $\Rightarrow$ **coexistence of hypoventilated areas with compensatory normo- or hyperventilated areas**
- **Consequences:**
  a) **Formation of HYALINE MEMBRANES within the alveoli**, composed of desquamated alveolocytes, fibrin and proteins from the inflammatory exudate
  b) **Partial, HYPOXEMIC or type I respiratory failure is <u>exacerbated</u>** by the: **appearance of *arterio-venous shunts*** and the ***alteration of the ventilation/perfusion ratio***

3) The FIBROTIC stage
- **Characteristics:**
  a) Becomes evident **after 3-4 weeks from the occurrence of the lung injury**
  b) **The activation/proliferation of fibroblasts at the interstitial level** and **their migration at the level of alveolar hyaline membranes**

c) **The appearance of myofibroblasts** with increased **collagen production and extracellular matrix deposition** is responsible for:
   - progressive interstitial and alveolar fibrosis with decreased lung compliance (stiff lungs) with global alveolar hypoventilation
   - vascular obstruction/remodeling with increased pulmonary vascular resistance

- **Consequences:**
  - **in severe cases, global, HYPERCAPNIC type II respiratory failure**
  - **pulmonary hypertension and cor pulmonale**

5. PATHOPHYSIOLOGY OF ARTERIAL HYPERTENSION

BLOOD PRESSURE – BRIEF PHYSIOLOGY OVERVIEW

DEFINITION

Blood pressure (BP) or *arterial pressure* (AP) is **the force generated by the pulsatile blood flow on the arterial walls**, being responsible for *normal tissue perfusion.*

- **SISTOLIC Blood Pressure** (SBP):
  - represents the maximal value of BP reached during *ventricular systole*
  - depends on **systolic volume** *(directly proportional)* and the **elasticity of the aorta** *(inversely proportional)*
  - increases progressively with *age* due to decreased arterial elasticity (this is why **isolated SBP** is common in the **elderly**)
- **DIASTOLIC Blood Pressure** (DBP):
  - is the minimal value of BP, corresponding to *ventricular diastole*
  - depends on **peripheral vascular resistance** *(directly proportional)*

MAJOR DETERMINANTS

The major determinants of BP are *cardiac output* (CO) and *peripheral vascular resistance* (PVR) according to the formula: **BP = CO x PVR**

1. CARDIAC OUTPUT

- **Definition** – blood volume ejected by a ventricle within *a minute*
- **Determinant factors** – CO varies *directly proportional* with the **product** between **systolic volume** (SV) and **heart rate** (HR):
  - *systolic volume* – varies directly proportional with *cardiac contractility (inotropism)* and the *preload (venous return)* and inversely proportional with the *afterload (peripheral vascular resistance)*
  - *heart rate* – depends on *cardiac autonomic innervation* (sympathetic stimulation increases the HR, parasympathetic/vagal stimulation decreases the HR) and on *catecholamines secretion*

2. PERIPHERAL VASCULAR RESISTANCE

- **Definition** – the force that *opposes the blood flow in the vascular system*
- **Determinant factors** – PVR varies *directly proportional* to **viscosity of the blood** (η) and **vessel length** (L) and *inversely proportional* to **vessel radius to the fourth power** (r^4)

The vascular area with the largest vascular flow resistance is represented by the **arterioles**. As a result, PVR depends on **arteriolar smooth muscle tone**, and this can be controlled by:

a) Autoregulatory mechanism
b) Nervous mechanisms
c) Hormonal mechanisms

a) VASCULAR TONE regulation through AUTOREGULATORY mechanisms

- **Role** – to adapt tissue perfusion to the *local metabolic needs* in conditions of *variations of the mean arterial pressure* between **60 and 180 mmHg**
- **Mechanisms:**
  ① **metabolic** – *decreased* tissue perfusion (tissue hypoxia) causes the **release of local vasodilating metabolites** (eg., lactate, adenosine, K^+) with consecutive decrease of local resistance and restoration of the normal tissue perfusion
  ② **endothelial** – *decreased* tissue perfusion (tissue hypoxia) causes the **release of local vasodilating mediators** (nitric oxide/NO and prostacyclin/PGI_2) with consecutive decrease of local resistance and restoration of the normal tissue perfusion

③ **myogenic –** *increased* tissue perfusion ***directly*** causes (via mechanically activated Ca^{2+} channels) **vascular smooth muscle contraction** with consecutive increase of the local resistance and restoration of the normal tissue perfusion

b) VASCULAR TONE regulation through <u>NERVOUS</u> mechanisms

- **Role** – control vascular tone through **2 components:**
  - **sympathetic** – vasoconstrictor effect via α_1-adrenergic receptor stimulation
  - **parasympathetic** – vasodilating effect via stimulation of endothelial NO release

c) VASCULAR TONE regulation through <u>HORMONAL</u> (humoral) mechanisms

- **Role** – control vascular tone via the release of **2 types of factors:**
  - **vasoconstrictors –** *systemic* (eg., angiotensin II, catecholamines) and *local* (eg., ET-1, TxA_2, type F prostaglandins, serotonin)
  - **vasodilatators –** *systemic* (eg., natriuretic peptides) and *local* (eg., NO, PGI_2, type E prostaglandins, kinins)

Observation:
Endothelial dysfunction, defined as the predominant release of *vasoconstricting factors* contributes to arterial hypertension (HT) worsening and "target" organ damage (complicated HT), but it is difficult to say whether this is the cause or the consequence of HT.

MECHANISMS of BLOOD PRESSURE REGULATION and their CONTRIBUTION to HT

BP regulation is performed by **3 types of mechanisms: neural, hormonal (humoral) and renal** (which become impaired, in different degress, in the presence of HT), as follows:

- **short/medium term regulation of BP** (minutes, hours, days) is based on the ***neural*** and ***hormonal*** *(humoral)* ***mechanisms***
- **medium/long term regulation of BP** (days, weeks, months) is based on the ***hormonal****, and especially, on the* ***renal mechanisms***

A. <u>NEURAL</u> mechanisms of BP regulation

Neural mechanisms of BP regulation are based on **baroreceptors** and **chemoreceptors** activity at the level of the *carotid sinus* and *aortic arch* and include activation of **depressor** and **pressor reflexes.**

a) Sino-carotidian and aortic BARORECEPTOR reflexes

- **Characteristic** – they are *depressor reflexes* triggered by *increased BP*
- **DEPRESSOR reflex description:**
  - the *increased discharge rate of arterial baroreceptors* **inhibits** the pressor area (sympathetic) and **stimulates** the depressor area (parasympathetic) from the medulla oblongata
  - the *decrease of the sympathetic-adrenergic tone* will **reduce the cardiac output** (by decreasing HR and contractility) and will **decrease the PVR** (by vasodilation)

- **Role:**
  - involved in the **rapid and short term regulation** of BP (eg., *transition from supine to standing position, exercise, acute hemorrhage*)
  - are **ineffective in preventing the onset of chronic hypertension** due to the baroreceptor **„resetting"** phenomenon at high values of BP (the phenomenon starts after 24-48 hours from the onset of BP increase)

b) Sino-carotidian and aortic CHEMORECEPTOR reflexes

- **Characteristic** – are *pressor* reflexes activated by *hypoxemia* (↓ PaO_2), *hypercapnia* (↑ $PaCO_2$) and *acidosis* (↓ pH)
- **PRESSOR reflex description:**
  - *the increased discharge rate of arterial chemoreceptors* **stimulates** the pressor area (sympathetic) and **inhibits** the depressor area (parasympathetic) from the medulla oblongata
  - *the increase of the sympathetic-adrenergic tone* will **increase the cardiac output** (by increasing HR and contractility) and will **increase the PVR** (by vasoconstriction)
- **Role:**
  - mainly involved in **regulation of the pulmonary ventilation**
  - may **exacerbate a preexisting HT**, e.g.: *systemic hypertension* in patients with *obstructive sleep apnea* and *pulmonary hypertension* in patients with *COPD*

B. <u>HORMONAL (HUMORAL)</u> mechanisms of BP regulation

The hormonal (humoral) mechanisms of BP regulation include:

a) ***Renin-angiotensin-aldosterone system*** with systemic and local effects
b) ***Natriuretic peptides*** – are responsible for countering the effects of the RAA system
c) ***Catecholamines*** released from the adrenal medulla – potentiate the pressor effect of the sympathetic nervous system
d) ***Antidiuretic hormone*** **(ADH)** – potentiates the pressor mechanism of the RAA system by water retention and a vasoconstrictor effect limited to the splanchnic circulation

a) RENIN-ANGIOTENSIN-ALDOSTERONE (RAA) system (RAAS)

- **Clasification – 2 RAA systems** are involved in the regulation of BP:

  ① The CLASSIC RAAS:
  - it is the main system responsible for BP increase by ***vasoconstriction*** *and* ***hydro-saline retention***

  ② The LOCAL RAAS - independent of the classic one
  - are described in the *vasculature, heart, brain, adipose tissue*
  - are responsible for *tissue angiotensin II* generation, considered ***maladaptive*** because it contributes to the ***cardiovascular remodeling*** and ***progression of HT,*** respectively

- **Phases of RAA SYSTEM ACTIVATION:**

  I. Synthesis of angiotensin I (AI)
  - under the action of *renin* released from the renal juxtaglomerular apparatus (but also locally), angiotensinogen (hepatic α_2-globulin) is converted to **angiotensin I (inactive)**

  II. Synthesis of angiotensin II (AII)

- under the action of *angiotensin converting enzyme (ACE)*, with a maximum effect in the *pulmonary capillary endothelium*, angiotensin I is converted into **angiotensin II**, responsible for the **ADVERSE** effects of RAAS activation: ***vasoconstrictor, anti-natriuretic, pro-fibrotic and pro-inflammatory***

III. Synthesis of angiotensin III and angiotensin (1-7)

- angiotensin II is metabolized under the action of 2 enzymes:
  - ✓ *aminopeptidase A* with formation of **angiotensin III (AIII)**
  - ✓ *angiotensin-converting enzyme-2 (ACE-2)* with formation of **angiotensin (1-7)**
- AIII and the Ang (1-7) heptapeptide are the components of the so-called **"protective arm" of the RAA system**, being responsible for the **FAVORABLE** effects of the RAAS: ***vasodilating, natriuretic, anti-fibrotic and anti-inflammatory***

- **Stimulation of RENIN release** – is controlled by **3 mechanisms:**
  - **baroreceptor** – triggered by the *decrease of the renal perfusion pressure*
  - **chemoreceptor** – triggered by the *decrease of the Na^+ concentration at the level of the macula densa*
  - **nervous** – triggered by the *increase of local sympathetic stimulation* and the *high level of blood catecholamines* (that act on the β_1-adrenergic receptors from the renal juxtaglomerular apparatus)
- **ANGIOTENSIN II receptors** – there are **2 types of receptors** expressed mainly at the **vascular, renal and cardiac** level, but also at the level of the adrenal cortex, the brain and the peripheral sympathetic nervous system:
  - **AT_1 receptors** – mediate the **adverse effects** of **AII**
  - **AT_2 receptors** – mediate the **positive effects** of **AII** via **AIII**
- **<u>SYSTEMIC</u> effects of ANGIOTENSIN II** – **<u>short</u>-term** increase of BP through:
  - **systemic arterioloconstriction** – mediated by **2 mechanisms***:*
    - ✓ *direct* – by PVR increase
    - ✓ *indirect* – by stimulation of the release of noradrenaline (norepinephrine) from the peripheral sympathetic nervous system
  - **retention of salt and water** – by **2 mechanisms**:
    - ✓ *direct* – by increasing Na^+ reabsorbtion from the *proximal convoluted tubule (PCT)*
    - ✓ *indirect* – by releasing aldosterone (ALDO) from the adrenal cortex and, subsequent increase in Na^+ and water reabsorption at the level of the *distal convoluted tubule (DCT) and collecting duct (CD)*
  - **increase of ADH release**
  - **increase of the thirst sensation**
- **<u>LOCAL</u> effects of ANGIOTENSIN II** – **<u>long</u>-term** increase of BP through:
  - **proliferative and profibrotic effect** - AII exerts a *mitogenic and trophic* effects on *vessels* and *heart*, being responsible for *cardio-vascular remodeling* characterized by:
    - ✓ proliferation of vascular smooth muscle cells
    - ✓ proliferation of fibroblasts with collagen synthesis/deposition
    - ✓ cardiomyocyte hypertrophy

– **proinflammatory effect** – exacerbation of endothelial dysfunction by increasing the *expression of adhesion molecules* at the level of endothelial cells
– **damage of** the so-called **target organs of HT**

Observations:
Currently, the pharmacological therapy of HT ensures the control of BP values and the reduction of cardiovascular events by combating the unfavorable effects of the activation of neuro-humoral mechanisms, in the case of RAA system activation, using 2 main drug classes: angiotensin-converting enzyme inhibitors (ACEI) and AT-1 receptor blockers (ARB). ACEI are the drugs with the suffix "il" (captopril, enalapril, perindopril, ramipril, lisinopril, fosinopril, trandolapril). ARBs are drugs with the suffix "sartan" (candesartan, losartan, valsartan, irbesartan, telmisartan).
The use of ACE inhibitors has a dual benefit:
i) *reducing the action of AII* (preventing its formation) and
ii) *reducing the breakdown of bradykinin* (BK) (since ACE, also called kininase II, is the enzyme that breaks down BK into inactive peptides.
Increased plasma bradykinin has numerous beneficial effects: vasodilation, stimulation of diuresis, inhibition of platelet adhesion and aggregation, anti-fibrotic effect and prevention of remodeling, but it also increases the risk of side effects: dry cough and angioedema, especially in atopic individuals).
The use of ARBs favors the *metabolism of AII through the "protective arm" pathway of the RAAS* and is associated with a lower rate of angioedema and chronic irritative cough.
The other 3 drug classes used (often in combination with one of the antagonists of the RAAS) in antihypertensive treatment are: beta-blockers, calcium channel blockers and diuretics (thiazide/thiazide-like, potassium-sparing and loop diuretics).

b) NATRIURETIC peptides

- **Definition** – major hormonal (humoral) factors responsible for **countering the effects of the chronic RAAS activation**
- **Classification:**
  – **ATRIAL natriuretic peptide** *(*ANP) – is secreted by the *atrial cardiomyocytes* when the atrial filling pressure increases and causes the decrease of BP by: *increased natriuresis* and *diuresis*, *vasodilation* and *inhibition of ADH release*
  – **BRAIN natriuretic peptide** (BNP) – was originally isolated from the brain of experimental animals, but in humans is secreted by the *ventricular cardiomyocytes* in conditions of heart failure; it reduces BP by: *increased natriuresis* and *diuresis.* Currently is used as *diagnosis and therapeutic marker of heart failure*.
  – **C-type natriuretic peptide** – is released from the *vascular endothelium* and decreases BP by *vasodilation*

C. <u>RENAL</u> mechanisms of BP regulation

The kidney is involved in the **long-term regulation of BP** by *extracellular fluid volume control*, because if the intake of salt and water remains constant, *the renal excretion of Na^+ and H_2O* is strictly dependent on the mean arterial pressure as follows:

– **at a mean arterial pressure ~ 100 mmHg** – the renal excretion of Na^+ and H_2O balances the intake of salt and water and *urinary output* is normal
– **at a mean arterial pressure > 100 mmHg** – the renal excretion of Na^+ and water increases several times to bring the mean arterial pressure back at the normal value of the *equilibrium point* (of ~ 100 mmHg) – Fig. 5.1

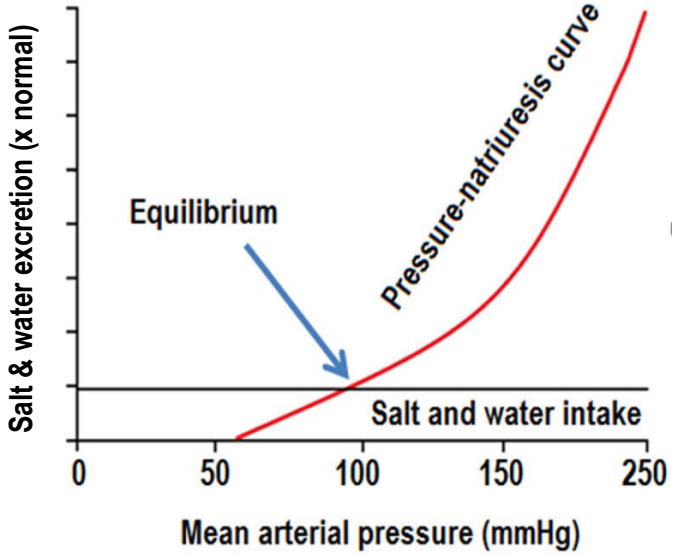

Figure 5.1. Role of the kidney in BP regulation.

ARTERIAL HYPERTENSION (HT)

DEFINITION: persistent increase **of systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg** (values that also represent the targets of antihypertensive therapy).

EPIDEMIOLOGY

- HT is **the most common disease in the world** – over one billion hypertensive patients (> 75% of the elderly population), many of them *asymptomatic* for a long time
- prevalence of HT increases with *age* and is more *common in the black population*
- under the age of 50, the prevalence is higher in men, but after the age of onset of menopause in women, the ratio reverses
- HT is both a **disease** and the **most important risk factor** for: *atherosclerosis and coronary artery disease, stroke, heart failure, peripheral artery disease* and *chronic kidney disease*

Observation: Blood pressure screening is a priority in cardiovascular prevention.

CLASSIFICATION

a) <u>ETIOPATHOGENIC</u> classification:

- *primary (essential) HT* (95% of cases) with unknown etiology
- *secondary HT* (5% of cases) with known etiology

b) Classification <u>ACCORDING TO BP VALUES</u> – Table 5.1.

Table 5.1. Classification of office BP values and HT grades (adapted from The *2023 European Society for Hypertension Guidelines for the Management of Arterial Hypertension)*.

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal BP	< 120	*and*	< 80
Normal BP	120-129	*and*	80-84
High normal BP	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**
Isolated diastolic hypertension	**< 140**	***and***	**≥ 90**

The BP category is defined by the highest level of BP, whether systolic or diastolic.
Isolated systolic or diastolic hypertension is graded 1, 2 or 3 according to SBP and DBP values in the ranges indicated.

PATHOPHYSIOLOGY:

1. <u>VOLUME</u> hypertension

- **Characteristic** – occurs mainly in *young people* and is *the initial, labile phase* of HT
- **Pathomechanism** – **increased CO** with normal PVR
- **Causes: increased venous return to the heart** through:
  - *increased venous tone* by sympathetic-adrenergic stimulation (vascular α1-adrenergic receptors) and excessive RAA system activation
  - *increased volemia* by excessive intake of Na^+ and water and/or renal retention of Na^+ and water with alteration of the *pressure-natriuresis relation*

2. <u>RESISTANCE</u> hypertension

- **Characteristic** – occurs mainly in the *elderly* and is the *sustained*, *stable phase of HT* evolving towards *the complicated HT* with *hypertension-mediated organ damage (HMOD)*
- **Pathomechanism** – i**ncreased PVR** with normal/decreased CO
- **Causes:**
  - **functional vasoconstriction** with *reversible* increase of PVR due to:
    - ✓ excessive sympatho-adrenergic stimulation
    - ✓ excessive activation of the RAA system
    - ✓ genetic defects of Na^+ and Ca^{2+} transporters in the cell membrane
  - **structural vascular hypertrophy** with *irreversible* increase of PVR due to:
    - ✓ increased collagen and stiffening of the arterial walls
    - ✓ insulin-resistance with compensatory hyperinsulinemia (insulin has a proliferative effect on the vascular smooth muscle cells)

Observation:
Resistance HT causes the **worsening** of a **volume HT** by the maladaptive perpetuation of a physiological mechanism: the increase in tissue perfusion as a result of the increase in CO, will cause an increase in PVR through the *myogenic mechanism* to *protect the capillaries from hyperperfusion.*

ETIOPATHOGENIC FORMS

I. PRIMARY (ESSENTIAL, idiopathic) hypertension

DEFINITION: HT of unknown cause (idiopathic)

ETIOLOGY – multifactorial, depends on a complex interaction between *genetic factors* (non-modifiable), *environmental* and *lifestyle-related risk factors* (modifiable) and the *ageing process*

1. GENETIC factors (non-modifiable) - represented by:

- **hereditary predisposition** – increased prevalence in subjects with a family history of HT and in monozygotic twins
- **polygenic character** – more than 1000 gene mutations associated with elevated BP levels, which individually contribute only in small proportions (by approx. 0.5-1 mmHg) but in combination, they can determine 60% of a person's BP level. Genes are permissive, environmental factors being required for the occurrence of HT as disease.

2. LIFESTYLE & ENVIRONMENTAL risk factors (modifiable) - represented by:

- obesity and metabolic syndrome
- insulin resistance and hyperinsulinemia
- type 2 diabetes mellitus (T2DM)
- hypercholesterolemia
- sedentary life-style
- chronic psychological stress
- obstructive sleep apnea syndrome (OSAS)
- increased salt consumption
- alcohol in high doses
- air pollution and noise

3. AGE & GENDER: increased prevalence in M $<$ 55 years and in F $>$ 55 years.

PATHOPHYSIOLOGY

Primary HT is due to the alteration of the **main BP regulatory mechanisms:**

1. Alteration of the NEURAL MECHANISMS:

- **Characteristic** – the *increased sympathetic-adrenergic stimulation* is responsible for peripheral sympathetic hyperactivity with release of catecholamines from adrenergic nerve endings and the adrenal medulla
- **Pathogenesis:**

  Causes:
  - genetic factors (hereditary predisposition)
  - chronic psychological stress (personality, profession)
  - obstructive sleep apnea syndrome (activation of arterial chemoreceptors by repeated episodes of hypoxemia/hypercapnia causes the increased sympathetic tone and HT)

  Effects:
  - **cardiac** – increased CO due to *positive inotropic* and *chronotropic effect*s mediated by the stimulation of β_1-adrenergic cardiac receptors

– **vascular** – increased PVR due to *arterioloconstriction* and increased CO through *increased venous tone, venous return and preload* mediated by to stimulation of α_1 - adrenergic vascular receptors
– **renal** – activation of renin release mediated by the stimulation of β_1-adrenergic receptors from the renal juxtaglomerular apparatus

Clinical forms of HT associated with excessive sympathetic stimulation*:*
– HT in the *young adult*
– HT in *obese patients with obstructive sleep apneea*
– HT in the *early stages of diabetes*
– HT in patients with *chronic kidney disease (CKD)*
– HT in patients with *compensated heart failure*

2. Alteration of the <u>HORMONAL (HUMORAL)</u> MECHANISMS

- **Characteristics:**
  – are represented by *the excessive activation of the RAA system* and hemodynamic changes associated with *abdominal obesity/metabolic syndrome* and *insulin-resistance & compensatory hyperinsulinism*
  – are responsible for the *development, stabilization* (chronic hypertension) and *progression of hypertension* (complicated HT with hypertension-mediated organ damage)
- **Pathogenesis:**
  ① **Excessive activation of the RAAS** is responsible for the deleterious effects of increased angiotensin II and ALDO (see above)
  ② **Abdominal obesity** and **metabolic syndrome** contribute to HT development by **3 mechanisms:**
    – *hypersecretion of leptin by adipocytes* – causes hemodynamic changes by increasing central sympathetic stimulation and activation of the RAAS
    – *secretion of angiotensinogen by adipocytes* – provides the substrate for RAAS activation
    – *synthesis of a fibrinogen precursor in adipocytes* – increases blood viscosity

Abdominal obesity – defined by increased waist circumference ≥ 94 cm in men and ≥ 80 cm in women in Europe (≥ 102 cm in men and ≥ 88 cm in women, in USA).

Metabolic syndrome – is defined by the presence of **abdominal obesity,** as mandatory criterion, plus **minimum 2 of the following criteria**:
– increased TG ≥ 150 mg/dL or treatment for hypertriglyceridemia
– decreased HDL-cholesterol < 40 mg/dL in males and < 50 mg/dL in females
– increased SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg *or* diagnosed HT
– fasting glycemia ≥ 110 mg/dL *or* impaired glucose tolerance *or* diagnosed diabetes

③ **Insulin-resistance** & **hyperinsulinemia** – is defined as the decrease of peripheral tissues' response to insulin leading to compensatory hyperinsulinemia; they contribute to primary HT progression by aggravation of endothelial dysfunction and atherosclerosis due to the **direct effects of insulin**:
  – stimulation of vascular smooth muscle cells (VSMCs) proliferation, i.e.*mitogenic* effect

- increased sympathetic activation
- potentiation of the effects of vascular remodeling induced by angiotensin II
- decreased endothelial NO production
- proinflammatory and prothrombotic effect

3. Alteration of the RENAL MECHANISMS

- **Characteristic** – in essential HT there is a *genetic and/or acquired inability* of the kidney to remove the excess of Na^+ and water, so that the same amount of salt is eliminated at higher BP values and over a longer period of time
- **Pathogenesis:**
  Sodium retention in the body leads at the:
  - **extracellular level** to increased volemia, preload and CO
  - **intracellular level** to the accumulation of Na^+ in the vascular walls with the following consequences at**:**
    - ✓ *vascular intima* – aggravation of endothelial dysfunction
    - ✓ *vascular media* – increased vascular smooth muscle cells tone and reactivity to the action of catecholamines and AII
    - ✓ *baroreceptor areas* – arterial stiffness and decreased baroreceptors sensitivity

Observations:
There is extensive experimental and clinical evidence that primary HT is also associated with inflammation and dysregulated immune response, hence the term **immunoinflammation** being involved in the disease pathogenesis. Although it cannot be postulated that these processes are causatively linked to HT or are secondary effects of chronic HT, they are both largely driven by oxidative stress, the excessive production of reactive oxygen species (ROS) with altered redox state.
More recently, pressogenic effects of gut microbial dysbiosis have also been reported.
From therapeutical point of view, the multimechanistic and interactive pathophysiology explains why a combination of drugs with different mechanisms are currently prescribed to lower BP.

II. SECONDARY hypertension

DEFINITION: HT due to specific causes

ETIOLOGY:

a) HT secondary to **RENAL** DISEASES
b) HT secondary to **ENDOCRINE** DISEASES
c) HT seconary to **OSA syndrome**
d) HT due to **MECHANICAL** causes: COARCTATION OF AORTA

a) HT secondary to RENAL DISEASES

1. RENAL PARENCHIMAL HT

- **Definition** – HT due to the **decrease of the renal parenchyma** and of **glomerular filtration,** being associated with **chronic kidney disease (CKD)** regardless of its etiology. It is the **most common cause of secondary hypertension in adults**.
- **Etiology**: CKD is the final stage of all chronic kidney diseases:
  - **diabetic nephropathy – the main etiology**

- chronic glomerulonephritis and pyelonephritis
- nephropathies from collagenoses (SLE, scleroderma, rheumatoid arthritis)
- polycystic kidney
- obstructive uropathy (late in evolution, when glomerular sclerosis and renal atrophy occur)

- **Pathogenesis:**
  - **main mechanism** – responsible for the *increased CO (volume HT),* is:
    - ✓ decrease in the mass of functional nephrons responsible for the *impairment of Na^+ and water excretion*, with hydro-saline retention, increased plasmatic volume and preload
  - **secondary mechanisms** – responsible for the *increased PVR (resistance HT), with the stabilization and exacerbation of HT,* are:
    - ✓ *increased RAA system activation* (**increased plasmatic renin and ALDO levels**) due to *nephroangiosclerosis* and the *progressive decrease of glomerular filtration* (increased serum creatinine)
    - ✓ *increased activation of the sympathetic nervous system*
    - ✓ *endothelial dysfunction* with a decrease in NO (vasodilator) and an increase in endothelin (vasoconstrictor), aggravated by the decrease in the synthesis of vasodilator substances (PG and kinins) through the reduction of the renal parenchyma

    The latter two mechanisms are common in patients with end-stage CKD, i.e., chronic renal failure with uremia.

2. RENAL VASCULAR HT

- **Definition** – HT caused by **unilateral** (rarely, bilateral) **stenosis of the renal artery**
- **Etiology:**
  - *atherosclerosis* ($^2/_3$ of cases) – predominantly in the *elderly* (with comorbidities: peripheral artery disease, diabetes)
  - *fibromuscular dysplasia* ($^1/_3$ of cases) – predominantly in *young and middle-aged women*
- **Pathogenesis** – **activation of the RAA system** with **increased plasma renin and ALDO** due to *decreased renal perfusion*
- **Differential diagnosis** – with other common causes of **secondary hyper-ALDO**:

– patients with chronic kidney disease – activation of RAAS duet to decreased renal perfusion
– women with increased consumption of estrogenic contraceptives – increased AII synthesis
– patients with chronic liver disease – decreased AII degradation in liver

b) HT secondary to <u>ENDOCRINE</u> DISEASES

1. HT due to PRIMARY HYPERALDOSTERONISM

- **Definition** – HT caused by **excessive ALDOSTERONE secretion**
- **Etiology** – *unilateral tumor (adenoma) of the adrenal cortex (Conn syndrome)* or *bilateral glandular hyperplasia*
- **Pathogenesis – primary hypersecretion of ALDO** with **<u>increased plasma ALDO</u>** and **<u>decreased</u>** plasma renin, which causes HT via hydro-saline retention (volume hypertension); the increased volemia (and renal perfusion) suppresses the release of renin.

- **Manifestations**:
  - **TRIAD: HT, hypokalemia** (< 3.5 mmol/l), and **metabolic alkalosis** (in the absence of other causes of hypokalemia: diarrhea, diuretic treatment etc.)
  - hyperkaliuria and increased urinary elimination of ALDO may be present

2. HT due to PHEOCHROMOCYTOMA

- **Definition** – HT caused by **excessive CATECHOLAMINES secretion**
- **Etiology** – *tumor of the chromaffin tissue* within the *adrenal medulla (85% of cases)* called *pheochromocytoma* or *tumors of the abdominal sympathetic ganglions* called *paragangliomas (15% of cases)* with variable location (neck, chest, pelvis, bladder)
- **Pathogenesis** – **primary hypersecretion of CATECHOLAMINES**: norepinephrine (NE), epinephrine (E) and their metabolites. HT is the consequence of **increased sympathetic stimulation** which has the following effects:
  i) *cardiovascular*, mediated by cardiac β1-adrenergic receptors, predominantly stimulated by E – with tachycardia, increased CO and predominantly systolic HT (when E secretion dominates) and by vascular α-adrenergic receptors, predominantly stimulated by NE – with vasoconstriction and systolic-diastolic HT (when NE secretion dominates)
  ii) *metabolic* - with an increase in basal metabolism, blood sugar and free fatty acids (in the absence of hyperthyroidism)
- **Manifestations**:
  - ***paroxysmal* HT** - very high blood pressure values (e.g., 260/130 mmHg) during crises associated with the **TRIAD: headache, palpitations, diaforesis**
  - ***persistent* HT,** with or without paroxysmal crises
  - increased urinary elimination of catecholamines and their metabolites:normetanephrine, metanephrine, vanil-mandelic acid
  - increased basal values of plasma metanephrines

3. HT due to CUSHING SYNDROME

- **Definition** – HT caused by **excessive CORTISOL secretion**
- **Etiology** – *difuse hyperplasia of the adrenal cortex* due to:
  = ACTH hypersecretion by a pituitary adenoma
  = ectopic, paraneoplastic ACTH secretion by a peripheral tumor: bronchial or pancreatic cancer)
  – *an adenoma of the adrenal cortex*
- **Pathogenesis** – **primary hypersecretion of CORTISOL** causes HT by:
  - ✓ water and salt retention
  - ✓ stimulation of the synthesis of RAA system components
  - ✓ increase in sympathetic activity
  - ✓ potentiation of the vasoconstrictor response of the vascular smooth muscles
- **Manifestations**:
  - HT associated with a "*cushingoid*" phenotype ("full moon" face, central obesity, atrophy of the muscles in the extremities, hirsutism etc.)
  - plasma cortisol and free cortisol in the urine/24 hours are increased

4. HT due to THYROID DISEASES

4.1. HYPERTHYROIDISM

- **Definition** – HT caused by **excessive THYROXINE secretion**
- **Pathogenesis** – **HIGH thyroxine** causes **isolated systolic hypertension** via the:
  - Increased inotropism and CO - thyroxine in high amount increases the expression of myocardial β1-adrenergic receptors with sympatho-adrenergic stimulation
  - decreased PVR due to *vasodilation* secondary to increased basal metabolism (and heat production)

4.2. HYPOTHYROIDISM

- **Definition** – HT caused by **decreased THYROXINE secretion** (less frequent as compared to HT due to hyperthyroidism)
- **Pathogenesis** – **LOW thyroxine** causes HT via the :
  - decreased glomerular filtration rate with water retention and hypervolemia
  - increased PVR due to *vasoconstriction* secondary to decreased basal metabolic rate (exacerbated by frequently associated hyperlipidemia that accelerates atherosclerosis with subsequent vascular narrowing)

5. HT due to HYPERPARATHYROIDISM

- **Definition** – HT caused by **excessive parathormon (PTH) secretion**
- **Etiology** – **adenoma of parathyroid glands**
- **Pathogenesis** – **primary hypersecretion of PTH and hypercalcemia** cause HT by:
  - ✓ increased sympathetic activity with increased inotropism and PVR
  - ✓ arterial stiffness
  - ✓ nephrocalcinosis secondary to hypercalcemia

6. HT due to ORAL CONTRACEPTIVES

- **Definition** – HT caused by chronic use or treatment with **estrogen-containing oral contraceptives**
- **Pathogenesis** – **estrogens stimulate the hepatic synthesis of angiotensinogen** and induces HT by *excessive activation of the RAAS* in the presence of increased availability of the AII substrate

c) HT secondary TO <u>OSA SYNDROME</u>

- **Definition** – is a secondary HT, **resistant to treatment**, present in 50% of patients with OSAS (defined by recurrent episodes of apnea/hypopnea with nocturnal onset, through the collapse of the upper airways)
- **Pathogenesis** – hypoxemia (PaO_2 < 60 mmHg) during the episodes of apnea/hypopnea causes, through sympatho-adrenergic activation, systemic vasoconstriction with an increase in PVR that will persist throughout the day
- **Manifestations**: snoring, obesity, morning headache, daytime sleepiness

d) HT secondary to MECHANICAL CAUSES – COARCTATION OF AORTA

- **Etiology** – *stenosis of the aortic isthmus* (congenital narrowing of the aorta occuring below the emergence of the left subclavian artery, most frequently in the initial part of the descending aorta)
- **Pathogenesis:**
  - **increased BP above the coarctation** – increased stiffness of the aortic arch (muscular hyperplasia, accelerated atherosclerosis) and baroreceptors desensitization
  - **decreased BP below the coarctation** – causes decreased kidney perfusion and activation of the RAA system
- **Manifestations:**
  - **increased SBP above the stenosis** (arms, cephalic extremity) diagnosed during childhood or adolescence, symptomatic (headache, palpitations, epistaxis) accompanied by a left subclavian systolic murmur with interscapulovertebral radiation
  - **decreased blood pressure below the stenosis** (torso, legs) manifested by *weak/absent* pulsations in femoral arteries or *delayed* as compared to the radial pulse
  - the development of collateral circulation with increased blood flow in the intercostal arteries causes their pulsations and the appearance of costal erosions at chest X ray

COMPLICATIONS

a) Hypertension-mediated organ damage (HMOD)

- **Pathogenesis:** chronic HT causes:

  ①**Increased left ventricular (LV) afterload** – responsible for:
  - ***pressure overload*** of the LV with *concentric maladaptative left ventricular hypertrophy (LVH) and diastolic dysfunction*
  - ***increased myocardial O_2 demand*** with: *ischemia* and *risk of myocardial infarction*

  ②**Vascular lesions** – caused by combined effects: *chronic high pressure on the arterial walls*, *vascular smooth muscle hypertrophy, endothelial dysfunction and accelerated atherosclerosis.* Vascular lesions participate in HT ***initiation*** and ***progression*** by:
  - **endothelial dysfunction** (decreased NO/increased ET-1) – leads to the *impairment of endothelial-dependent vasorelaxation* (with no clear causal relation being established so far, i.e, endothelial dysfunction is both cause and consequence of HT)
  - **vascular remodeling** – increases *media thickness* as compared to the diameter of the vascular lumen (is the marker of vascular remodeling in HT)
  - **increased arterial stiffness** – explains *isolated systolic HT* observed in the elderly

- Primary HT is **asymptomatic** for a relatively long period of time.
- Symptoms are the result of the **long-term effects of HT** on the ”target” organs: heart, brain, kidney, aorta, peripheral arteries, retina (Table 5.2.).

Table 5.2. Hypertension-mediated organ damage: pathomechanisms and consequences.

Target organ	Pathomechanisms	Consequences
1. Heart	▪ Increased afterload and workload of the heart	▪ Concentric LV hypertrophy (diastolic dysfunction) ▪ Left heart failure (systolic dysfunction)
2. Coronary arteries	▪ Increased O_2 demand ▪ Decreased coronary blood flow and supply with O_2 ▪ Accelerated atheroscleosis	▪ Angina pectoris ▪ Myocardial infarction ▪ Sudden cardiac death
3. Brain	▪ Decreased cerebral blood flow ▪ Accelerated atheroscleosis ▪ Damage of the vascular walls ▪ Axonal demyelination	▪ Transient ischemic attacks ▪ Ischemic stroke ▪ Lacunar stroke ▪ Hemoragic stroke ▪ Cerebral aneurysm ▪ Vascular dementia
4. Kidney	▪ Renin and aldosterone secretion stimulation ▪ Decreased renal blood flow ▪ Increased pressure in renal arterioles ▪ Hyaline arteriolosclerosis	▪ Salt and water retention and hypervolemia exacerbation ▪ Decreased glomerular filtration rate ▪ Nephrosclerosis ▪ Chronic kidney disease ▪ Chronic renal failure
5. Aorta	▪ Damage of the vascular wall	▪ Dissecting aneurysm
6. Peripheral arteries	▪ Decreased peripheral blood flow ▪ Accelerated atherosclerosis	▪ Intermittent claudication ▪ Gangrene
7. Retina	▪ Increased arteriolar pressure	▪ Hypertensive arteriopathy (vascular sclerosis with narrowing of the lumen) ▪ Hypertensive retinopathy (exudates and retinal hemorrhages, papilledema)

b) MALIGNANT or accelerated HT

- **Definition** – severe form of HT, potentially lethal, characterized by a **rapid increase of the DBP > 130 mmHg** and complicated with **rapidly progressive "target" organ damage** (weeks/months instead of years)
- **Etiology** – occurs in women as a complication of *pregnancy* (eclampsia) and in younger patients with *kidney or collagen diseases*
- **Pathogenesis** – the characteristic vascular lesion is **arteriolar fibrinoid necrosis** (typically, glomerular arterioles are affected)

- **Clinical manifestations:**
  - *retinal hemorrhage, exudates (± papilledema)* highlighted by the fundus examination
  - *intense occipital headache* (mainly in the morning) *due to cerebral vasoconstriction* – expression of the mechanism of myogenic autoregulation of cerebral circulation in order to provide brain protection against increased BP values
  - *hypertensive encephalopathy (± cerebral edema)* – expression of the failure of the myogenic autoregulation. It is manifested by: severe headache, vertigo, vomiting, visual impairment (transient blindness), tinnitus, transient paralysis, seizures, stupor, coma
  - *progressive renal failure* – manifested by: oliguria, progressive azotemia exacerbation, progressive proteinuria, microscopic haematuria
  - *progressive heart failure* – manifested by: exacerbated dyspnea and pulmonary edema
  - *relative resistance to antihypertensive treatment*
  - poor short-term survival prognosis

6. PATHOPHYSIOLOGY OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

ATHEROSCLEROSIS (ATS)

DEFINITION: a **disease of the vascular INTIMA** characterized by **chronic inflammation, thickening and stiffness of the arterial walls with progressive narrowing of the lumen**. The disease primarily affects the ***elastic arteries*** (aorta, carotid, iliac) and ***medium muscular arteries*** (coronary, cerebral, popliteal) and is the main cause of: **coronary artery disease, stroke and peripheral artery disease**.

RISK FACTORS

1. NON-MODIFIABLE factors

- **Age:** > 55 years in men and > 65 years in women
- **Male gender**: male > female premenopausal
- **Familial history**: familial history of early cardiovascular disease in Ist degree relatives

2. MODIFIABLE factors

a) CLASSICAL factors:

- **Arterial hypertension (HT)**
- **Diabetes mellitus (DM)**
- **Obesity and metabolic syndrome**
- **Hyper/dyslipidemia** (increased LDL-C and decreased/nonfunctional HDL-C)
- **Smoking**
- **Sedentary life-style**
- **Psychological stress**
- **Excessive alcohol consumption**

Observations:

The control of the modifiable risk factors through lifestyle modification is the main objective of the cardiovascular prevention activity, this also being an important therapeutic target of current treatment guidelines which recommend:

- smoking cessation
- decrease total cholesterol and LDL–C (customized, depending on the cardiovascular risk)
- BP control (according to the recommendations of the current guidelines)
- glycemic control (glycated hemoglobin HbA_{1c} < 7%)
- body weight control (through a hypolipidic diet - below 30% of total calories, of which saturated fat below 7% of total calories and cholesterol intake below 300 mg/day), a BMI < 25 kg/m^2 being recommended)
- reducing the sedentary lifestyle (weekly physical effort of 150 minutes or more in the form of moderate-intensity aerobic activity or 75 minutes of high-intensity aerobic activity)
- reduced alcohol consumption

b) NOVEL risk factors (some of them are used both as biomarkers for the cardiovascular risk and response to treatment):

1. **Increased serum markers of inflammation**:
   – **high-sensitivity C reactive protein** (**hs-CRP**), is currently used to assess the **cardiovascular risk**
   – **fibrinogen**
   – **IL-6, IL-1b and TNF-α**
2. **Increased level of lipoprotein (a) – Lp(a)** is a **modified LDL** (contains apoprotein (a), in addition to apoprotein B100, bound to the particle) and is an independent risk factor for arteriosclerotic cardiovascular disease and calcific aortic valve stenosis. Lp(a) has a: i) *prothrombotic* effect by inhibiting fibrinolysis (it decreases the activation of plasminogen), ii) *proatherogenic* effect by favoring the penetration of cholesterol and oxidized phospholipids at the subintimal level with the formation of "foam" cells (thus accelerating ATS progression), iii) *pro-inflammatory* effect by promoting inflammatoy cell recruitment, adhesion to the endothelium and chemotaxis, iv) *vascular remodeling* effect due to mitogenic properties (it stimulates the proliferation and migration of smooth muscle cells inside the ATS plaques) and v) *promotes valvular calcification* (thus, aggravating aortic stenosis).
3. **Hyperhomocysteinemia (Hcy) –** increased plasma level of homocysteine
   Causes: i) *deficiency of vitamins B12, B6 or folate (vitamin B9),* all cofactors of the enzymes involved in Hcy metabolism and/or ii) *mutations in the genes encoding for these enzymes*.
   Consequences: i) *toxic effect on the endothelial cells* with the aggravation of endothelial dysfunction, ii) *increased vascular stiffness,* and iii) *prothrombotic status* by increasing platelet adhesion to the vascular wall, thus, being a risk factor for myocardial infarction and ischemic stroke.

PATHOGENESIS – 4 steps of ATHEROSCLEROTIC PLAQUE formation**:**

1. **ENDOTHELIAL DYSFUNCTION** – injury of the arterial endothelium is the **FIRST STEP** in the development of ATS
2. **FATTY STREAKS formation** – the earliest visible ATS lesion, as **irregular yelow-white discolorations consisting of lipid-laden monocytes and macrophages** (foam cells) together with T lymphocytes (Th1 type response); they are present from the first decade of life and either develop into the ATS plaques *or* remain static
3. **FIBROUS PLAQUES formation** – the **main lesion and hallmark of ATS**, consisting of **a central core rich in lipids** and an **external fibrous capsule**, being responsible for the **progressive vascular occlusion**
4. **COMPLICATED lesions** – erosion/rupture of the plaques, especially the *"vulnerable"* ones leads to **thrombosis** at the lesion level and the risk of **complete vascular occlusion.**

1. ENDOTHELIAL DYSFUNCTION

- **Definition: loss of the protective functions of the vascular endothelium** due to the **occurrence of microlesions** under the action of **several factors**:
  - ✓ **toxic/metabolic** (smoking, hyperlipidemia, hyperglycemia) – favor the subendothelial deposition of **modified (oxidized, glycosylated) LDL**

- ✓ **mechanic** (hypertension) – favors ATS plaques development at the **arterial bifurcations** (carotid, coronary arteries) where the flow is turbulent ("shear-stress")
- ✓ **immune** (pro-inflammatory cytokines IL-1, IL-6, TNF-α) – perpetuate the **low-grade chronic inflammation,** constant present in the setting of advanced ATS

▪ **Consequences:**

a) <u>Impairment of the VASOMOTOR and ANTITHROMBOTIC functions</u>, which normally *prevent platelet adhesion and aggregation*, due to:

- ✓ decreased production of nitric oxide (NO) and prostacyclin (PGI_2)
- ✓ increased production of endothelin (ET) and thromboxane (Tx)

① The **NITRIC OXIDE – ENDOTHELIN system**

▪ **In normal conditions** – both compounds are synthesized by the **vascular endothelium**, with predominance of **vasodilation** and **platelet anti-aggregation**

a. Nitric oxide (NO) – was discovered by Furchgott, Ignarro, Murad (Nobel Prize, 1998) and has the following effects:

- ✓ vasodilation
- ✓ inhibition of platelet adhesion and aggregation
- ✓ anti-inflammatory
- ✓ inhibition of proliferation and migration of vascular smooth muscle cells (VSMC)

b. Endothelins (ET-1,2,3,4, major isoform ET-1) – were discovered by Yanagisawa in 1988 and have the following effects, mediated by ET A and B receptors:

- ✓ arterial (mediated by ET A) and venous (mediated by ET B) vasoconstriction
- ✓ stimulation of platelet adhesion and aggregation
- ✓ pro-inflammatory via increased production of cytokines (TNF-α, growth factors)
- ✓ proliferation & migration of VSMC from media towards the intima

▪ **In atherosclerosis:**

- – increased production of oxygen free radicals (especially the superoxide anion, $\bullet O_2^-$) leads to inactivation of NO by the formation of the *peroxynitrite anion* ($\bullet ONOO$) with the production of *oxidative stress*
- – modified LDL *inhibits the production of NO* and *stimulates the synthesis of ET-1*
- – **vasoconstriction** and **platelet adhesion/aggregation** are favored

② The **PROSTACYCLIN – THROMBOXANE system**

▪ **In normal conditions** – both compunds are produced from arachidonic acid via the cyclooxygenase pathway

a. Prostacyclin (PGI_2):

- ✓ produced by *endothelial cells*
- ✓ induces *vasodilation*
- ✓ *inhibits* platelet adhesion and aggregation

b. Thromboxane (Tx A_1, A_2):

- ✓ produced by *platelets*
- ✓ induces *vasoconstriction*
- ✓ *stimulates* platelet adhesion and aggregation

▪ **In atherosclerosis:**

- – endothelial lesions *decrease the prostacyclin* (PGI_2) *synthesis*

- in activated platelets *increases the thromboxane* (Tx) *synthesis*
- **vasoconstriction** and **platelet adhesion/aggregation** are exacerbated

b) <u>Alteration of the SELECTIVE BARRIER function</u> *with increased ENDOTHELIAL PERMEABILITY for LDL* will have 2 consequences**:**

① **Deposition of LDL in the vascular walls,** both under *free form* (linked to proteoglycans) as well as *in cells* (in macrophages and VSMC)

② **Generation and deposition of modified LDL (mLDL) in the vascular walls**: **oxidized LDL** (in the presence of *reactive oxygen species*) and **glycated LDL** (in the presence of *hyperglycemia* in diabetics)

c) <u>Alteration of the ANTI-INFLAMMATORY function</u> due to the increased expression of adhesion molecules on the surface of endothelial cells with 2 consequences:

① **The perpetuation of the recruitment of inflammatory cells - monocytes, T lymphocytes at the level of the intima with chronic local inflammation**

② **Progression of atherosclerotic plaques**

2. FATTY STREAK FORMATION consists of:

- **Transformation of monocytes into active macrophages** that will uptake LDL/mLDL becoming the so-called ***foam cells,*** which:
  - by aggregation generate the **fatty streaks**
  - by apoptosis generate the **lipid core of the ATS plaque**

3. MATURE ATS PLAQUES FORMATION consists of:

① **Secretion by macrophages, T lymphocytes, VSMC and endothelial cells of:**
- **pro-inflammatory cytokines** – IL-1, IL-6 and TNF–α
- **growth factors** – transforming growth factor beta (TGF–β), fibroblast growth factor (FGF)

② **Vascular smooth muscle cells proliferation** (under the action of cytokines and growth factors) and their **migration** from the vascular media towards the vascular intima, where they **are activated**, being responsible for:
- **mLDL intake and contributing (*via apoptosis*) to the release of cholesterol that forms the lipid core of the plaque**
- **production of collagen and other extracellular matrix components (eg., proteoglycans), thus forming the fibrous capsule of the atherosclerotic plaque**

③ **Calcium deposition** in atherosclerotic plaques with the progressive stiffening of the vascular walls.

4. COMPLICATED ATS LESIONS

The evolution of the mature plaques can be towards**:**

①**Progressive increase in volume with in variable degrees of blood flow limitation** (ATS plaques are asymptomatic as long as the balance between oxygen supply/demand is not affected). **STABLE plaques** are considered those with :
- ✓ *small central core*
- ✓ *reduced number of inflammatory cells*

- ✓ *thick external capsule*

② **Rupture/erosion with local THROMBOSIS** and **major reduction of blood flow** responsible for acute coronary syndromes or sudden cardiac death. **Complicated plaques with the risk of rupture** are called **VULNERABLE or UNSTABLE plaques** and are characterized by a:

- ✓ *central core rich in lipids*
- ✓ *increased number of inflammatory cells* (macrophages are the hallmark of chronic inflammation)
- ✓ *thin external capsule*

Thrombosis of atheroma plaques can occur by **2 mechanisms:**

- **The first mechanism** is represented by superficial endothelial erosion of a plaque. The subendothelial connective tissue matrix is exposed to contact with the blood and platelet adhesion to collagen is initiated. The thrombus that forms is *adherent to the surface of the plaque*.
- **The second mechanism** is related to rupture/fissure/ulceration of the capsule of an advanced plaque, and blood enters from the vascular lumen into the interior of the plaque. The lipid core, the tissue factor produced by macrophages (which activates coagulation and platelet aggregation) and the collagen within the plaque have major thrombogenic potential. *The formation of the thrombus in the subintimal space of the plaque increases its volume*, changes its shape, and then the thrombosis extends into the vascular lumen.

CORONARY ARTERY DISEASE (CAD)

DEFINITION: the most frequent consequence of ATS characterized by the **imbalance between coronary oxygen supply and myocardial oxygen demand** with subsequent **MYOCARDIAL ISCHEMIA**.

ETIOLOGY

- **the main cause** (99% of cases): **coronary atherosclerosis**, i.e., the partial obstruction of the epicardial coronary arteries (the main conductance vessels of the coronary circulation) by atheroma plaques with/without superimposed thrombosis and/or coronary spasm
- **coronary microvascular dysfunction** with angina pectoris
- other (1% of cases):
  - ✓ *aortic stenosis*
  - ✓ *coronary arteries embolism*
  - ✓ *coronary vasculitis*

MYOCARDIAL O_2 SUPPLY and DEMAND

1. MYOCARDIAL O_2 SUPPLY

- **Definition** – the oxygen supply of cardiomyocytes, which depends on both the *myocardial O_2 extraction* and *magnitude of coronary blood flow*.

a) Myocardial O_2 EXTRACTION

- **Characteristics:**
  - represents the difference between *arterial* and *venous* O_2 concentration in the coronary circulation
  - in physiological conditions is ~ 50% (higher than in peripheral tissues) and may further increase when needed up to 75%

b) The CORONARY BLOOD FLOW (CBF)

- **Characteristics:**
  - depends on the: *coronary perfusion pressure (directly proportional)* and *coronary vascular resistance (inversely proportional)*
  - because *coronary perfusion pressure* is maintained *constant* by blood pressure homeostasis mechanisms, **the main modality to increase CBF and, thus O_2 supply** is to **decrease coronary artery resistance** by **coronary vasodilation.**

c) The CORONARY RESISTANCE (CR) has 2 components:

① **The INTRINSIC component** – determined by *vascular smooth muscle tone* and controlled by **3 autoregulation mechanisms** that are active mainly in the ***small, distal coronary arteries*** (resistance vessels)**:**

- ✓ **metabolic** regulation – the decrease of CBF causes the release of local *vasodilating metabolites* (e.g., adenosine, lactate) that decrease CR and increase CBF
- ✓ **endothelial** regulation – the decrease of CBF causes the release of local *vasodilating mediators* (eg., NO, PG I_2) that decrease CR and increase CBF
- ✓ **nervous** regulation – the sympathetic innervation and release of catecholamines causes *coronary vasodilation* through β_2-adrenergic receptors that decreases CR and increases CBF

② **The EXTRINSIC component** – determined by the *extravascular compression* and varies according to the *phases of the cardiac cycle* as follows:

- **During the diastole:**
  - ✓ The end-diastolic intracavitary pressure (EDP) is decreased and the extrinsic component of **CR becomes minimal** during the *isovolumetric relaxation phase* (when CBF is maximal)
  - ✓ **normal, myocardial blood perfusion occurs predominantly during the diastole** when the CBF depends on the difference between the aortic diastolic pressure and the ventricular EDP – e.g., if DP = 80 mmHg and EDP = 5 mmHg, the coronary perfusion pressure (PP) = 75 mmHg (Fig. 6.1)
  - ✓ in ATS, the **perfusion pressure decreases distal to the obstruction elicited by the athromatous plaque** (e.g., DP = 40 mmHg and PP falls from 75 to 35 mmHg) with subsequent myocardial ischemia in the territory served by the obstructed artery (Fig. 6.1)
- **During the systole**: the intracavitary pressure increases to perform ejection and the extrinsic component of **CR becomes maximal** during the *isovolumetric contraction phase* (when CBF is minimal)

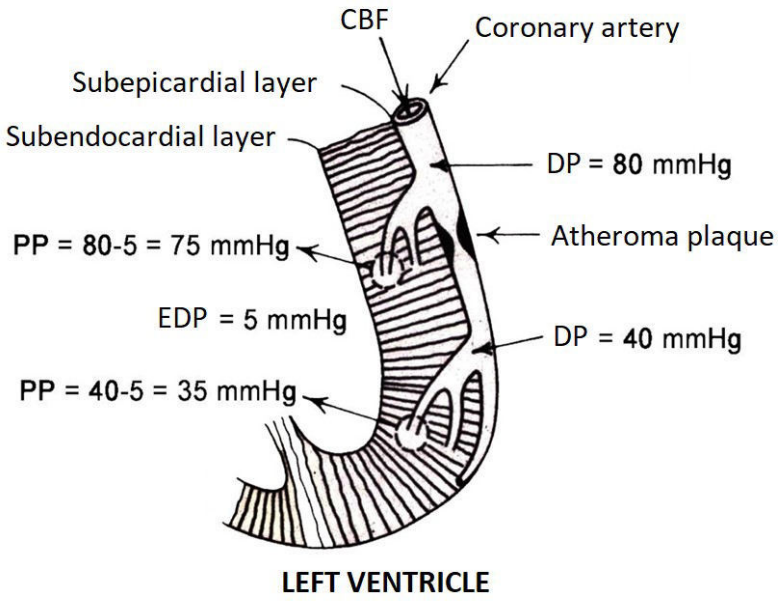

Figure 6.1. Perfusion pressure (PP) in healthy and ATS coronary arteries.
CBF – coronary blood blow, DP – diastolic pressure in aorta, EDP – end-diastolic pressure in ventricle

- The CBF decline is more pronounced at the **endocardial level** with **2 consequences**:
  - ***ischemia is more common in the subendocardial layer*** as compared to the subepicardial layer of ventricular myocardium
  - ***propagation of the necrosis*** in acute transmural myocardial infarction ***occurs from the endocardium towards the epicardium***

- **Causes of ischemia due DECREASED O_2 SUPPLY** are the following:
  - **CAD with atherosclerotic obstruction – the main cause**
  - *decreased aortic diastolic pressure* (DP) in: severe hypotension, hypovolemia, shock
  - *increased ventricular end-diastolic pressure (EDP)/volume* or *preload* in: ventricular hypertrophy from cardiomiopathies, heart failure
  - *increased HR* due to shortening of the diastole in: tachyarrhythmias
  - *dysfunction of the coronary microcirculation* (vessels with a diameter < 4 mm, which are not visualized during coronary angiography) responsible for **microvascular angina** or **INOCA** (**I**schemia and **N**on **O**bstructive **C**oronary **A**rtery Disease), more frequent in women

2. MYOCARDIAL O_2 DEMAND

- **Definition** – the oxygen demand of cardiomyocytes or the myocardial O_2 consumption, which depends on:
  - *myocardial energy consumption during systole* when the ventricle must supply the pressure necessary for blood ejection)
  - *the speed of metabolic processes and of biological oxidation* which generates the energy used for contraction
- **The MAJOR determinants** of the myocardial O_2 demand are**:**
  - systolic parietal tension or afterload

- heart rate (HR)
- contractility (inotropism)

- **Causes of ischemia due INCREASED O_2 DEMAND** are the following:
  - *increased systolic parietal tension* in:
    - ✓ HT, aortic stenosis – for the *left ventricle*
    - ✓ pulmonary HT, COPD, mitral stenosis – for the *right ventricle*
  - *increased HR* by *sympathetic stimulation* (during physical effort), or secondary to the *increase in the speed of metabolic processes* (eg, in hyperthyroidism/thyrotoxicosis, fever)
  - *increased inotropism* under the action of positive inotropic agents: dopamine, dobutamine, cardiotonic glycosides (digitalis).

MECHANISMS of MYOCARDIAL ISCHEMIA:

1. ATHEROSCLEROTIC coronary obstruction

- **Cause** – ATS preferentially affects the ***large* coronary arteries** and the formation of atherosclerotic plaques leads to lumen narrowing and the occurrence of a pressure gradient (the perfusion pressure decreases distal to the obstruction).
- **Consequences** – the hemodynamic consequences depend on the ***coronary vasodilator reserve*** and ***collateral circulation***. Myocardial ischemia is avoided in the *short-term* by means of the autoregulation mechanisms (decrease of intrinsic CR) but leads to a **decrease of the coronary vasodilator reserve**:

  ①Coronary obstructions that decrease the vascular lumen by up to **80%** will:
  - ✓ progressively decrease the coronary vasodilator reserve
  - ✓ induce *effort angina*

  ✓ trigger compensatory development of the collateral circulation (

  ② Coronary obstructions that decrease the vascular lumen by more than **80%** is a **critical stenosis,** which:
  - ✓ *deplete the coronary vasodilator reserve*
  - ✓ induce *rest angina*
  - ✓ *represent indications for* revascularisation therapy – *angioplasty/stent placement and coronary artery bypass graft surgery (CABG)*

2. Coronary SPASM

- **Cause** – endothelial dysfunction associated to ATS and increased expression of α-adrenergic receptors that elicit vasoconstriction upon stimulation
- **Consequence** – **coronary spasm** in ***large* coronary arteries** *normal and/or with ATS lesions* where the autoregulation mechanisms do not work.
  Coronary spasm is involved in the pathogenesis of:
  - **unstable angina**, especially the **variant Prinzmetal angina** (vasospastic angina)
  - **acute myocardial infarction** (AMI)

3. Alteration of O_2 TRANSPORT and DIFFUSION

a) O_2 TRANSPORT impairment – occur in:

- **severe anemias** with persistent decrease of the hemoglobin (Hb) concentration

- **pathological Hb caused by various intoxications** (and cannot carry O_2):
  - CO intoxication → carboxyhemoglobin
  - nitrite intoxication → methemoglobin
  - sulfate intoxication → sulfhemoglobin
- **genetic variants of abnormal Hb (rare):**
  - Hb with low affinity for O_2 (cannot bind O_2 in the lungs)
  - Hb with high affinity for O_2 (cannot release O_2 to the tissues)
- **hypoxemia (↓ PaO_2) in respiratory failure**

b) O_2 DIFFUSION impairment – occur in:

- **maladaptive cardiac hypertrophy,** especially the **concentric** one
  The central areas of hypoxic myocardial fibers become necrotic and are replaced by fibrous tissue in a process called *myocardosclerosis with cardiac remodeling.*

EFECTS of MYOCARDIAL ISCHEMIA:

1. METABOLIC abnormalities

- **Cause** – O_2 deficiency is responsible for the anaerobic metabolism of the energetic substrates

a) LIPID metabolism

- **in normal conditions** – *beta-oxidation of fatty acids provides 2/3 of the energetic needs of the heart*
- **in ischemia** – *impairment of fatty acids beta-oxidation* occurs due to:
  - O_2 deficiency
  - inhibition of fatty acids transfer from the cytosol to mitochondria caused by the carnitine system dysfunction, with 2 consequences:
    - ✓ **decreased fatty acids oxidation**
    - ✓ **mitochondrial dysfunction** and **cellular energy deficiency** = decreased creatine phosphate (CP) and ATP reserves

b) CARBOHYDRATE metabolism

- **in ischemia** – activation of *glycogenolysis* (mobilisation of glucose from deposits) and *activation of anaerobic glycolysis* with **2 consequences:**
  - **exacerbation of the ATP deficiency** with subsequent **impairment of ionic pumps activity,** namely:
    - ✓ decreased Ca^{2+} pump function → decreased myocardial relaxation and ***initial diastolic dysfunction***
    - ✓ decreased Na^+/K^+ pump function → alteration of the resting membrane potential and ***bioelectrical changes***
  - **overproduction of lactate** and **lactic acidosis** responsible for:
    - ✓ competition between H^+ and Ca^{2+} ions at the level of troponin C, with decreased myocardial contractility and consecutive ***systolic dysfunction***

2. BIOELECTRICAL abnormalities

- **Cause** – *decrease of Na^+/K^+ ATPase activity* (Na^+/K^+ pump)
- **Consequence** – impairment of transmembrane ionic transport with intracellular accumulation of Na^+, responsible for the:
  - **partial depolarisation** of the ischemic cardiomyocytes, with *decreased amplitude and duration of the action potential.* The working atrial and ventricular muscle cells with a fast response become slow response cells → risk of *arrhythmias due to ectopic pacemakers*
  - **repolarisation inhomogeneities** between the normal and ischemic tissue with:
    - ✓ *ST segment changes* on the ECG, which can be of 2 types:
      - *ST elevation* in transmural ischemia
      - *ST depression* in subendocardial ischemia
    - ✓ risk of *reentry arrhythmias*

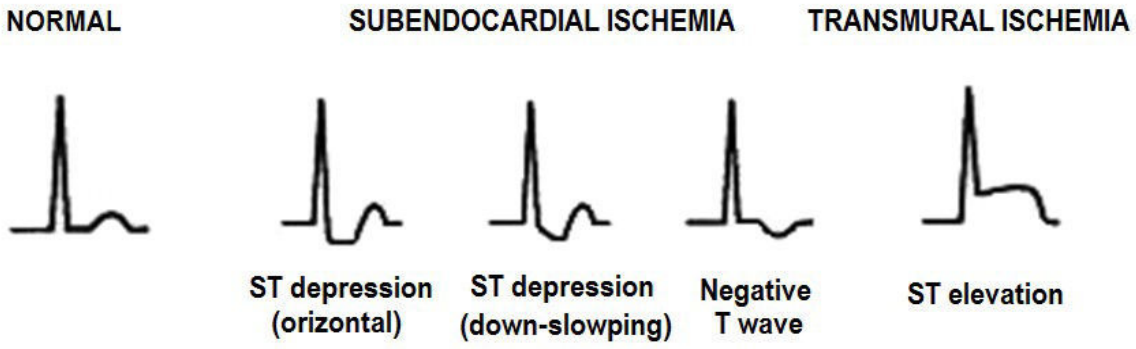

Figure 6.2. ECG changes in myocardial ischemia.

3. Abnormalities of RELAXATION and CONTRACTION

- **Causes:**

  ① **Impairment of DIASTOLIC performance** due to the:
  - energetic deficit leading to the *inhibition of the Ca^{2+} dependent ATPase* (Ca^{2+} pump) at the sarcoplasmic reticulum (SERCA/*Sarco-Endoplasmic Reticulum Calcium-ATPase*)
  - increased concentration of free interfilamentary Ca^{2+} during the diastole, which causes the **early impairment of relaxation**, decreased of ventricular compliance and ***early* impairment of the diastolic performance**

  ② **Impairment of SYSTOLIC performance** due to the:
  - decreased trans-sarcolemmal Ca^{2+} influx in *phase 2 of the action potential* (with shorter duration) causes the consecutive decrease of Ca^{2+} release from the sarcoplasmic reticulum, with decreased availability of intracellular Ca^{2+} to bind to troponin C
  - reduced affinity of troponin C for Ca^{2+} caused by *local acidosis* (competition between H^+ released from lactate and Ca^{2+} at the level of troponin C)
  - both changes lead to **decreased contractility** with ***subsequent* impairment of the systolic performance**

- **Consequences** – are diagnosed by *echocardiography* as relaxation impairment or contractility abnormalities

CLINICAL FORMS of CORONARY ARTERY DISEASE:

I. CHRONIC coronary syndromes
II. ACUTE coronary syndromes

I. CHRONIC coronary syndromes

- **Classification:**
  1. **STABLE angina**
  2. **SILENT myocardial ischemia**

1. STABLE angina

- **Definition** – **transient** myocardial ischemia responsible for **reversible** cellular changes, **without** necrosis
- **Etiology** – **increased O_2 demand** after high sympathetic-adrenergic stimulation (e.g., physical effort, smoking, cold exposure, emotional stress) in the presence of ***PARTIAL atherosclerotic obstruction*** **of the coronary arteries**
- **CLINICAL manifestations – *pain crises*:**

– **CLASSICAL or TYPICAL angina** – *3 characteristics:*
  - ✓ **typical pain**: sensation of pressure, constriction, **retrosternal** or **precordial** "claw" with radiation in the shoulder, forearm and left arm (ulnar side) or in the mandible, right arm, at epigastric level, interscapulovertebral space
  - ✓ **triggering factors**: physical effort, emotions, exposure to cold
  - ✓ **relief at rest and/or with sublingual nitroglycerin**

– **ATYPICAL angina** – chest pain presenting only *2 of the characteristics* mentioned above

The PAIN due to angina pectoris:

– is the consequence of:
  - *stimulation of adrenergic nerve endings* by *local lactic acidosis*
  - *excessive stretching of ischemic myocardial fibers*

– *increases progressively*, reaches a plateau and then progressively decreases (at variance from the pain due to aortic dissection, which is maximal from the beginning)

– has a duration of *less than 20 minutes* - angina attacks have, on average, a duration of 3-5 minutes

- **ECG changes:**

CHRONIC ischemia leads to **<u>abnormal ventricular REPOLARIZATION</u>** with:
  - ✓ ST segment and T wave changes (the terminal phase of repolarization)
  - ✓ rhythm disorders, e.g., premature contractions, tachycardia and atrial fibrillation and conduction disorders, e.g., AV and bundle branch blocks

– **ECG changes in angina pectoris**:
  - ✓ **between the crises** the ECG can be normal or only non-specific T wave changes may be present

- ✓ **during the crisis** ischemia causes on ECG:
  - **ST segment changes** ⇒ indicate the **electrical INJURY**
    = subendocardial – *ST depression ≥ 1 mm* (downsloping or horizontal)
    = transmural – *ST elevation ≥ 1 mm in the limb leads and/or ≥ 2 mm in precordial leads*
  - **T wave changes** ⇒ indicate the **electrical ISCHEMIA**
    = flattening of T wave – isoelectrical T
    = negative T wave – inversion of T wave
  - **decrease of R wave amplitude**

T wave changes and the decrease of R wave amplitude are ***without*** diagnostic value if they are isolated, in the absence of ST changes.

2. SILENT myocardial ischemia

- **Definition** – myocardial ischemia **unaccompanied by angina attacks**, *asymptomatic* or only with *atypical symptoms* (eg., fatigue, discomfort, dyspnea), which is common in:
  - **women, the elderly and diabetics**
  - subjects with *previous myocardial infarction*
  - subjects with *stable angina that associates episodes of silent ischemia*
- **Etiology** – **partial atherosclerotic coronary obstruction** and/or **coronary spasm** in the presence of ***sympathetic innervation abnormalities*** occuring in patients with:
  - *diabetes mellitus* (diabetic neuropathy) – the most frequent clinical situation
  - *personal history of myocardial infarction* – by nerve damage and increase of the pain threshold
  - *personal history of coronary artery by-pass surgery* – by surgical denervation
- **Diagnosis:** ECG signs of electrical INJURY and/or ISCHEMIA changes on Holter ECG monitoring.

II. ACUTE CORONARY syndromes

- **Classification:**
  1. **Unstable angina**
  2. **Acute myocardial infarction:**
     a. **Without ST segment elevation (non-STEMI*)**
     b. **With ST segment elevation (STEMI*)**
  3. **Sudden cardiac death**

where ***STEMI** = ST-Elevation Myocardial Infarction

1. UNSTABLE ANGINA

- **Definition** – ***severe transient*** *acute myocardial ischemia* with **reversible** cellular changes, **without necrosis** and *without persistent increase of the serum myocardial infarction markers* (negative troponin at 2 determinations)
- **Etiology** – **increased O_2 demand** in the presence of **complicated ATS lesions** (rupture/erosion of the plaque with thrombosis on the ATS plaque) **with or without**

coronary spasm, with **SUBTOTAL coronary obstruction** and **LABILE thrombus** (autolysis in 10 - 20 minutes)

- **CLINICAL forms**:
  a) ***De novo* angina** – newly installed severe angina with onset in the previous 24 hours
  b) **Aggravated stable angina** – angina at rest or angina on minimal exertion with prolonged duration of the painful episode
  c) **Prinzmetal angina** or vasospastic angina
- **ECG changes** – identical with those in stable angina:
  – transient ST segment depression or elevation in Prinzmetal angina
  – transient inversion of the T waves
- **Evolution –** towards acute myocardial infarction (20% of cases) or it can be complicated by arrhythmias

Prinzmetal angina (vasospastic angina)

- **Definition** – particular form of unstable angina, more frequent in women and characterised by ***transient TRANSMURAL*** *acute ischemia*
- **Etiology – coronary spasm of an epicardial artery** with/without atherosclerotic lesions
- **CLINICAL manifestations** – angina occurs at *minimal effort* or *at rest*, usually *during the night* (in the second half of the night or in the early hours of the morning), with a cyclic character and can be associated with other *vasospastic phenomena*, e.g., migraine or Raynaud phenomenon
- **ECG changes:**
  – **transient ST elevation** that disappears after crisis or after nitroglycerin administration

2. ACUTE MYOCARDIAL INFARCTION (AMI)

a) Without ST elevation (non-STEMI)

(Old nomeclature: non-Q myocardial infarction, subendocardial infarction)

- **Definition** – **severe <u>persistent</u>** acute myocardial ischemia (> 20 minutes) with **irreversible** cellular changes caused by: i) **SUBENDOCARDIAL necrosis**, ii) **transient TRANSMURAL NECROSIS** or iii) **MICROINFARCTIONS** accompanied by the **persistent positive value of serum markers** (troponins, CK-MB)
- **Etiology**
  – **complicated ATS lesions** (fissure/erosion of the plaque with thrombosis on the ATS plaque) with or without coronary spasm, with **SUBTOTAL/TOTAL coronary obstruction** with a **<u>LABILE</u> thrombus** and the **presence of collateral circulation**
  – **EMBOLIZATION of the coronary microcirculation**
- **ECG** – i) ST-segment elevation, new T-wave inversions; ii) transient ST-segment elevation or iii) normal ECG (repeated evaluations are necessary because a normal ECG does not exclude a non-STEMI infarction)

b) With ST elevation (STEMI)
(Old nomenclature: Q wave myocardial infarction, transmural infarction)

- **Definition** – **severe <u>persistent</u>** acute myocardial ischemia (> 20 minutes) with **irreversible** cellular changes caused by **persistent TRANSMURAL necrosis** and accompanied by the **persistent positive, <u>markedly increased</u> values of serum markers** (troponin, CK-MB)
- **Etiology – complicated ATS lesions** (fissure/erosion of the plaque with thrombosis on the ATS plaque) with or without coronary spasm, with **TOTAL coronary obstruction and <u>STABLE</u> thrombus.**

<u>Manifestations of ACUTE MYOCARDIAL INFARCTION</u>

A. The PAIN due to myocardial infarction has eatures of the pain:
- **localisation and irradiation** similar to the pain from angina pectoris
- ***acute* onset** and a ***more severe* character**
- **does NOT respond** to rest and/or nitroglycerin (only to opioids)
- associated with: *anxiety/agitation,* nausea/vomiting, asthenia (parasympathetic effects) and diaphoresis and cutaneous vasoconstriction with pallor (sympathetic effects)

B. ECG changes
ACUTE persistent ischemia causes the <u>impairment of both ventricular **DEPOLARIZATION**</u> and **<u>REPOLARIZATION.</u>**
The infarcted zone has 3 areas with distinct electrical changes:
1. The area of electrical **necrosis**
2. The area of electrical **injury**
3. The area of electrical **ischemia**

1. The NECROTIC area
- is the central area with **totally depolarised***, electrically inactive cells* (they lose the ability to generate and propagate the excitation impulse)
- causes on the ECG in the *direct leads* (that have a direct view of the myocardial infaction area):
  - the **pathological Q wave** with duration > 0,04 sec and amplitude > 25% of the R wave in the same lead or
  - the **QS complex**

2. The INJURY area
- is the area with ***partially depolarised*** *cells* with *slow-type response* that surround the necrosis area
- is caused by the occurrence of *injury currents* (differences of potential between the ischemic and normal myocardium) of **2 types**:
  - ✓ systolic (in phase 2 of the action potential)
  - ✓ diastolic (in phase 4 of the action potential)
- causes on the ECG:
  - ✓ **ST elevation** in the **direct** leads
  - ✓ **ST depression** in the **indirect** leads and in subendocardial myocardial infarction

3. The ISCHEMIC area

– is the peripheral area (surrounding the injury area) characterised by the *reversed sequence of repolarisation* (normal, from the epicardium towards the endocardium); due to reduced action potential duration of the in the subendocardial area, repolarisation occurs now from endocardium towards epicardium.
– causes on the ECG: the **negative T wave**

2. <u>DIRECT</u> ECG signs of MYOCARDIAL INFARCTION

– appear in the leads *directly* exploring the area of STEMI infarction
– present a dynamic in time according to the *evolution of the infarction*:

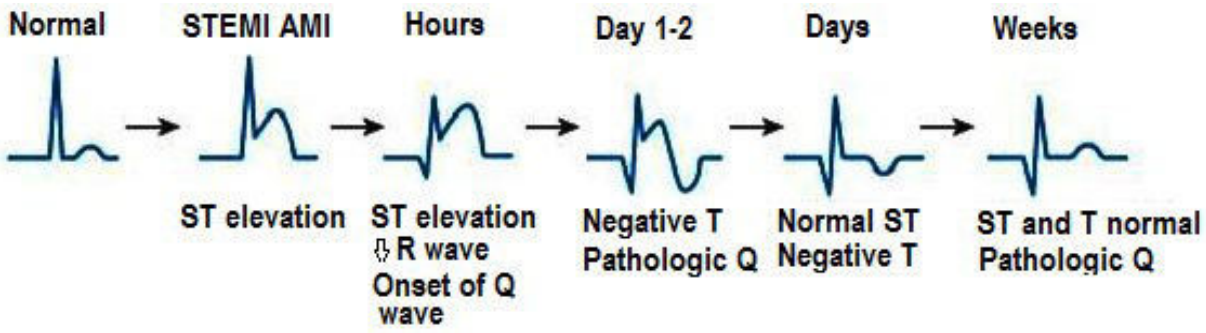

Figure 6.3. ECG changes in STEMI**.**

- **In ACUTE STEMI** – hours, days:
  – ST elevation is **the first ECG sign** and indicates the electrical ***injury***
  – the pathological Q wave or QS complex indicates the electrical *necrosis*
  – the negative T wave indicates the electrical *ischemia*
- **In SUBACUTE (RECENT) STEMI** – days, weeks:
  – the ST segment returns to the isoelectric line - the electrical *injury disappears*
  – the pathological Q wave indicates the *persistence of necrosis*
  – the negative T wave persists or returns to the isoelectric line (*persistence or disappearance of ischemia*)

Observation:
The persistence of the ST elevation in subacute myocardial infarction represents a risk of MI expansion.

- **In CHRONIC myocardial infarction** – months, years:
  – injury and ischemia disappear
  – **pathological Q wave or QS complex** (markers of *necrosis*) persist for the entire lifetime

3. <u>INDIRECT</u> ECG signs of MYOCARDIAL INFARCTION

Are represented by:

- **ST segment depression** present in:
  ✓ ECG leads that *directly* explore the site of non-STEMI infarction
  ✓ ECG leads that *indirectly* explore the STEMI infarction (through a normal heart wall)
- Leads **V1** and **V2** that *indirectly* explore the **posterior AMI** will show:
  - pathological R waves in V1 and V2 (the R wave is the reciprocal wave of the Q wave)

- **R/S ratio** ≥ **1** *and/or*
- **R wave** duration ≥ **0,03 sec**

C. LABORATORY diagnosis

a) <u>SPECIFIC</u> serum markers:

Cardiomyocyte necrosis is followed by the release into the circulation of two types of serum markers used in the laboratory diagnosis of MI:

- ***proteins*: cardiac troponins T and I** and **myoglobin**
- ***enzymes*: creatine kinase (CK)**

1. Troponins (cTnT, cTnI)

Cardiac troponins T and I have each specific amino acid sequences (that differ from the skeletal isoforms, being encoded by unique genes) and immunoassays have been developed which recognize cardiac forms of both troponins (and do not crross-react with the skeletal forms). Their serial measurements, in dynamic (minimum 3 values in the first 24h: upon admission, 4-6 hours later and at 12 hours after admission) are mandatory for the positive diagnosis of myocardial infarction. Recently, ***high-sensitive cardiac troponins (hs-cTn)*** assays were introduced for the clinical use that allow the early detection (the first 3 h) of serum increases in the range of ng/ml.

- **Dynamic:**
  - increase 3-12 hours after the onset of pain
  - maximum level at 24 h
  - return to normal in 7-14 days
- **Clinical value:**
  - *the* ***most specific serum markers of myocardial necrosis***
  - the levels in the first 24 hours have a prognostic value and are used for the **assesment of the mortality risk post-myocardial infarction**, regardless the type, STEMI or non-STEMI

2. Creatine kinase (CK) - CK-MB isoenzyme

Creatine kinase (CK) is an enzyme localized in the heart, muscle and brain and presents three isoforms:

- CK-MM isoenzyme – specific for the skeletal muscle
- CK-BB isoenzyme – specific for the brain
- CK-MB isoenzyme – specific for the myocardium

- **Dynamic:**
  - increases 3-6 hours after the onset of pain
  - maximum level at 24 h
  - returns to normal in 2-4 days
- **CLINICAL value:**
  - its values decrease faster post-infarction as compared to troponin
  - the return to normal followed by another increase indicates **reinfarction**
  - **increased values in association with Tn increase are associated with poor prognosis**, indicating high risk of postinfarction mortality

Table 6.1. Dynamic of serum markers in myocardial infarction.

Temporal dynamic	Troponins	CK-MB	Myoglobin
Onset	3-12 h	3-6 h	2-4 h
Maximal value	24 h	24 h	6-9 h
Return to normal	7-14 days	2-4 days	1 day

b) <u>NON-SPECIFIC</u> serum markers:

1. SERUM myoglobin

- **Dynamic:**
  - increases 2-4 h after the onset of pain
  - maximal value after 6-9 h
  - return to normal after 1 day
- **CLINICAL value:**
  - the **EARLIEST marker** of myocardial necrosis
  - **is not cardiospecific** – increases in rhabdomyolysis too
  - normal myoglobin in two samples taken 2 – 4 h apart excludes AMI

2. Markers of ACUTE INFLAMMATION

- **leukocytosis with neutrophilia** – for 3-7 days
- **increased ESR** – for 1-2 weeks
- **increased C-reactive protein**; **persistent CRP increase** after discharge is associated with **high risk of cardiovascular mortality** (even in the absence of significant Tn increase)

The positive diagnosis of myocardial infarction requires the presence of **2** of the following **3 criteria**:

- *pain*
- *increased serum markers of necrosis*
- *ECG abnormalities*

7. PATHOPHYSIOLOGY OF RHYTHM AND CONDUCTION DISORDERS

ELECTROPHYSIOLOGICAL PRINCIPLES OF CARDIAC ARRHYTHMIAS – BRIEF PHYSIOLOGY OVERVIEW

The fundamental electrophysiological properties of the HEART whose disruption is the basis for the appearance of rhythm and conduction disorders are: **automaticity, excitability** and **conductivity**.

A. CARDIAC AUTOMATICITY

- **Definition** – the specific ability of the excito-conduction system to **spontaneously and regularly generate action potentials (impulses)** in the absence of **external stimuli**.
- **Mechanism:**
  - the instability of the maximum diastolic potential (MDP, – 60mV) at rest induces a spontaneous diastolic depolarization up to the threshold potential (TP, – 40mV), point at which a propagated action potential called pacemaker potential (PP) will automatically be generated
  - the slow diastolic depolarization (SDD) is at the base of normal automaticity and results from a:
    - **Reduced influx of Na^+ ions** transported by the:
      i) I_b basal current and, especially by
      ii) I_f („funny") pacemaker current. The term "funny" current denotes ion flow through channels activated in hyperpolarized cells (- 60 mV or more) unlike most voltage (or time) dependent ion channels, which are activated by depolarization.
    - **Transient influx of Ca^{2+} ions** transported by the **I_{CaT} current** transported through the T-type Ca^{2+} channels that are voltage-dependent.

Observation:
The I_f current is inhibited by *Ivabradine*, a drug prescribed for the treatment of stable angina and heart failure with reduced EF for patients in sinus rhythm and with a HR $\geq$ 75 b/min, due to its effect of reducing the pacemaker activity (a "pure" reduction effect of the heart rate) with a secondary increase of the coronary blood flow (and of the oxygen supply, respectively) and without the affectation of myocardial contractility/relaxation and ventricular repolarization.

- **Types of CARDIAC PACEMAKERS:**
  ① **The DOMINANT pacemaker (primary)** – the **sinoatrial (SA) node**
  - is the **physiological** heart pacemaker
  - has an intrinsic discharge rate of **60-100/min** and is responsible for the **sinus rhythm**
  - inhibits by *overdrive suppression* the latent pacemakers that will be depolarized faster than their intrinsic automatic discharge rate

  ② **The LATENT pacemakers (secondary)** – the **atrio-ventricular (AV) node** and **His-Purkinje system**
  - become active only if the activity of the SA node is **suppressed**
  - they have an intrinsic discharge rate of **40-60/min** for the AV node (junctional rhythm) and of **30-40/min** for the His-Purkinje system (idioventricular rhythm)

  ③ **The ECTOPIC pacemakers** – areas of impulse generation ***out of the SA node***
  - **types:**
    - ✓ the pacemaker cells of the AV node and His-Purkinje system (automatic, with a slow response)
    - ✓ the "working" myocardium cells (non-automatic cells, with rapid response)
  - *these cells become active by* partial depolarization in pathological conditions *(i.e., ischemia) when they gain the ability to spontaneously generate excitation impulses; this property is called* ***abnormal automaticity,*** *representing the* ***basis of cardiac arrhythmias***

B. CARDIAC EXCITABILITY

- **Definition** – the specific ability of the cardiac cells to respond to a threshold stimulus by generating a **propagated action potential**
- **Types of cardiac cells** – according to the characteristics of the resting and action potential, there are **FAST** and **SLOW response cardiac cells** (Table 7.1)

Table 7.1. The characteristics of the two main types of CARDIAC CELLS.

Characteristics	FAST response cells	SLOW response cells
▪ **Localisation**	Atrial working muscle cells Ventricular working muscle cells His-Purkinje system	SA node AV node Partially depolarized cells from the ischemic areas
▪ **Excitability**	increased	decreased
– Resting potential	– 90 mV	– 60 mV
– The slope of phase 0	rapid	slow
– The amplitude of phase 0	high	reduced
– The refractory period	long	short
▪ **Conduction velocity**	*Atria*: 0,3-0,4 m/s *Ventricles:* 0,5-0,6 m/s *Preferential atrial pathways:* 1m/s *His-Purkinje system:* 3-5 m/s	*SA node:* 0,05 m/s *AV node:* **0,02-0,03 m/s - the slowest conduction velocity**

C. CARDIAC CONDUCTIVITY

- **Definition –** the specific ability of the cardiac cells to **conduct the action potential** generated by the SA node through the cardiac tissue
- **The conduction velocity –** depends on the *cell excitability* and varies *directly proportional to the amplitude of the AP and the slope of phase 0* (Table 7.1)
- **The NORMAL conduction sequence:**
  1. The impulse originating in the SA node induces **atrial depolarization** and is transmitted with high velocity through the preferential atrial pathways/working atrial muscle cells up to the AV node (the atrial tissue is activated like a "forest fire", but once the depolarization wave reaches the fibrous tissue, the insulator between the atria and the ventricles, it dies out)
  2. The slow response cells from the AV node act as an **AV physiological block** (a delay with the duration of 0,10-0,16 sec)
  3. From the AV node, the impulses are rapidly conducted towards the ventricles through the **His-Purkinje system**, inducing thus the **ventricular depolarization**.

RHYTHM DISORDERS – CARDIAC ARRHYTHMIAS

DEFINITION – **cardiac arrhythmias** (or **dysrhythmias**) refers to broad spectrum of **heart rate or rhythm disorders**

CLASSIFICATION – according to:

1. **Heart rate** – *bradycardia* (< 60 b/min) and *tachycardia* (> 100 b/min)
2. **Site of origin** – *sinus*, *supraventricular* (atrial and junctional), *ventricular* arrhtyhmias
3. **Duration** – *acute* (several days) and *chronic* (months/years)
4. **Type of onset** – *paroxysmal* (sudden onset and finish) and *non-paroxysmal* (gradual onset and finish)

ETIOLOGY – the causes of cardiac arrhythmias are listed in Table 7.2.

Table 7.2. Causes of cardiac arrhythmias.

Causes	Conditions accompanied by arrhythmias
1. Functional	Exercise, fever, severe chronic anemia (high sympathetic tone) Athletes (high parasympathetic tone/vagotonia)
2. Toxic	Excess of coffee, tobacco, alcohol (elicit sinus tachycardia) Medication (digitalis, beta-blockers etc.)
3. Organic cardiopathies	Ischemic and hypertensive heart disease Cardiomyopathies, valvular diseases, heart failure
4. Electrolyte imbalances	Hypo-/Hyperkalemia Hypo-/Hypercalcemia
5. Mechanical	Cardiac catheterization Cardiac surgical interventions
6. Congenital	Ventricular preexcitation syndromes Long QT syndrome
7. Endocrine diseases	Hypo-/Hyperthyroidism Obesity, diabetes
8. Pulmonary diseases	Decompensated COPD

CLINICAL MANIFESTATIONS – depend on the severity of the arrhythmias (Table 7.3):

Table 7.3. Manifestations of cardiac arrhythmias.

Clinical form	Manifestations
MILD forms	✓ Palpitations
MODERATE forms	✓ Dizziness ✓ Profuse sweating ✓ Dyspnea ✓ Angina pain
SEVERE forms	✓ Confusion ✓ Lipothymia/Syncope ✓ Pulmonary edema/Cardiogenic shock

PATHOGENESIS

Arrhythmias result from **abnormal generation** and/or **abnormal conduction** of the cardiac impulses.

1. Impairment of IMPULSE GENERATION

a) ESCAPE rhythms

- **Definition** – manifestation of the **latent** or **ectopic pacemakers automaticity** which take over the heart command.
- **Classification:**
  - i) **PASSIVE** escape rhythm
  - ii) **ACTIVE** escape rhythm

i) PASSIVE escape rhythm

- **Definition** – manifestation of the **NORMAL automaticity** of the ***latent*** **pacemakers**
- **Pathogenesis** – *the decrease/abolishment of the SA node automaticity and/or the blockage of the impulse transmission from the SA node to the atria* (sinoatrial block) will allow the *escape from the SA node control* of the latent pacemakers, which will ***passively*** take over the command of the heart.
- **Origin** of the rhythm:
  - *AV node – junctional* passive escape rhythm with a heart rate of 40-60/min
  - *His-Purkinje system – idioventricular* passive escape rhythm with heart rate of 30-40/min

ii) ACTIVE escape rhythm

- **Definition** – manifestation of an **INCREASED automaticity of the *latent* pacemakers** *or an* **ABNORMAL automaticity of the *ectopic* pacemakers**
- **Pathogenesis** – the exceeding of the normal SA node automaticity by the automaticity of a latent/ectopic pacemaker which ***actively*** takes over the command of the heart
- **Origin** of the rhythm:
  - ***latent pacemakers*** – the AV node with the occurrence of *junctional tachycardia (accelerated junctional rhythm)* or the His-Purkinje system with the installation of *idioventricular tachycardia (accelerated idioventricular rhythm)*
  - ***ectopic pacemakers*** – partially depolarized working muscle cells, where abnormal automaticity are responsible for *multifocal atrial tachycardia* and *certain forms of ventricular tachycardia*.

b) TRIGGERED ACTIVITY

- **Definition –** the term define **abnormal depolarizations in the form of early or late depolarization afterpotentials,** with 3 characteristics:
  - ✓ occur at the level of **partially depolarized cells of the atrial or ventricular working muscles and of the His-Purkinje system**
  - ✓ consist of **transient oscillations of the membrane potential** that do NOT occur spontaneously but are **dependent on a previous action potential (AP) ("triggered")**
  - ✓ are responsible for the occurence of **premature contractions** (single response) or **tachyarrhythmias (repetitive responses)**
- **Consequences** – triggered activity represent the pathomechanism of *isolated premature contractions*, *runs of premature contractions, atrial and ventricular tachycardia*

i) EARLY afterdepolarization (EAD)

- **Definition – transient oscillations of the membrane potential** occurring at the **end of phase 2 (plateau)** or during **phase 3 (rapid repolarization) of the action potential (AP)**
- **Pathogenesis:**
  - occurs on **BRADYCARDIC rhythms** and in conditions associated with rhe **PROLONGATION** of the **AP DURATION** (QT interval prolongation on ECG)
  - the normal repolarization is interrupted due to the **reactivation of a depolarizing influx of positive charges** (Ca^{2+} in phase 2 or Na^{+} in phase 3 of the AP), which will trigger a single or a repetitive response (Fig.7.1 up)
- **Examples of arrhythmias** – *a type of polymorphic ventricular tachycardia* called ***torsade de pointes,*** associated with prolonged QT interval

ii) DELAYED afterdepolarization (DAD)

- **Definition – transient oscillations of the membrane potential during phase 4 of the action potential** (i.e., at the end of normal repolarization)
- **Pathogenesis:**
  - occurs in conditions associated with **CALCIUM OVERLOAD of cardiomyocytes** due to**:**
    - ✓ the spontaneous release of Ca^{2+} from the sarcoplasmic reticulum and/or
    - ✓ the decrease in reuptake of Ca^{2+} ions by SERCA during the diastole
  - relies upon the **activation of the $3Na^{+}/1Ca^{2+}$ exchanger (NCX)** which induces a depolarizing Na^{+} influx (the NCX activation is aimed at providing Ca^{2+} expulsion from the cell), which will the trigger a single or a repetitive response (Fig.7.1 down)
- **Examples of arrhythmias** – tachyarrhythmias induced by:
  - digitalis toxicity (whose mechanism of action consists in the inhibition of the Na^{+}-K^{+} ATP-ase, active in phase 4 of the AP)
  - excess of catecholamines
  - hypercalcemia

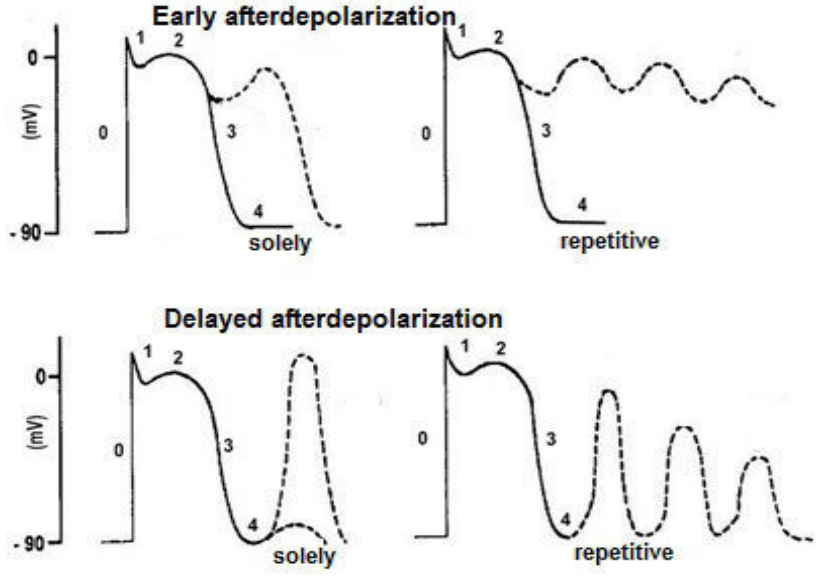

Figure 7.1. Triggered activity: **early** (top) and **delayed** (bottom) **afterdepolarizations.**

2. Impairment of IMPULSE CONDUCTION

a) DECREMENTAL conduction

- **Definition** – progressive decrease in the conduction velocity, the amplitude of action potential and the extent of impulse spread until the propagation fails.
- **Localisation** – may be present at the level of the**:**
  - ***AV junction*** – due to increased vagal stimulation (vagal hypertonia accentuates the physiological block)
  - ***Purkinje network*** –due to a slow response in the setting of myocardial ischemia/hypoxia
  - ***"working" myocardium*** – due to a slow response in the setting of ischemia/hypoxia or in a post-infarction fibrotic area

b) REENTRY

- **Definition – self-sustaining abnormal cardiac rhytm,** which involves **the repetitive conduction of an ectopic impulse within a reentry circuit** with the generation of **circular propagation impulse waves** responsible for the **repetitive depolarization** of a myocardial area
  It is **the most frequent mechanism of abnormal impulse conduction.**

- **Pathogenesis:**
  The continuous movement of an ectopic impulse in a closed-loop circuit of reentry requires **3 conditions** (Fig. 7.3):
  ① **The existence of a reentry circuit** that comprises **two pathways**, slow and rapid, with *different conduction velocities* and *refractory periods*, united through a common proximal part and a common distal part, to form a loop:
  - *a slow pathway* – with reduced conduction velocity and short refractory period
  - *a fast pathway* – with high conduction velocity and long refractory period

  ② **The existence of a unidirectional block**
  ③ **The existence of an 'excitation gap'** – an area of excitable myocardium that exists between the head of the reentrant wavefront and the tail of the preceding wavefront, which allows the reentrant wavefront to continue propagation around the circuit.

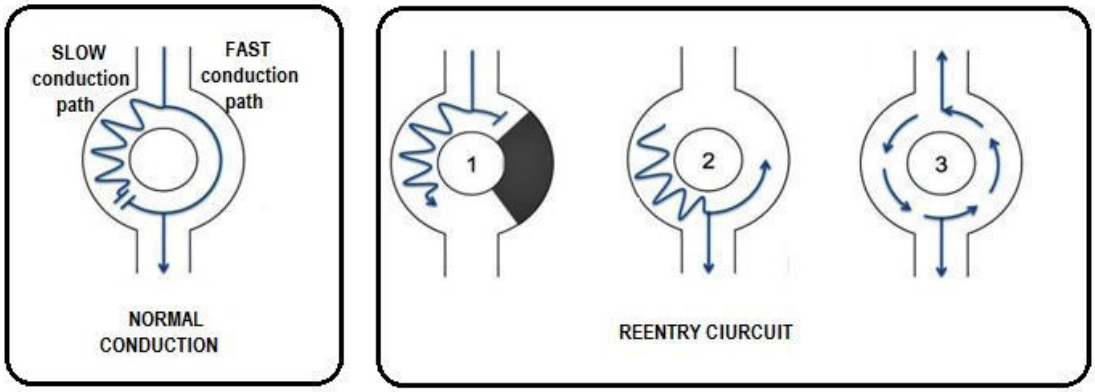

Figure 7.3. Schematic representation of a **reentry circuit**.

The reentry circuit – description (Fig. 7.3):

– a normal impulse (originating from the sinus node) arriving at the common proximal pathway goes down both (slow and rapid) paths. Because of slow conduction (in the left path) the tissue in the distal common pathway will be depolarized via the path with rapid conduction and a normal sinus beat results (normal conduction)

– an ectopic impulse (i.e., a premature beat) which enters the common proximal pathway finds the rapid pathway in the refractory period and is **blocked** - **unidirectional block**, being **conducted only through the slow pathway**, which is in the excitable period (1)

– when the impulse reaches the distal common pathway it will be conducted both **anterogradely** as well as **retrogradely** via the rapid pathway which has just come out of the refractory period (2)

– upon arriving in the proximal portion again, the impulse resumes the slow pathway, which is in the excitable period, resulting in a *circular impulse propagation wave* that stimulates the myocardium at a high rate (3)

- **TYPES of reentry:**
  - **a) According to the LENGTH of the reentry circuit:**
    - **Microcircuits** of **reentry** – located in the AV node, His-Purkinje system, atrial or ventricular working muscle
    - **Macrocircuits** of **reentry** – involve the presence of an accessory pathway with rapid conduction that connects the atrium to the ventricle (e.g., the Kent fascicle in WPW syndrome)
  - **b) According to the SUBSTRATE of the reentry circuit:**
    - ***Anatomical*** **reentry** – occurs in the presence of an:

    = *area of fibrosis post-infarction* (at its border conduction is slower as compared to the normal myocardium); the inexcitable anatomical obstacle surrounded by a circular pathway in which the wavefront can reenter will create a fixed and stable reentrant circuit

    = *atrio-ventricular accessory pathway* (with faster conduction as compared to the AV node)
    - ***Functional*** **reentry** – is due to the heterogeneities in the electrophysiologic properties of the involved tissue (area with different conduction velocities and refractory periods)
- **Examples of arrhythmias** – most tachyarrhythmias with sudden onset and high heart rate: *paroxystic atrial and ventricular tachycardias, atrial and ventricular flutter and fibrillation*

TYPES OF CARDIAC ARRHYTHMIAS:

- **Definition** – pathological situations in which the heart **is not in a sinus rhythm**
- **Classification of arrhythmias according to the SITE OF ORIGIN**:

I. Sinus arrhythmias

II. Supraventricular arrhythmias:

- ✓ Atrial arrhythmias
- ✓ Junctional arrhythmias

III. Ventricular arrhythmias

I. SINUS ARRHYTHMIAS

1. SINUS tachycardia

- **Definition** – the increased automaticity of the SA node which will discharge impulses at a ***rate higher than 100 b/minute****,* unrelated to the level of physical or emotional stress or disproportionate to it.
- **Causes:**
  - **Extrinsic –** the physiological response to conditions that may be:
    - ✓ Acute: physical exertion, emotions, pain, fever, infections, acute heart failure, acute pulmonary embolism, hypovolemia
    - ✓ Chronic: pregnancy, anemia, hyperthyroidism
  - **Intrinsic:**
    - intrinsic dysfunction of the SA node (very rare)

2. SINUS bradycardia

- **Definition** – the decreased automaticity of the SA node which will will discharge impulses at a ***rate lower than 60 b/minute*** (or below 50 b/min during the night)
- **Causes:**
  - ✓ **Extrinsic:**
    - hypothermia, hypothyroidism, cholestatic jaundice, intracranial hypertension
    - treatment with beta-blockers, digitalis, antiarrhythmic drugs
  - ✓ **Intrinsic:**
    - acute ischemia and infarction of the sinus node (complication of AMI)
    - chronic degenerative changes, e.g., sinus node fibrosis (sick sinus syndrome) or diffuse atrial fibrosis

3. SINUS NODE dysfunction or SICK SINUS SYNDROME

- **Definition** – **intrinsic SA node dysfunction,** which frequently occurs in **aged patients** due to **atrial and excito-conduction system fibrosis** and presents various ECG changes that can successively manifest in the same patient: *persistent sinus bradycardia, sinus pause, sinoatrial block, bradycardia-tachycardia syndrome, supraventricular tachycardia*
- **Consequence** – an increased susceptibility to supraventricular arrhythmias via a reentry mechanism (fibrillation and flutter)

II. SUPRAVENTRICULAR arrhythmias

1. Premature ATRIAL contraction (PAC)

- **Definition** – **premature atrial depolarization** produced by a stimulus generated by an **ectopic site** situated in the atrial myocardium
- **Pathomechanism** – **abnormal automaticity** *or* a **isolated delayed afterdepolarization** within the atrial myocardium

2. Premature JUNCTIONAL contraction (PJC)

- **Definition** – **premature heart depolarization** produced by a stimulus generated by an **ectopic junctional site**
- **Pathomechanism** – **increased automaticity** of the **AV node**
- **The site of the ectopic pacemaker** – induces on the ECG the **relationship between** the **QRS complex** and the **ectopic P' wave** which is **inverted** in most leads because the atria will be retrogradely activated:
  - *supranodal site* (in the upper part of the AV node) – the ectopic P' wave **precedes** the QRS complex and the PR interval is < 0,12 s
  - *central nodal site* (in the central part of the AV node) – the ectopic P' wave **coincides** with the QRS complex (is masked by the QRS complex)
  - *infranodal site* (in the lower part of the AV node) – the ectopic P' wave **follows** the QRS complex

3. SUPRAVENTRICULAR tachycardia

- **Definition** – a succession of at least **6 atrial or junctional premature contractions** originating above the bundle of His and usually characterized on the ECG by **thin (normal) QRS complexes**
- **Classification**:
  - *paroxysmal* supraventricular tachycardia - sudden onset and ending
  - *non-paroxysmal* supraventricular tachycardia – gradual onset and ending

a) PAROXYSMAL supraventricular tachycardia (PSVT)

- **Definition** – at least **6 successive atrial** or **junctional premature contractions,** with **regular heart rate** of **150-250 b/min**
- **Pathomechanism** – **reentry:** i) at the level of the AV node, ii) via an aberrant atrio-ventricular pathway or iii) due to electrical inhomogeneities within the atrial myocardium.
- **Types:**

  1. Atrioventricular Nodal Reentry Tachycardia (AVNRT) – occurs in young patients **without structural heart disease** and is the most common cause of **palpitations in the normal heart, especially in women**:
  - it involves a **microreentry circuit** localized in the **AV node** - the nodo-Hisian region is longitudinally dissociated into 2 conduction paths with different velocities and refractory periods responsible for the appearance of an intranodal reentry loop (with a tendency to self-perpetuate and continuously depolarize the atria and ventricles)
  - the attack of paroxysmal tachycardia is **triggered by a PAC** which usually finds the rapid pathway in the refractory period and the slow pathway in the excitable period
  - the attack of paroxysmal tachycardia **can be suppressed** by **vagal maneuvers**

  2. Atrioventricular Reentrant Tachycardia (AVRT) – occurs in young patients **without structural heart disease in association with cardiac abnormalities**:
  - it involves an **anatomical macroreentry circuit** caused by the presence of an **aberrant atrio-ventricular pathway** (e.g., Kent bundle) with a faster conduction as compared to the AV node
  - the attack of paroxysmal tachycardia can be **triggered by a PAC** but also by a **premature ventricular contraction**

- the ectopic impulse can be conducted in an **orthodromic way** (anterogradely through the normal pathway and retrogradely through the accessory pathway ⇒ tachycardia with *thin* QRS complexes) as well as in an **antidromic way** (anterogradely through the accessory pathway and retrogradely through the normal pathway ⇒ tachycardia with *wide* QRS complexes)
- the attack of paroxysmal tachycardia **can be suppressed** by **vagal maneuvers**

3. Tachycardia due to ATRIAL reentry – occurs in patients **with structural heart disease (after interventions for congenital heart disease) or is idiopathic**:
- it involves a **microreentry functional circuit** located **around the SA node** and in other **atrial areas** due to the inhomogeneity of the refractory periods of the atrial working muscle cells
- the attack of paroxysmal tachycardia ***DOES NOT RESPOND*** **to vagal maneuvers**

b) NON-PAROXYSMAL supraventricular tachycardia (rare)
- **Definition** – at least **6 successive atrial** or **junctional premature contractions,** with **regular heart rate**, with **gradual onset and end**
- **Pathomechanisms**:
  - **abnormal atrial automaticity -** the appearance of *multiple ectopic foci* is responsible for **multifocal atrial tachycardia** frequently characterized by a progressive increase ("warm-up"), respectively decrease ("cool-down") of the atrial rate; it occurs frequently in patients with severe/decompensated COPD
  - **an active escape rhythm within the AV node** – the *increase of the jonctional pacemaker automaticity* is responsible for **junctional tachycardia** or **accelerated junctional rhythm**
  - the vagal maneuvers can increase the atrio-ventricular block **but DO NOT suppress** the **tachycardia**

4. Atrial FLUTTER
- **Definition** – an arrhythmia with **REGULAR atrial rate** between **250 and 350 b/min** (most frequently, being 4 times more common in men)
- **Pathomechanism** – **single anatomical *macro*reentry circuit**, typically located in the **right atrium**, around the tricuspid valve anulus
- **Causes:**
  - ✓ **Cardiac**: coronary artery disease, cardiomyopathies, mitral valvulopathies
  - ✓ **Extracardiac**: COPD, pneumothorax, hyperthyroidism
- **Characteristics:**
  - **ECG: P waves are absent** and replaced by the **"F"** waves, with "sawtooth" pattern, best visualized in the **limb leads II, III, and aVF**
  - frequently, there is an **atrio-ventricular (A-V) block** with 2/1, 3/1, 4/1 conduction ratio, which is responsible for a **regular ventricular rate** that reflects a fixed mathematical relation between the flutter waves and the resulting QRS complexes.
  - **sympathetic stimulation** (physical effort) *will decrease the A-V block degree* and the ventricular rate will **increase**

– **vagal maneuvers** (carotid sinus massage, Valsalva maneuver) *will increase the A-V block degree* and the ventricular rate will **decrease**

5. Atrial FIBRILLATION (AF)

- **Definition** – an arrhythmia with **IRREGULAR atrial rate** between **300 and 600 b/min**
- **Characteristics:**

  - is the **most common arrhythmia in clinical practice** in elderly patients (> 65 years, being 1.5 times more common in men), but also occurs in young people, especially in its paroxysmal form

  - is the **most common cause of systemic and cerebral emboli, especially in the elderly**, being favored by **atrial dilation and stasis**
- **Causes:**
  - ✓ **Cardiac**: **hypertension, heart failure** (congestive), mitral valvulopathies, cardiomyopathies, coronary artery disease, cardiac surgery (all factors that cause: increased atrial mass/pressure, atrial inflammation/infiltration or atrial fibrosis)
  - ✓ **Extracardiac**: **hyperthyroidism** (AF may be the solely disease manifestation, thyroid function testing being mandatory), obesity, diabetes, COPD, pneumothorax
- **Pathomechanism - <u>multiple functional</u> *micro*reentry circuits in the atrial working muscle** with **total disorganization of** the **atrial electrical activity**
- **Clinical classification** – atrial fibrillation can be:
  - ✓ **newly diagnosed** - regardless of the duration or severity of the symptoms
  - ✓ **paroxysmal** - converted spontaneously or with medication to sinus rhythm in no more than 7 days
  - ✓ **persistent** – continuous, duration > 7 days and requires electrical cardioversion
  - ✓ **long-standing persistent** – continuous, duration > 1 year
  - ✓ **permanent** - continuous, with the joint decision of the patient and the doctor to abandon attempts at reconversion (through medication or electrically) to sinus rhythm. The persistent/permanent forms will determine *structural changes: fibrosis and atrial remodeling,* which create the anatomical substrate for the perpetuation of arrhythmia ("atrial fibrillation begets atrial fibrillation").
- **Characteristics:**
  - **ECG: P waves are absent** and replaced by the **"f"** waves, which are irregular undulations of the isoelectric line between the QRS complexes, visible in leads **V_1** and **V_2**
  - there is a *functional, low degree non-systematised atrio-ventricular block*, which induces:
    - ✓ **irregular QRS complexes,** with **an irregular ventricular** rate of **120–180 b/min** (ventricular tachyarrhythmia) that diminishes after therapy administration
    - ✓ **„pulse deficit"**, defined as the difference in the *central* pulse and the *peripheral* pulse (determined by the simultaneous auscultation at the heart apex and palpation at the radial artery), with **the pulse rate being lower than the heart rate** (the ventricular contractions preceded by very short diastoles with insufficient ventricular filling are perceived stetacoustically, but will not result in a peripheral pulse wave)
  - from **mechanical point of view,** the atrial contraction is **hemodynamically ineffective:**
    - ✓ cardiac output might decrease by 25-30% due to the loss of the atrial pump, therefore AF is a **precipitating factor of heart failure decompensation**

- ✓ blood stasis within the atria favors coagulation and the occurrence of mural thrombi, increasing the **risk for pulmonary or cerebral embolism/stroke**, therefore long-term anticoagulant therapy is mandatory

III. VENTRICULAR arrhythmias

1. Premature VENTRICULAR contractions (PVC)

- **Definition** – **premature ventricular depolarization** produced by a stimulus generated by an **ectopic site** located within the ventricular myocardium
- **Pathomechanisms** – **abnormal automaticity** or **a single delayed afterdepolarization** within the ventricular myocardium, which induces an asynchrony in the ventricles activation (the ventricle which contains the ectopic site is activated first, followed by the other ventricle)
- **Classification:**
  - *according to the rate and the relationship with the previous beats* – isolated, frequent PVCs (> 10/hour) or systematised PVCs (bigeminy, trigeminy, quadrigeminy)
  - *according to the morphology* (the number of ectopic sites) – unifocal (monomorphic) or multifocal (polymorphic) PVCs
  - *according to the significance* – benign PVCs (isolated, in a healthy heart), potentially malignant PVCs (frequent, polymorphic, early with R-on-T phenomenon, systematised) or malignant PVCs (which initiate ventricular tachycardia or fibrillation with the risk for sudden cardiac death, e.g. in patients with cardiac failure)

2. VENTRICULAR tachycardia (VT)

- **Definition** – **a regular succession of at least 3 PVCs with the rate of 120-220 b/min**
- **Causes** – VT appears in the presence of the**:**
  - areas of pathological myocardium characterized by: ischemia, fibrosis, hypertrophy, dysplasia: e.g, post-infarction scar, cardiomyopathies, mitral valve prolapse, arrhythmogenic right ventricular dysplasia
  - *electrolyte* imbalances: hypokalemia, hypocalcemia
- **Pathomechanisms:**
  - **abnormal automaticity - ectopic foci** within the ventricular myocardium
  - **triggered activity - EAD** which causes PVC with R/T phenomenon and triggers VT
  - **reentry microcircuits:**
    - → **anatomical reentry**, with a *stable* reentry circuit responsible for sustained **monomorphic tachycardia** or
    - → **functional reentry**, with an *unstable* reentry circuit which can be divided into 2-3 other microcircuits that change their direction causing "spiral" reentry, being responsible for sustained **polymorphic tachycardias**, including **torsade de pointes**
- **Classification:**
  - *according to the onset* – paroxysmal VT (HR > 100 b/min) and non-paroxysmal VT or accelerated idioventricular rhythm (HR of 60-100 b/min)
  - *according to the persistence* – sustained (> 30 s) and non-sustained (< 30 s) VT
  - *according to the morphology* – monomorphic and polymorphic VT

- **"Torsade de pointes"** – a particular form of **polymorphic ventricular tachycardia**, frequently associated with **prolonged QT interval**
  - **Pathomechanism** – is triggered by an **EAD** and sustained through **functional reentry**
  - **ECG: aberrant QRS complexes** that gradual change in the amplitude and "twist" around the isoelectric line (similar to the 'torsade de pointes' movement in ballet)
  - the attack usually terminates spontaneously but frequently recurs and may degenerate into ventricular fibrillation

3. VENTRICULAR FLUTTER and FIBRILLATION

- **Definition** – life-threatening or malignant tachyarrhythmias with **ventricular rate** between **130-300 b/min**
- **Pathomechanism** – **multiple reentry microcircuits** in the ventricular musculature which leads to a **disorganized, chaotic ventricular electrical activity**
- **Characteristics:**
  - **ECG**: the disappearance of the QRS complexes which are replaced by:
    = regular waves with a ***constant*** *high rate* – giving a pattern of continuous sine wave in **ventricular flutter**
    = irregular waves with ***variable*** *high rate* in **ventricular fibrillation**
  - the **mechanical ventricular activity** is completely disorganized*:*
    - ✓ ventricular contractions are **hemodynamically ineffective**
    - ✓ **cardiac arrest** occur in the absence of therapy (and should be distinguished from ***asystole*** when the heart mechanical activity is missing due to the absence of electrical activity, and the ECG has the aspect of an isoelectrical line)
  - **ventricular fibrillation** is the **most frequent cause of sudden cardiac death.**

CONDUCTION DISORDERS – CARDIAC BLOCKS

A. ATRIO-VENTRICULAR (A-V) blocks

- **Definition** – represent a **delay or interruption of the conduction of impulses from the atria to the ventricles**.
- **Causes** – conduction blocks are classified as either first-degree, second-degree (with 2 types) and third-degree blocks and occur in:
  - young individuals with a high vagal tone or well-trained athletes, in the absence of structural heart disease - first-degree and second-degree type I A-V blocks
  - patients with structural heart disease: chronic idiopathic fibrosis/sclerosis of the conduction system (Lenegre and Lev diseases – 50% of cases), myocardial infarction, myocarditis, valvular diseases, cardiomyopathies, congenital heart diseases, post-cardiac surgery, medication toxicity (beta-blockers, digoxin, calcium channel blockers, amiodarone), hyperkalemia - second-degree type II and third-degree A-V blocks

1. FIRST DEGREE A-V block

- **Definition** – the **delay,** *without interruption*, in the impulse conduction from atria to ventricles, i.e. abnormally slow conduction through the A-V node

- **ECG: <u>constant</u> prolongation of PR interval** > 0.20 sec

2. SECOND DEGREE (INCOMPLETE) A-V block

- **Definition** – the **intermittent blockage** of the atrio-ventricular conduction
- **Classification:**

a) Mobitz type I (**Wenckebach**)

ECG:

- – **<u>progressive</u> prolongation of PR interval** with each beat until the atrial impulse is not conducted, i.e. a P wave is blocked and the corresponding QRS complex is dropped (Wenckebach phenomenon)
- – the A-V nodal conduction resumes with the next beat and the sequence is repeated
- – the ECG interval between two blocked P waves is called the *Wenckebach period*

b) Mobitz type II

- **ECG:**
  - – *intermittent* and *systematic* blockage of the atrio-ventricular conduction
  - – the P waves are blocked and QRS complexes dropped usually in a repeating cycle of 3:1 or 4:1 block; in the high-grade 2:1 block, every 2nd P wave is blocked
  - – the PR interval of the conducted P waves is normal and constant
  - – Mobitz type II A-V block can be associated with severe bradycardia and hemodynamic instability and has a higher rate of progression towards the third-degree (complete) heart block or asystole, therefore patients require a permanent pacemaker

3. THIRD DEGREE (COMPLETE) A-V block

- **Characteristics:**
  - – the **complete block** of the atrio-ventricular conduction
  - – the atrial activity **does not correlate** with the ventricular one, hence **atrio-ventricular dissociation** occur, i.e., there are two independent rhythms occurring simultaneously
  - – the ventricles are controlled by a **passive escape rhythm, either junctional or ventricular, always** with a **regular and slower rate than the atrial one**
  - – the complete A-V block can induce the **Adam-Stokes syncope** - the sudden loss of consciousness caused by the cerebral ischemia, which may appear in the time interval between the onset of the block and the occurrence of the escape rhythm
- **ECG:**
  - – P waves are not related to the QRS complexes and P wave rate is always higher than the QRS rate
  - – in the presence of a junctional escape rhythm, the resulting QRS complexes will be narrow and occur at the intrinsic rate of the AV node (40 to 55 b/min)
  - – in the presence of a ventricular escape rhythm, the QRS complexes will be wide and at the intrinsic rate of the ventricular pacemaker (20 to 40 b/min)
  - – patients with complete heart block are at a greater risk of developing asystole, ventricular tachycardia, and sudden cardiac death; insertion of a permanent pacemaker is required.

B. INTRAVENTRICULAR blocks

The His bundle divides in the interventricular septum into the **right** and **left bundle branches;** the left bundle branch is further divided into the **anterior** and **posterior fascicles**.

1. RIGHT BUNDLE BRANCH block (RBBB)

- **Definition** – **intraventricular conduction blockage** of the **right branch of the His bundle**
- **Pathomechanism** – when the right bundle branch is interrupted, electrical stimuli from the A-V node conducts to the bundle of His and down the left bundle branch. The left ventricle depolarizes first while the right ventricle is depolarized afterwards, by proceeding from the left ventricle slowly through the musculature. Activation of the right ventricle is so much delayed that it follows the left ventricle activation (according to an abnormal QRS vector directed to the right ventricle that gives the R' wave in V_1 and the deep S wave in V_6).
- **ECG: typical changes in the PRECORDIAL leads:**
  - wide QRS complexes > 0,12 s
  - "rSR'" pattern or double-R ("M") QRS pattern in leads V_1 and V_2
  - broad terminal S-wave in leads V_5 and V_6
  - the opposition of the terminal phase of repolarization, i.e., ST segment and T wave discordant to the terminal QRS vector, with:
    = ST depression and inverted T waves in the right precordial leads V_1 and V_2
    = ST elevation and and upright T waves in the left precordial leads V_5 and V_6

2. LEFT BUNDLE BRANCH block (LBBB)

- **Definition** – **intraventricular conduction blockage** of the **left branch of the His bundle**, before its bifurcation into the anterior and posterior fascicles
- **Pathomechanism** – the activation of the right ventricle is normal and the activation of the left ventricle follows via the musculature and is delayed (according to a vector that makes a slower and larger loop to the left and is seen as a broad, tall R-wave in leads V_5,V_6, I, aVL).
- **ECG: typical changes in the PRECORDIAL leads:**
  - wide QRS complexes > 0,12 sec
  - "M" pattern or "rSR'" pattern in leads V_5, V_6, I and aVL
  - wide and deep S wave or QS pattern in leads V_1 and V_2
  - the opposition of the terminal phase with:
    = ST depression and negative T wave in leads V_5, V_6, I and aVL
    = ST elevation and and upright T waves in leads V_1 and V_2

3. FASCICULAR blocks or HEMIBLOCKS

- **Definition** – intraventricular conduction blockage over one of the two fascicles of the left bundle branch
- **Pathomechanism** – activation of the left ventricle will be activated simultaneously with the right one, but according to another sequence than the normal one
- **ECG: typical changes in the LIMB leads:**
  a) Left anterior hemiblock = blockage of the anterior fascicle of the left bundle branch
  - narrow QRS complex < 0,12 sec
  - qR complexes in lead I and rS complexes in lead III or „divergent image"
  - left axis deviation $\geq -35^{\circ}$

b) Left posterior hemiblock = blockage of the posterior fascicle of the left bundle branch
- narrow QRS complexes < 0,12 sec
- rS complexes in lead I and qR complexes in lead III or „convergent image"
- right axis deviation ≥ + 110°

C. PREEXCITATION SYNDROMES

DEFINITION: a broad term that defines congenital anomalies characterized by **the presence of additional or accessory, abnormal pathways in the heart** (in addition to the normal pathway), **which conduct atrial impulses to the ventricles faster than the normal conductive system (A-V node),** resulting in the early activation of the ventricles, i.e., **preexcitation**

TYPES of accssesory pathways:

The following accessory pathways have been described so far:
- ✓ **Atrio-ventricular** (connects atria with ventricles at the level of the free ventricular wall or the septum) – the **bundle of Kent** responsible for **Wolf-Parkinson-White (WPW) preexcitation syndrome**
- ✓ **Atrio-nodal or atrio-fascicular – bundle of James** (connects atria with the A-V node or with the His bundle) or just accelerated conduction at the level of the A-V node responsible for the **Lown-Ganong-Levine (LGL) preexcitation syndrome**
- ✓ **Fasciculo-ventricular or nodo-ventricular – Mahaim fibers** (accessory connections taking off from the His bundle and fascicles to the right ventricle = fasciculoventricular fibers or from the A-V node to the right ventricle = nodoventricular fibers)

<u>Wolf-Parkinson-White (WPW) syndrome</u>
- **Definition: the most common preexcitation syndrome** where the ventricular preexcitation occurs through the **atrio-ventricular by-pass tract or the Kent bundle** – an accessory pathway which connects the **atrium** to the **ventricle,** by-passing the A-V node
- **ECG changes**:
  - ✓ PR interval < 0,12 sec – shorter atrio-ventricular conduction time via the accessory pathway
  - ✓ delta ("Δ") wave – slurring, slow initial component of the QRS complex which occurs due to ventricular preexcitation
  - ✓ wide QRS complex > 0,10 sec – due to the asynchrony of ventricular activation
  - ✓ discordant ST-segment and T-wave changes (i.e. in the opposite direction to the major component of the QRS complex – due to the *secondary* alteration of the ventricular repolarization sequence
  - the WPW syndrome is **frequently complicated** by:
    - ✓ ***paroxysmal supraventricular tachycardia*** via an anatomical macroreentry circuit triggered by an atrial or ventricular premature beat
    - ✓ ***atrial fibrillation with rapid ventricular rhythm***

8. PATHOPHYSIOLOGY OF VALVULOPATHIES, CARDIOMYOPATHIES AND MYOCARDITIS

VALVULOPATHIES

A. MITRAL STENOSIS

- **Definition:** valvulopathy characterized by the **narrowing of the mitral orifice with *incomplete diastolic opening*** (i.e., the occurence of an obstacle in the flow of blood from the left atrium into the left ventricle during diastole).
- **Etiology:**

– **rheumatic heart disease – major cause**
Mitral stenosis occurs as sequelae of a pharyngeal infection with the group A beta-hemolytic streptococci, more common in **females**. Rheumatic heart disease is the consequence of valvular damage caused by an abnormal immune response elicited by multiple episodes of acute rheumatic fever (disease onset usually between the third and fourth decades of life). Molecular mimicry accounts for manifestations of carditis: valvular disease, myocarditis or pericarditis. The chronic humoral – type II and cellular – type IV (Th1 and T17 mediated) hypersensitivity reactions together with immune-mediated chronic inflammation affect the left-sided cardiac valves (most frequent, mitral valve) with: i) fibrosis/thickening/calcification of the cusps, ii) fusion of the commissures, iii) thickening/shortening of the tendinous chordaes, responsible for the progressive reduction of the valve orifice (stenosis).

– degenerative – calcification of the mitral leaflets and annulus (e.g., in the elderly and patients with advanced chronic kidney disease - rare)

– congenital heart disease

- **Pathogenesis** – the reduction of the mitral orifice by > **50%** (normal area = 4 - 6 cm^2) has the following hemodynamic consequences :
  - **increased left atrial pressure** (to ensure normal ventricular filling), **hypertrophy and then, dilation of the left atrium**. The increase in left atrial pressure causes:
    – stasis (congestion) in the venous pulmonary circulation with increased pulmonary venous pressure and risk of **acute pulmonary edema**
    – reflex pulmonary arterioloconstriction with increased pulmonary vascular resistance and **pulmonary arterial hypertension,** which induces ***pressure* overload** of the right ventricle that causes **right ventricular hypertrophy** and **right ventricular failure**
  - **decreased cardiac output** – due to decreased (left) ventricular filling
- **Clinical manifestations:**

1. Caused by **blood stasis and dilation of the left atrium:**
   - ✓ **palpitations –** the clinical expression of the premature contractions and of the **most common arrhythmia** being **<u>atrial fibrillation</u>**
   - ✓ **compression on neighboring organs –** dysphonia, dysphagia, left inter-scapulo-vertebral stabbing pain

- ✓ **atrial thrombosis** with risk of **systemic embolism** (favored by atrial fibrillation, advanced age, severe stenosis) most frequently at the level of the cerebral vessels, responsible for *stroke* but also at the peripheral level with *acute ischemia of the limbs*

2. Caused by **retrograde stasis in the pulmonary circulation - dyspnea, orthopnea, cough, hemoptysis, recurrent lung infections**, with:
   - ✓ risk of **acute pulmonary edema**
   - ✓ **pulmonary HT** with right ventricular hypertrophy and then dilation and evolving towards **right heart failure (HF)** and possibly towards secondary tricuspid regurgitation

B. MITRAL INSUFFICIENCY

- **Definition:** valvulopathy characterized by the **regurgitation (return) of blood from the left ventricle into the left atrium during the systole** due to the ***incomplete closure* of the mitral valve.**
- **Etiology:**
  - rheumatic heart disease (M > F)
  - degenerative: i) *calcifications* in the elderly, diabetics and those with chronic kidney disease (CKD) or ii) *myxomatous*, responsible for *mitral valve prolapse* that occurs in men (40-70 years) and has a severe evolution
  - congenital/hereditary: i) *fibro-elastic deficiency*, responsible for *mitral valve prolapse* that occurs in women (20-40 years) and has a good evolution and ii) *Marfan syndrome*
  - functional – left ventricular dilation with mitral valve annulus widening in: *dilated and hypertrophic cardiomyopathy, myocarditis, left HF with post-infarction remodeling*
  - valvular ruptures – *acute* mitral failure, in bacterial endocarditis
- **Pathogenesis** – the hemodynamic consequences depend on the:
  - type of onset: chronic (most) or acute
  - degree of regurgitation
  - left atrium compliance
  - left ventricle contractility

  - ❑ **In ACUTE regurgitation**:
    - the degree of regurgitation is usually **high**, and left atrial compliance is **low**
    - a **marked increase in left atrial pressure** causes **stasis and congestion in the pulmonary circulation** with **acute pulmonary edema**
    - usually left ventricular contractility is normal (Frank-Starling mechanism can compensate for acute volume overload/increased preload) therefore **cardiac output is normal**, rarely decreased
  - ❑ **In CHRONIC regurgitation**:
    - initially the **degree of regurgitation** is not high, but it **increases gradually** in time
    - the compensatory **left atrium hypertrophy and dilation** lead to an increased atrial compliance; in these conditions even a marked regurgitation will not significantly increase the pressure in the left atrium
    - volume overload causes an **eccentric left ventricular hypertrophy**; the dilation of the mitral valve ring increases the degree of regurgitation with **progressive dilation of the left ventricle** *("Mitral regurgitation begets mitral regurgitation")*

– if dilation increases over a certain limit, contractility is altered leading to **left ventricular failure** and the **decrease of cardiac output**

- **Clinical manifestations:**

1. Signs of pulmonary venous congestion:
- **acute** mitral regurgitation causes *dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema*
- **chronic** mitral regurgitation causes *symptoms during physical exercise*

2. Fatigue – occurs due to decreased cardiac output and tissue perfusion

3. Palpitations – are caused by atrial fibrillation induced by left atrial dilation (increased risk of systemic embolism)

C. AORTIC STENOSIS

- **Definition:** valvulopathy characterized by **incomplete opening of the aortic valve during the systole,** with the appearance of an **obstacle in the flow of blood from the left ventricle into the aorta.**
- **Etiology**
  - **degenerative – major cause,** calcifications and ATS in the elderly and patients with CKD, with an increasing prevalence due to the aging of the population
  - rheumatic heart disease
  - congenital – bicuspid aortic valve
- **Pathogenesis:**
  - when the aortic orifice narrows **below 1 cm²** (normally, 2,5 – 4,5 cm^2) significant hemodynamic consequences appear:
    - ✓ the high systolic pressure gradient between the left ventricle and the aorta causes pressure overload of the left ventricle with **concentric hypertrophy**
    - ✓ the thickening of the ventricular walls causes a decreased ventricular compliance with **pulmonary venous congestion/stasis**
  - cardiac output can NOT be increased during **effort** (fainting or angina occur since the functional significance of the obstruction is greater with exercise)
  - in time, **myocardial ischemia** occurs due to the imbalance O_2 supply - O_2 demand
    - ✓ O_2 supply is *low* by shortening of the diastole and the increase in the telediastolic pressure of the left ventricle (secondary to the decrease in ventricular compliance) with compression of the coronary circulation
    - ✓ O_2 demand is *increased* due to the lengthening of the ejection time, the increase in systolic parietal pressure and left ventricular hypertrophy
- **Clinical manifestations:**

1. Myocardial ischemia:
- angina pectoris (50% of patients)
- malignant ventricular tachyarrhythmias
- total atrioventricular block

2. Angina or fainting during effort – through a decrease in CO

3. Syncope – through decrease in cerebral perfusion

4. Signs of pulmonary venous congestion

– the decreased left ventricular compliance leads to increased end-diastolic pressure and pulmonary venous pressure with **the risk of acute pulmonary edema** r

D. AORTIC INSUFFICIENCY

- **Definition:** valvulopathy characterized by the ***incomplete closure*** **of the aortic orifice during the diastole** leading to the regurgitation (return) of the blood from the aorta into the left ventricle.

- **Etiology**:
  – **degenerative** - calcifications, fibrosis in the case of the elderly, possible association with aortic stenosis
  – rheumatic heart disease
  – functional – marked dilation of the aorta
  – other causes: syphilis (luetic aortitis), ankylosing spondylitis, Marfan syndrome
  – valvular ruptures: acute aortic insufficiency in bacterial endocarditis

- **Pathogenesis** – in most cases aortic regurgitation has a chronic evolution:
  – left ventricular volume overload causes an **eccentric hypertrophy** (ventricular compliance is increased, so that the pulmonary stasis/congestive phenomena do not occur initially and the disease is asymptomatic for a long time)
  – **SBP increases** (expulsion of an increased systolic volume) and **DBP decreases** (part of the blood from the aorta regurgitates into the left ventricle) – the differential pressure and pulse pressure increase and **hyperdynamic circulation** occurs
  – in time **left ventricular failure** develops with its retrograde and anterograde consequences (effort dyspnea, orthopnea, nocturnal paroxysmal dyspnea, acute pulmonary edema)

- **Clinical manifestations:**

1. Left ventricular failure retrograde symptoms:

– effort dyspnea, orthopnea, nocturnal paroxysmal dyspnea, acute pulmonary edema

2. Hyperdynamic pulse:

– *Corrigan pulse* – pulsations of the carotid arteries ("arterial dance")
– *De Musset sign* – rhythmic pulsation of the head synchronized with the heart rate
– *Muller sign* – systolic rhythmic pulsation of the uvula
– *Quincke pulse* – capillary pulsations in the nail beds

CARDIOMYOPATHIES (CM)

DEFINITION - heterogeneous group of **myocardial disorders** characterized by **structural and functional abnormalities of the heart muscle,** *in the* ***ABSENCE*** of coronary artery disease, arterial hypertension, valve disease or congenital heart disease capable of producing these lesions.

CLASSIFICATION:

A. **Hypertrophic cardiomyopathy**
B. **Dilated cardiomyopathy**
C. **Restrictive cardiomyopathy**
D. **Arrhythmogenic right ventricular cardiomyopathy**
E. **Unclassified cardiomyopathies (e.g. Takotsubo cardiomyopathy)**

The first 3 entities represent the ***main types of cardiomyopathies encountered in clinical practice***, which are further classified into:

a) **FAMILIAL / PRIMARY (GENETIC) forms,** with known or unknown **genetic defect** - caused by:
   - ***mutations*** of the ***sarcomere*** and ***cytoskeleton*** proteins – most frequent
   - **storage diseases** (e.g., glycogenoses) or **mitochondrial diseases** - rare
b) **NON-FAMILIAL / SECONDARY forms** - of known etiology: ***inflammatory, toxic, metabolic, neuromuscular***

A. HYPERTROPHIC cardiomyopathy (HCM)

- **Definition** – cardiomyopathy characterized by **left ventricular HYPERTROPHY** and **DIASTOLIC dysfunction** *in the absence* of diseases associated to ***CONCENTRIC LV hypertrophy*** (e.g., hypertension, aortic stenosis)
  Previous (old) name of HCM - asymmetric septal hypertrophy
- **Etiology**:
  a) **FAMILIAL form (primary)** – HCM is the **most common form of familial CM** and it is a ***genetically transmitted*** **autosomal dominant cardiovascular disease** that is most frequently caused by **mutations in genes** encoding proteins of the **sarcomere** (β-myosin heavy chain, α-tropomyosin, troponins, actin)
  b) **NON-FAMILIAL form (secondary)** – frequently associated with:
     - **metabolic and endocrine diseases**: obesity, children born to diabetic mothers, acromegaly
     - **infiltrative diseases**: amyloidosis
     - **drugs**: anabolic steroids
     - **athletic heart**

HCM is the **most common cause of sudden death in young athletes.**

Observation: Between 25-30% of HCM cases are idiopathic.

- **Pathogenesis**:
  ① **The CONTRACTILE DEFICIT hypothesis** – **mutations of genes encoding** the **sarcomere proteins** cause the decreased contractility
  The associated **release of trophic factors** is responsible for:
  – **cardiomyocyte HYPERTROPHY** with **abnormal LEFT VENTRICULAR hypertrophy** and **mainly of the interventricular septum** with **ASYMMETRIC SEPTAL HYPERTROPHY**

– **interstitial FIBROSIS** due to an increased synthesis of *collagen* by fibroblasts, with **MYOCARDIAL ARCHITECTURAL DISRUPTION** and the risk of **ventricular arrhythmias**
– **thickening of the medial layer of the small intramural coronary arteries**, with **MYOCARDIAL ISCHEMIA (often silent)** via a triple mechanism:
  ✓ luminal narrowing of the coronary arteries
  ✓ increased external compression of vessels by the hypertrophied ventricular wall
  ✓ decreased capillary density (as compared to the increased ventricular mass)
  all resulting in foci of myocardial necrosis and scarring areas of fibrosis

Observation ! This hypothesis does not explain the occurrence of non-sarcomeric HCM.

② **The ENERGETIC DEFICIT hypothesis** – abnormalities in the **ATP synthesis and transfer** will *decrease the expression and activity of the* Ca^{2+}*-ATPase* (SERCA), which will lower re-uptake of Ca^{2+} in the sarcoplasmic reticulum, with diastolic dysfunction.

- **Functional consequences:**
  1. ***DIASTOLIC left ventricular dysfunction*** due to **decreased ventricular compliance and impaired relaxation**, which causes ***backward stasis in the left atrium*** (and risk of **atrial fibrillation**) and ***in the pulmonary circulation*** with **dyspnea, orthopnea**
  2. ***Dynamic left ventricular outflow tract obstruction*** due to systolic anterior motion of the anterior mitral valve leaflet, which causes **muscle fatigue, risk of effort syncope**, and in time, **functional mitral insufficiency**
  3. ***Chronic myocardial ischemia,*** which causes **chest pain and risk of sudden death** due to **malignant tachyarrhythmias** (the presence of episodes of unsustained ventricular tachycardia on Holter ECG is predictive for sudden cardiac death)

B. DILATED cardiomyopathy (DCM)

- **Definition –** cardiomyopathy characterized by **left ventricular DILATION and SYSTOLIC dysfunction** *in the absence* of diseases associated to ***ECCENTRIC LV hypertrophy*** (e.g., aortic regurgitation) or coronary artery disease.

  Observation: Right ventricular dilation and/or dysfunction may also be present, but their presence is NOT necessary for the diagnosis of DCM.

- **Etiology**:
  a) FAMILIAL form – DCM results from:
  – mutations in the genes encoding several **sarcomere proteins:**
    ✓ contractile proteins (actin, β-myosin heavy chain)
    ✓ regulatory proteins (α-tropomyosin, troponin)
    ✓ Z disk proteins (α-actinin)
  – mutations in the genes encoding the **cytoskeleton proteins** (desmin, dystrophin)
  b) NON-FAMILIAL form – DCM is the **most common clinical form of non-familial secondary cardiomyopathy** of multiple etiologies (Tab.8.1.).

Table 8.1. Causes of non-familial DILATED cardiomyopathy.

Category	Causes
Inflammatory	**Infectious** Viral (eg., Coxsackie virus group B, parvovirus B19, adenovirus) Parasites (eg, Chagas disease)
	Non-infectious Colagenoses Peripartum cardiomyopathy (recurrence risk in subsequent pregnancies) Myocardial infiltrative diseases: amyloidosis, sarcoidosis
Toxic	Chronic alcoholism Chemotherapeutic agents (e.g., doxorubicin)
Metabolic	Hypothyroidism

- **Pathogenesis**:
  - ① **The CONTRACTILE DEFICIT hypothesis** – mutations of genes encoding the ***sarcomere proteins*** cause the decreased contractility with the following consequences:
    - increased **release of trophic factors** (local AII, inflammatory cytokines) that cause **initially limited cardiomyocyte hypertrophy** followed by **a progressive reduction in the number of cardiomyocytes, increased interstitial fibrosis** and **pathological myocardial remodeling**
    - increased **cardiomyocyte apoptosis**
  - ② **The ENERGETIC DEFICIT hypothesis** – impairment of Ca^{2+} homeostasis with decreased expression and activity of SERCA
  - ③ **The AUTOIMMUNE RESPONSE hypothesis**
    - the structural similarity between **viral antigens** and some **myocardial proteins** *or* the **change of myocardial peptides** that become **self-antigenic** under the action of the etiological factor elicite a **chronic AUTO-IMMUNE response**
    - **autoantibodies** against ***myocardial structures*** (e.g., beta-adrenergic receptors, actin, myosin, troponin, SERCA) have been identified in the blood of patients with DCM; whether they are the cause or consequence of the disease remains to be elucidated
- **Functional consequences:**
  1. ***SYSTOLIC left ventricular dysfunction,*** which causes:
     - *decreased ventricular contractility and low cardiac output* with **muscle fatigue**
     - *increased end-diastolic pressure* (preload), which is retrogradely transmitted into the pulmonary circulation causing **dyspnea and orthopnea**
  2. ***DILATION / ENLARGEMENT of left ventricle,*** which in time progresses and leads to ***functional mitral insufficiency*** with two effects: i) mitral valve insufficiency, which further lowers the ejection fraction (and increases the ventricular wall stress) and ii) backward left atrium stasis and dilation with ***the risk of atrial fibrillation.***

C. RESTRICTIVE cardiomyopathy (RCM)

- **Definition** – the less common form of cardiomyopathy characterized by **increased ventricular INFILTRATION** and **DIASTOLIC dysfunction** in a non-dilated ventricle.
  RCM results from abnormal *infiltration* of substances *between* myocytes, increased *storage* of abnormal metabolic products *within* myocytes, or *fibrotic* injury.

- **Etiology**:

a) FAMILIAL form – is induced by:
- Mutations in the genes encoding ***sarcomere proteins*** (eg, troponin I, myosin light chain)
- **Glycogen storage diseases**
- Idiopathic

b) NON-FAMILIAL form:
- **Amyloidosis – the most frequent etiology**
- **Sarcoidosis**
- **Hemochromatosis** (iron storage)
- **Fibrosis** (post-radiation, scleroderma)
- Endocarditis from hypereosinophilic syndrome (Loeffler syndrome)
- Endomyocardial fibrosis

- **Functional consequences:**
  In RCM, both ventricles are **small and stiff** with **DECREASED COMPLIANCE,** which is responsible for:
  1. Increased end-diastolic pressure with anterograde and retrograde consequences at the level of both ventricles:
  - at the level of **left ventricle:**
    - ✓ *forward effect:* inability to increase CO during exertion with **muscle fatigue**
    - ✓ *backward effect*: stasis/congestion in the left atrium and pulmonary circulation with **dyspnea, orthopnea**
  - at the level of **right ventricle:**
    - ✓ *backward effects:* stasis/congestion in the right atrium and systemic circulation with **distension of the jugular veins, hepatomegaly, peripheral edema**

D. ARRHYTHMOGENIC RIGHT VENTRICULAR cardiomyopathy (ARVC)

- **Definition** – a rare cardiomyopathy characterized by:
  i) **segmental or diffuse progressive replacement** of **right** ventricular cardiomyocytes with **fibro-adipose tissue**
  ii) progressive expansion from the **epicardium towards the endocardium** with subsequent *free ventricular wall thinning and right ventricle dilation* and
  iii) in time, the **left** ventricle is also affected (the prevalence is 75%).

- **Etiology**:
  a) FAMILIAL form – caused by mutations in genes encoding proteins of *desmosomes*
  b) NON-FAMILIAL form – in which chronic myocardial inflammation is involved

- **Functional consequences:**
  - the occurrence of patches of myocardial tissue separated by fibro-adipose tissue creates an **anatomical substrate for reentry macro-circuits**, which are responsible for the:
    - ✓ episodes of **unsustained ventricular tachycardia** or frequent premature contractions originating in the right ventricle during 24-hour Holter ECG monitoring
    - ✓ **malignant tachyarrhythmias** and the increased risk for **sudden cardiac death** (on the ECG, epsilon waves appear in V1-V3, which are low-amplitude late potentials occurring at the end of the QRS corresponding to areas of slowed conduction)

    Observation! ARVC is responsible for ~20% of cases of sudden cardiac death in young athletes.
  - **progressive myocardial atrophy** with **regional or global dysfunction of the right ventricle**
  - in time, impairment of the **left ventricle** (**biventricular dysfunction**)

E. UNCLASSIFIED cardiomyopathies

Takotsubo cardiomyopathy (stress cardiomyopathy, apical ballooning syndrome)

- **Definition** – cardiomyopathy characterized by:
  - ✓ **clinical, lab** (pain, biomarkers) **and ECG features** of **acute coronary syndrome**
  - ✓ **acute, reversible SYSTOLIC dysfunction of the left ventricle APEX** and **normal or increased contractility of the left ventricle BASE**

  in the **absence** of **coronary ATS lesions** at coronarography.
- **Etiology** – intense **emotional stress** ("broken heart" syndrome) or **physical stress** associated with intense pain (e.g., surgical intervention)
- **Predisposing factor:**
  - *low estrogen levels* – cardiomyopathy occurs in more than 80% of cases in **postmenopausal women** (estrogens protect myocardium from the cardiotoxic effects of catecholamines excess)
- **Pathogenesis** – 2 hypotheses**:**

  ① **Catecholamine cardiotoxicity hypothesis** – excessive sympatho-adrenergic stimulation during stress causes a **transient contractile dysfunction** which reflects the stimulation of both β1-adrenergic receptors with high density at the *base* of the heart, as well as β2-adrenergic receptors, with high density at the heart *apex*:
  - *β_2-adrenergic receptor stimulation* has a **negative inotropic effect** at the ventricular *apex,* which explains the **LV apical systolic dysfunction**
  - *β_1-adrenergic receptor stimulation* has a **positive inotropic effe**ct at the heart *base*, , which explains the **LV base hypercontractility**

  ② **Catecholamine-induced coronary microcirculation dysfunction hypothesis** – due:
  - impairment of NO release
  - excessive vasoconstriction (α_1-adrenergic receptor stimulation)
  - predominant impairment of myocardium perfusion at the heart apex

- **Functional consequences** – hypo- or akinetic apical ventricular segments and normal kinetics of the basal region, which are reversible (days) with the recovery of cardiac function (4-6 weeks).

MYOCARDITIS

- **Definition** – acute or chronic myocardial dysfunction caused by **inflammation of the myocardium,** in the ***absence*** of coronary disease, HT, valvulopathies or congenital heart diseases. The disease has considered to belong to the phenotype of **dilated cardiomyopathies** (by the European Society of Cardiology).

- **Etiology**:
  ① **Idiopathic** – in ≥ 50% of cases
  ② **Infectious:**
  - **viruses – the main etiology**: *enteroviruses (Coxsackie group B), adenoviruses, parvovirus 19, SARS-CoV2*, *cytomegalovirus, Epstein-Barr virus*
  - bacteria: *group* A *beta-hemolytic streptococcus - myocarditis* from *rheumatic fever*
  - protozoa: *Trypanosoma cruzi – myocarditis* from *Chagas disease* (endemic in South America)
  - spirochetes: *Borrelia burdorferi – Lyme disease carditis*

  ③ **Non-infectious:**
  - **hypersensitivity reactions** induced by:
    - **medication**: e.g., antibiotics, anticonvulsants, antidepressants
    - **vaccines**
    - **diseases associated with hypereosinophilia**: e.g., Loeffler syndrome - *hypereosinophilic myocarditis*
  - **cardiotoxic effects** of: chemotherapy – *anthracycline myocarditis*, drugs (cocaine, amphetamines), alcohol
  - **collagen diseases –** *lupus myocarditis*
  - **physical injuries** caused by: irradiation, hypothermia

- **Pathogenesis:**
  Viral myocarditis (the most common) evolves in **3 stages:**
  1. The first stage (1-4 days) – caused by the **direct cytotoxic effects of the virus** responsible for *necrosis and apoptosis of cardiomyocytes*
  2. The second stage (4-14 days) – caused by the **activation of the immune response against the viral antigens**:
     - **NK lymphocytes** release **perforins** with the cytolysis of infected cells and *worsening of focal myocardial necrosis*
     - **T lymphocytes** and **macrophages** release:
       - **pro-inflammatory cytokines**: TNF-α, IL-1, IL-6 responsible for ***acute inflammation***
       - **growth factors**: FGF, TGF-beta responsible for fibroblast proliferation triggering ***myocardial fibrosis***

3. The third stage (≥ 14 days, which may become chronic) - caused by an **autoimmune-mediated chronic inflammation** by **activated T lymphocytes** against the self antigens released by the damaged cardiomyocytes. These *autoreactive T lymphocytes* and the formation of *autoantibodies,* ex., *anti-cardiac myosin* will perpetuate the myocardial destruction even after virus clearance.
   The complications of this stage are:
   - *Acute:*
     - Acute HF
     - Acute coronary syndrome
     - Severe arrhythmias or sudden cardiac death
   - *Chronic:*
     - Chronic myocarditis with extensive fibrosis
     - Ventricular remodeling with dilative cardiomyopathy

- **Clinical manifestations:**
  - asymptomatic in mild forms
  - symptomatic: suggestive prodromal symptoms for viral infections (fever, sweating, myalgias) that precedes the onset of symptoms by 1-2 weeks:
    - Fatigue, dyspnea – caused by the decrease in CO during acute systolic HF
    - Palpitations – caused by **rhythm/conduction disturbances** due to the excito-conduction system affectation
    - chest discomfort/pain
  - cardiogenic shock in severe forms

- **Evolution:**
  - death in acute fulminant forms (10% of cases)
  - full recovery in weeks-months (50% of cases)
  - chronic complications (40% of cases)
    - ✓ chronic heart failure
    - ✓ dilated cardiomyopathy

9. PATHOPHYSIOLOGY OF PERIPHERAL VASCULAR DISEASES

ARTERIAL DISEASES

- **Definition –** decrease of blood flow in the ***peripheral arteries*** (other than coronary and cerebral arteries which are considered the *central arteries*), as result of certain pathological processes thar occur *isolated* or *in combination* and can be grouped into **3 categories**:
  - **structural alterations of the arterial wall**, either *degenerative* or secondary to *infections or inflammation*, leading to *dilation, aneurysm, dissection or rupture*
  - **narrowing of the arterial lumen** due to *atherosclerosis, thrombosis/embolism, granulomatous chronic inflammation*
  - **vasospasm** - excessive response to vasoconstrictors

A. AORTIC ANEURYSM

- **Definition** – ***abnormal, localised*** dilation of **all the 3 layers of the vascular wall** leading to an increase of the vascular lumen > **50% versus the normal values**
- **Localisation** (according to the frequency):
  - **abdominal aorta** (most frequently) – it may coexist with aneurysms of the *peripheral and cerebral arteries*
  - descending thoracic aorta
  - ascending thoracic aorta (least frequently)
- **Classification:**
  - **FUSIFORM aneurysm** (most frequent) – ***symmetrical*** dilation which involves the *entire* circumference of the aorta
  - **SACCIFORM aneurysm** – ***asymmetrical*** dilation which involves the circumference of the aorta only ***partially***
- **Etiology:**
  1. Atherosclerosis
  2. Cystic necrosis of the aortic media
  3. Infections of the aortic wall
  4. Chronic inflammatory arteritis

1. Atherosclerosis

- **Characteristics:** is the most common cause of aneurysm of the **descending thoracic and abdominal aorta**
- **Classic risk factors of ATS:**
  - ✓ gender (male)
  - ✓ age
  - ✓ HT > 50 years
  - ✓ hyper-/dyslipidemia
  - ✓ smoking

- **Pathogenesis:** the **imbalance between synthesis and degradation of the extracellular matrix proteins** at the level of an **atheromatous plaque,** which **are** responsible for the degradation of the **medial layer** and thus, **decrease the wall resistance to high blood pressure**

  The aneurysm is caused by the association of 2 factors:

  a. GENETIC predisposition
  - involves the polymorphism of genes with role in cellular proliferation and differentiation and is manifested by the **decreased number of vascular smooth muscle cells (VSMC)** that produce the *extracellular matrix* at the level of the atheroma plaque → **decreased extracellular matrix synthesis**

  b. Local LOW-GRADE CHRONIC INFLAMMATION of the AORTIC wall
  - maintained by the **pro-inflammatory effects** of **local angiotensin II**
  - caused by an **infiltrate with inflammatory cells** (mainly macrophages) that **excessively produce matrix metalloproteinases** (e.g., elastases, collagenases) at the level of the atheroma plaque → **increased extracellular matrix degradation**

2. CYSTIC necrosis of the AORTIC MEDIA

- **Characteristics:**
  - is the cause of the **ascending thoracic aorta aneurysm**
  - is frequently associated with **hypertension in the elderly**
  - is frequently associated with **congenital/hereditary diseases in young people**:
    - bicuspid aortic valve
    - genetic defects of the connective tissue - *Marfan syndrome* (fibrillin synthesis defect from the elastin structure), *Ehlers-Danlos syndrome* (procollagen synthesis defect), *Loeys-Dietz syndrome* (TGF-β receptor synthesis defect)
  - consists of: i) degeneration/fragmentation of ***elastic fibers*** and ii) accumulation of ***collagen and mucoid material*** in the **MEDIAL** layer of aorta

3. INFECTIONS of the aortic wall
- Bacterial infections: Salmonella, staphylococcus, streptococcus, b. Koch
- Fungal infections

4. Chronic INFLAMMATORY arteritis
- Takayasu arteritis (granulomatous inflammation of the aorta and its branches)

- **Clinical manifestations:**
  - generally, the aneurysm is *asymptomatic*, being discovered accidentally during a clinical exam or imaging technique
  - *in the abdominal aneurysm* there is a palpable *pulsating abdominal mass*, which is *expansive, painless, localised to the left*

- **Major complications:**
  1. **Intraabdominal haemorrhagic rupture**
  2. **Aortic dissection**
  3. **Compressions on the neighbouring structures:**
     - duodenal (transit disorders)

- nervous (backpain)
- urinary (renal colic)
- inferior vena cava (lower limb edema)

4. **Thrombosis with distal arterial embolism (limbs):**
   - obstruction of a *proximal* artery → acute ischaemia of the limb
   - obstruction of a *distal* artery → „*blue toe*" syndrome

B. Diseases of PERIPHERAL ARTERIES

1. PERIPHERAL ARTERY DISEASE (PAD)

- **Definition** – decreased blood flow caused by **chronic stenosis of LARGE and MEDIUM arteries** of the **lower limbs**: iliac arteries**,** superficial femoral arteries**,** popliteal arteries **and** tibioperoneal arteries
- **Etiology** – **ATHEROSCLEROSIS in 90% of cases** & presence of **classic risk factors**:
  - diabetes
  - smoking
  - hypertension
  - hyper/dyslipidemia
  - obesity
  - increasing age over 50 years (traditionally, a disease affecting men, nowadays the prevalence appears to be equal among senior men and women)
  - family history of PAD, CAD or stroke
- **Pathogenesis** – **O_2 supply/demand mismatch** due to ATS plaques, which narrow the arterial lumen and restricts blood flow to the distal extremity. Temporary ischemia of the muscles manifests as pain, cramping, or fatigue and ultimately makes the patient with PAD to slow down or stop walking.

  ① **INITIALLY** – **TRANSIENT ischemia,** which occurs during **EXERCISE**
  - **Cause** – **partial arterial stenosis** responsible for the **vasodilatory reserve decrease** and *moderate decrease in the muscle blood flow* via the impairment of the local regulatory mechanisms during exercise:
    - **impairment of the ENDOTHELIAL mechanism** with decreased local release of vasodilator factors (e.g, NO, PGI_2) within the *endothelial dysfunction*
    - **impairment of the METABOLIC mechanism** with the decreased/inefficiency of the vasodilator effect due to local release of adenosine from the stressed muscles during exercise
  - **Clinical manifestation:**
    - **INTERMITTENT CLAUDICATION** (equivalent of "to limp") , i.e., pain in the lower extremity muscles brought on by walking and relieved with rest

  ② **In EVOLUTION** – **CRITICAL ischemia,** which occurs at **REST**
  - **Cause** – **subtotal arterial stenosis** responsible for the **vasodilator reserve exhaustion** and *severe decrease in the muscle blood flow*

- **Clinical manifestations:**
  - ischemic rest pain: burning pain in the soles of the feet
  - trophic changes: cool, cyanotic skin, loss of hair

- **Clinical manifestations in relation with PAD stages** (Tab.9.1.)

Table 9.1. Stages of PAD (Leriche and Fontaine classification).

Stage	Signs/Symptoms
I	▪ **Absence of ONE or SEVERAL ARTERIAL PULSES** – Asymptomatic *or* mild effort pain ("silent arteriopathy") – Specific signs: cold feet, cutaneous pallor
II	▪ **EXERTION pain or INTERMITTENT CLAUDICATION** **- stage IIA:** NON-INVALIDANT claudication, pain free walking distance > **200 m** **- stage IIB:** INVALIDANT claudication, pain free walking distance < **200 m**
III	▪ **REST pain, worse in DECUBITUS and/or AT NIGHT.** The intractable pain: i) is due to tissue hypoxia/acidosis and ischemic neuritis, ii) can be, in part, relieved when patients dangle their lower legs over the side of the bed and iii) during exertion it manifests as INVALIDANT claudication.
IV	▪ **REST pain** is associated with **TROPHIC LESIONS:** *ulcerations or even gangrene* due to severe cutaneous hypoxia, tissue acidosis and necrosis.

① The EXERTION pain - INTERMITTENT claudication
- is the ***common EARLY symptom***
- the classic description is **cramping pain** in the muscles of the lower limb, aching, pressure, weakness or leg fatigue, brought on by walking and subsiding at rest
- the pain during walking occurs in the muscle group ***distal to site of stenosis:***
  - ✓ bilateral pain in the buttock and thigh muscles – when the *aortoiliac arteries* are occluded (Leriche syndrome)
  - ✓ pain in the thigh/calf muscles - when the *femoral artery* is occluded
  - ✓ pain in the calf/foot - when the *popliteal artery* or *tibio-peroneal artery* is occluded

② The REST pain
- as the disease progresses, and replaces the intermittent claudication
- occurs at **rest,** is aggravated by clinostatism and relieved by sitting on the edge of the bed/orthostatism, when the blood flow increase due to gravity temporarily diminishes it

③ Decrease/absence of PERIPHERAL PULSE
- is the ***EARLY sign***
- occurs *distal* to the site of stenosis
- is associated with *pallor, cold extremities, murmur in the large arteries displaying stenosis* (abdominal aorta, femoral artery)

④ TROPHIC lesions

a) MINOR lesions
- hair loss
- shiny skin
- deformed nails (striated, matte)

b) MAJOR lesions – **ulcerations and gangrene,** that occur subsequent to *minor trauma:*
- in *diabetics* and *smokers*
- in areas subject to *increased mechanical pressure*, such as the *toes, the lateral malleolus, the heel*
- in areas presenting *superficial cutaneous lesions*

Remember!
Diabetic arteriopathy is the ***most common chronic arterial disease***, with *early* onset, *extended* localisation and *severe skin trophic changes*.

2. VASCULITIC syndromes

- **Definition** – **chronic arterial disorders** characterised by:
  - *narrowing of the arterial lumen* due to thickening of the arterial intima/media ± thrombosis with *CHRONIC ARTERIAL ISCHEMIA*
  - *vasospasm* responsible for *ISCHEMIC ATTACKS*
- **Cause** – **chronic granulomatous inflammation** and **diffuse fibrosis of the arterial walls** occurring during the hypersensitivity reactions (HS) mediated by *immune complexes* (type III HS) or by a *cellular mechanism* (type IV HS)

a) TAKAYASU arteritis

- **Definition** – **SYSTEMIC chronic vasculitis:**
  - commonly located in the **LARGE arteries** (aorta and its branches)
  - mainly affecting ***women*** aged between ***10 – 40 years***
- **Pathogenesis** – narrowing of the arterial lumen by the **thickening of the VASCULAR INTIMA** caused by:
  - chronic inflammatory infiltrate with lymphocytes and macrophages
  - granulomas with multinucleated giant cells (chronic granulomatous inflammation)
  - diffuse fibrosis
- **Clinical manifestations:**
  ① **Systemic** – fever, asthenia, weight loss, nocturnal sweating
  ② **Local:**
  - aortic arch syndrome (affecting the brachiocephalic trunk, carotid and subclavian arteries)
    - prominent and tender carotid artery
    - decreased carotid pulse
    - pulse absent at the level of the radial arteries, but present at the level of the femoral arteries ("reverse coarctation")
  - signs of ischemia accordimg to the affected areas:
    - carotid arteries - cerebrovascular ischaemia
    - coronary arteries - myocardial ischaemia
    - subclavian arteries - intermittent arm claudication
    - renal arteries - secondary renovascular hypertension

b) TEMPORAL arteritis (Horton disease or GIANT-CELL arteritis)

- **Definition: SYSTEMIC chronic vasculitis:**
  - located in the **LARGE-MEDIUM** arteries, mainly involving the ***TEMPORAL artery***
  - more common in ***women over 50 years***

- **Pathogenesis**– narrowing of the **temporal artery** lumen due to:
  ① **INTIMA thickening** – caused by:
  - chronic inflammatory infiltrate with lymphocytes and macrophages
  - granulomas with multinucleated giant cells (chronic granulomatous inflammation)
  - diffuse fibrosis

  ② **MEDIA thickening** – chronic inflammatory infiltration

- **Clinical manifestations:**
  ① **Systemic** – fever, asthenia, weight loss, nocturnal sweating
  ② **Local:**
  - prominent temporal artery, tender at palpation
  - diminished local pulse
  - severe headache

  ③ **Due to the inflammation of other LARGE-MEDIUM arteries:**
  - *mandibular or lingual claudication* (triggered by mastication)
  - *rheumatic polymyalgia:* pain in the scapular and pelvic girdle
  - *ophthalmic complications:* impaired visual acuity, diplopia, risk of blindness

c) Obliterating THROMBOANGIITIS (BUERGER disease)

- **Definition – SEGMENTAL chronic vasculitis:**
  - located in **SMALL-MEDIUM arteries** in the distal segments of the limbs
  - mainly affects **plantar and digital arteries of the limbs**
  - common in ***males under 40***
  - major favoring factor: **SMOKING**

- **Pathogenesis:**
  ① **Smoking:**
  - activates an immune response in patients with a *genetic predisposition* (HLA-A9, HLA-B5)
  - it also may uncover a *coagulation defect*

  ② **The arterial lumen is narrowed** – due to the **pathogenic triad**:
  1. ***Chronic inflammatory reaction*** of the arterial wall
  2. ***Microthrombi*** formation
  3. ***Vasospasm***

- **Clinical manifestations**:
  ① ***DISTAL artery occlusion*** – responsible for:
  - *Intermittent claudication* in the *plantar and digital* region
  - *Diminished or absent* peripheral pulse
  - Trophic *skin* changes

② ***Raynaud phenomenon***
- Vasospasm of *digital arteries triggered triggered by exposure to cold*

③ ***Superficial migratory thrombophlebitis***

d) RAYNAUD syndrome

- **Definition** – **vasospastic disease** located in **SMALL arteries,** mainly the **DIGITAL arteries of the hands** and manifested as *ISCHEMIC ATTACKS* (vasospasm) triggered by **cold exposure** and/or **emotional stress**
- **Etiopathogenic classification:**

① **PRIMARY Raynaud syndrome or Raynaud DISEASE** - **idiopathic**
- unknown cause
- predominant in *women aged between 20 and 40 years*

② **SECONDARY Raynaud syndrome or Raynaud PHENOMENON**
- associated with:
  - *diseases of the connective tissue (e.g., scleroderma, rheumatoid arthritis, SLE)*
  - *occlusive arterial disorders (e.g., obliterating thromboangiitis)*

- **Pathogenesis –** exposure to **cold** and/or **emotional stress** triggers **severe VASOCONSTRICTION (digital and cutaneous arteries) of fingers or toes**

① **In Raynaud disease** – the **vasospasm** occursvia **two mechanisms**:
- excessive action of **norepinephrine** on **α–adrenergic receptors**, due to *increased*
  - *number of α-adrenergic receptors*
  - *sensitivity of the receptors to the action of norepinephrine*
- excessive release of **local vasoconstrictors:**
  - serotonin (acting on 5-HT 2 receptors)
  - thromboxane A2
  - endothelin 1

② **In Raynaud phenomenon:**
- **the arterial lumen narrows** as a consequence of the:
  - arterial wall sclerosis – in collagen disorders
  - arterial wall chronic granulomatous inflammation – in occlusive arterial diseases
- **vasospasm** is triggered by an increased sympathetic response to **cold**

- **Clinical manifestations:**

① **ISCHEMIC attack** – characterized by:
- the "**triphasic color reaction"**: **white** → **blue** → **pink/red**, resulting from peripheral bloof flow alterations (ischemia → stasis → hyperemia)
  - ✓ ***Pallor*** – vasospasm (ischemic phase)
  - ✓ ***Cyanosis*** – local accumulation of HbH > 5 g% (deoxygenation phase)
  - ✓ ***Redness*** – return of blood flow (reperfusion phase)
- **paresthesias, tingling, numbness or burning pain** induced by **vasospasm**

② **BETWEEN the ischemic attacks:**
- the extremities may be cold/damp or normal
- skin atrophy, irregular nail growth (rare, in secondary forms)

VENOUS DISEASES

A. VARICOSE VEINS (VARICOSE DISEASE)

- **Definition** – *tortuous*, *abnormally dilated superficial (subcutaneous) veins* of the lower limbs predominantly located on the *saphenous vein* and its tributaries.

- **Epidemiology:**
  - affect *20-30% of the general population*
  - are 2-3 times more common in *women*, especially after the age of *50 years*
  - over 2/3 of the patients have a *positive family history* of varicose disease

- **Classification:**
  - PRIMARY varicose veins – *primary* impairment of the ***superficial*** venous circulation
  - SECONDARY varicose veins – *primary* impairment of the ***deep*** venous circulation, which is responsible for the *secondary* damage to the superficial venous circulation

1. PRIMARY varicose veins

- **Etiology** – decreased resistance of the walls of ***SUPERFICIAL venous system*** *due* **congenital defects** in the structure/function of the venous valves, responsible for the **valvular incompetence**
- **Pathogenesis** – increased intraluminal pressure due to ***venous stasis*** (decreased venous return) causes **distension of the venous wall and dilation of the superficial veins**. ***Venous stasis*** is favored by:
  - ✓ **PROLONGED ORTHOSTATISM**
    - enhances the negative effect of gravity on the venous return
  - ✓ **OBESITY**
    - the increase in ***intra-abdominal pressure*** compresses the abdominal veins and prevents venous return in orthostatism
    - the interposition of ***adipose tissue*** between veins and muscles reduces the:
      - *structural support* of the veins provided by the muscle mass
      - *beneficial effect of the muscle pump* on venous return
  - ✓ **PREGNANCY**
    - the increase in ***intra-abdominal / intrapelvic pressure*** compresses the abdominal/ pelvic veins and prevents venous return in orthostatism
    - **progesterone** has a ***myorelaxant*** effect on the **vascular smooth muscle**

2. SECONDARY varices

- **Etiology** – impaired blood flow within the ***DEEP venous system***, caused by:
  - **postthrombotic incompentence/destruction of the valves** at the level of the **perforating veins** (which ensure the drainage of blood from the superficial to the deep venous system)
  - pelvic compression of tumoral etiology
  - congenital deep vein agenesis

- **Pathogenesis** – *retrograde shunting* of the blood from the deep venous circulation to the superficial one, through the **incompetent perforator veins**, is responsible for the **venous hypertension** and **dilation of superficial veins**
- **CLINICAL manifestations:**
  - dull pain or sensation of heaviness or pressure in the lower limbs, mainly following long periods of standing or after lifting heavy objects
  - edema of the lower limbs ("swollen leg" sensation) after standing / prolonged sitting position
  - nocturnal muscle cramps
- **MAJOR complications:**
  - venous thrombosis
  - chronic venous insufficiency (edema, skin trophic changes and venous ulcerations as manifestation)
  - rupture of the superficial varicose veins (haemorrhage)

B. VENOUS THROMBOSIS (THROMBOPHLEBITIS)

- **Definition** – formation of a **thrombus** accompanied by the **acute inflammation of the venous wall** in the *deep or superficial* venous system
- **Characteristics:**
  a. **VENOUS thrombi**:
    - consist of *fibrin, thrombin, many red blood cells* and *few platelets*
    - tends to propagate *in the direction of the blood flow*
    - consequences:
      - partial/total venous obstruction
      - risk of thrombus fragmentation and downstream **embolization**

  b. **ACUTE INFLAMMATION of the venous wall** – causes:
    - local and systemic manifestations
    - destruction of the venous valves

1. DEEP VENOUS THROMBOSIS (DVT)

- **Definition** – thrombosis and acute inflammation of the deep veins of the *lower limb,* responsible for:
  - **distal DVT,** when the thrombus remains confined inside the **veins** of the **calf**
  - **proximal DVT**, when the thrombus extends proximally and reaches the **popliteal vein**
- **RISK factors**
  - form the **Virchow TRIAD** that comprises:
    1. **Venous STASIS**
    2. **ENDOTHELIAL injury**
    3. **Blood HYPERCOAGULABILITY**

Two types of RISK factors are currently involved:

a) **TRIGGERING or TRANSIENT factors** – act by initiating the ***platelets adhesion*** to the injured venous endothelium and ***activating blood coagulation***

① **Factors related to ENDOTHELIAL injury:**

- traumas/major surgeries on the lower limbs/pelvis (gynecological, orthopedic)
- minor surgical interventions, under general anesthesia
- cancer-related surgeries

② **Factors related to venous STASIS**

- prolonged rest
  - ✓ immobilization (absolute bed rest > 3 days) - during an illness, because of a plaster cast or after a surgical intervention
  - ✓ recent journeys (seated position) over long distances (duration > 4 hours)
- pregnancy/postnatal period

b) **FAVORING or PERSISTENT factors** – act by **promoting the fibrin clot formation**

① **Factors related to blood HYPERCOAGULABILITY:**

- **PRIMARY hypercoagulability (hereditary thrombophilias)**
  - **mutation of the factor V gene** - is responsible for the synthesis of **factor V Leiden,** a mutant factor V, resistant to the action of activated protein C
  - **deficiency of endogenous soluble anticoagulants**
    - ✓ protein C
    - ✓ protein S (protein C cofactor)
    - ✓ antithrombin III
- **SECONDARY hypercoagulability**
  - **increased production of procoagulant factors** in:
    - ✓ *neoplastic disease (myeloproliferative neoplasms)*
    - ✓ *SLE (antiphospholipid syndrome)*
  - **increased resistance to circulating anticoagulant factors** in:
    - ✓ administration of estrogens (oral contraceptives)

② **Factors related to venous STASIS:**

- obesity
- advanced age
- heart failure

③ **Factors related to ENDOTHELIAL injury:**

- SLE (inflammation of the venous wall)

- **Clinical manifestations:**
  - asymptomatic in 50% of cases (the vein is not completely obstructed or there is collateral circulation)
  - the most frequent manifestations are those related to the **ACUTE INFLAMMATION:**

① **Systemic** – fever, leucocytosis with neutrophilia, increased ESR and CRP

② **Local**:

- pain, discomfort in the calf when lifting the foot or walking
- unilateral oedema of the foot/ankle
- red/warm or pale/cyanotic skin when arterial circulation is also affected

- **Major complications:**
  - ① **PULMONARY EMBOLISM** – **in case of PROXIMAL DVT**
    - thrombi at this level are larger and prone to ***embolization*** **–** fragments of the thrombus (emboli) reach the pulmonary arteries by traveling through the *large veins of the pelvis, the inferior vena cava, the right atrium and the right ventricle*
  - ② **POST-THROMBOTIC syndrome** – defined by:
    - **Secondary various veins** – as result of the venous valves destruction
    - **Chronic venous insufficiency** – as result of persistent deep venous obstruction, characterized by *edema and skin trophic changes*

2. SUPERFICIAL VENOUS THROMBOSIS (PARAPHLEBITIS)

- **Definition –** the benign form of *venous thrombosis* associated with the *inflammation of subcutaneous superficial veins* and which is **not** a cause of pulmonary embolism
- **Causes**:
  - complication at the site of venous catheterization
  - trauma of varicose veins
- **Clinical manifestations** – pain, erythema, tenderness or an indurated cord along a palpable superficial vein

Migratory thrombophlebitis (recurrent or idiopathic), which are multiple venous thromboses that can involve both the superficial and deep veins, may sometimes be the **early signs of cancer** (pancreatic, hepatic, breast, gastric, pulmonary) as part of **paraneoplastic syndromes**.

PULMONARY THROMBOEMBOLISM

- **Definition – acute obstruction of a branch of the pulmonary artery** by an embolus originating at the level of the:
  - **deep veins of the lower limbs** (DVT) in **> 90% of cases**
  - **heart** (right emboligenic cardiopathy) in **< 10% of cases:**
    - ✓ Atrial fibrillation
    - ✓ Acute myocardial infarction
    - ✓ Dilated cardiomyopathy
- **Types of embolism:**

  The most common cause of pulmonary embolism is **THROMBOTIC embolism.**

  Other causes of pulmonary embolism, called **NON-THROMBOTIC**, are:
  - **FAT embolism** due to mobilization of a**:**
    - ***bone marrow*** *fragment* after *fractures* or *orthopedic surgery* (e.g., knee, hip)
    - fragment of ***adipose tissue*** after a severe trauma or liposuction
  - **AMNIOTIC FLUID embolism –** penetration of the ***amniotic liquid*** into the maternal circulation during labor
  - **SEPTIC embolism** – in severe infections/sepsis with ***bacteria, fungi***

- **GAS embolism** – in accidental penetration of ***air*** in the systemic circulation during the *placement of a central venous catheter* or *surgical procedure.*

- **RISK factors – Virchow TRIAD:**
  1. **Venous STASIS**
  2. **ENDOTHELIAL injury**
  3. **Blood HYPERCOAGULABILITY**

- **FUNCTIONAL changes**
  - are the consequence of *mechanical obstruction by the embolus* and *reflex pulmonary vasoconstriction*
  - depend on the *size of the embolus*:
    a. **In case of SMALL emboli**, which affect **< 1/3** of the pulmonary circulation (obstruction at the level of subsegmental or intralobular arteries), the compensatory activation of the **passive regulatory** mechanisms of the pulmonary circulation occurs and leads to the *passive distension of already open capillaries* and the *recruitment of new capillaries* (normally closed)*:*
       - pulmonary vascular resistance increases **mildly** and **does NOT** affect the **heart** hemodynamically
       - vascular obstruction **does NOT** cause necrosis of the pulmonary parenchyma (pulmonary infarction)
       - if the **thromboembolism is RECURRENT**, **chronic pulmonary HT** sets in
    b. **In case of MEDIUM emboli,** which affect ≥ **1/3** of the pulmonary circulation (obstruction at the level of segmental or lobar arteries), the compensatory activation of the passive regulation mechanism of the pulmonary circulation is overcome, with the following consequences:
       - pulmonary vascular resistance increases **moderately** and causes **acute pulmonary HT** that **affects the heart hemodynamically** with **acute RIGHT HF**
       - pulmonary ischemia is responsible for **necrosis of the pulmonary parenchyma** (pulmonary infarction) and **inflammation of the adjacent pleura**
       - **partial acute respiratory failure** occurs (hypoxemic, type I)
    c. **In case of LARGE emboli (massive pulmonary thromboembolism),** affecting ≥ **1/2** of the pulmonary circulation (obstruction at the level of the trunk of the pulmonary artery or of one of the main pulmonary arteries):
       - pulmonary vascular resistance increases **severely** and causes **acute pulmonary HT** that **affects the heart hemodynamically with GLOBAL acute HF (right and left)**
       - pulmonary ischemia is responsible for **extensive necrosis of the pulmonary parenchyma** (pulmonary infarction)
       - **global acute respiratory failure** occurs (hypercapnic, type II)

a) HEMODYNAMIC changes:

- **Acute RIGHT heart failure:** acute pulmonary HT causes *right ventricular dysfunction*
- **Acute LEFT heart failure**: *dysfunction of the right ventricle* causes a *decreased filling of the left ventricle* with the following possible consequences:
  - decreased coronary perfusion with *myocardial ischemia or infarction*

- severe drop in blood pressure with *circulatory collapse*
- severe generalized decrease in tissue perfusion with *cardiogenic shock*

b) RESPIRATORY changes:

- **Acute PARTIAL respiratory failure (HYPOXEMIC)** – occurs in:
  - pulmonary thromboembolism with MEDIUM-sized emboli
  - pulmonary thromboembolism with SMALL-sized emboli in patients with pre-existing cardiopulmonary diseases

  Hypoxemia occurs via **3 pathomechanisms**:
  1. Alteration of the **V_A/Q ratio** – Coexistence of hypoventilated areas with normo-hyperventilated areas
  2. Impairment of **alveolo-capillary diffusion**
  3. Occurrence of an **intrapulmonary arterio-venous shunt**

  Hypocapnia is established by **reflex (compensatory) hyperventilation** in the unaffected areas.
- **Acute GLOBAL respiratory failure (HYPERCAPNIC)** – in case of MASSIVE thromboembolism.

1. Hypoxemia via alteration of the V_A/Q ratio

- **Pathogenesis:**
  - **a. Acute HYPOPERFUSION in the <u>diseased</u> areas**
    - Cause: *mechanical vascular obstruction* and *reflex vasoconstriction*
    - Consequences:
      - decreased surfactant production by **type II alveolocytes** with:
        - ✓ *alveolar edema which inactivates surfactant and triggers alveolar collapse*
      - ischemic lesion of the alveolar wall with **necrosis of the alveolar wall** (pulmonary infarction) responsible for:
        - ✓ *alveolar hemorrhage* → causes ***hemoptysis***
        - ✓ *inflammation of the adjacent pleura* → *causes* ***dry cough*** *and* ***chest pain*** *(severe chest stabbing sensation, with a pleuritic character)*
  - **b. Acute HYPOVENTILATION in the <u>diseased</u> areas**
    - Cause:
      - *reflex bronchoconstriction* – secondary to *alveolar hypoperfusion*
      - *alveolar edema* – due to the *decreased surfactant production*
      - *alveolar hemorrhages* – determined by *necrosis of the alveolar wall*
    - Consequence: hypoxemia
  - **c. Reflex alveolar HYPERVENTILATION in the <u>non-diseased</u> areas**
    - Cause: hypoxemia
    - Consequences:
      - increased ventilatory work ***acute onset dyspnea*** or ***tachypnea at rest***
      - hypocapnia

2. Hypoxemia via the impairment of ALVEOLO-CAPILLARY DIFFUSION

- **Pathogenesis:**
  - **Reduction of the alveolo-capillary exchange surface (A)** – due to the *mechanical vascular obstruction* (reduction of the surface of the capillary bed that participates in exchanges)
  - **Increased diffusion distance / membrane thickness** – due to the *alveolar edema*

3. Hypoxemia via occurrence of an INTRAPULMONARY ARTERIO-VENOUS SHUNT

- **Pathogenesis:**
  - **Alveolar collapse with the appearance of areas of ATELECTASIS** – due to the:
    - decreased surfactant production
    - surfactant inactivation by the *alveolar edema*
  - **acute pulmonary HT** – responsible for:
    - opening of the *collateral circulation* (shunts) between the arterial and venous pulmonary territory

10. PATHOPHYSIOLOGY OF HEART FAILURE

CARDIAC PERFORMANCE – Brief physiology overview

- **Definition** – cardiac performance can be defined at the level of the:
  - **myocardial muscle** – cardiac performance is expressed through the cardiac muscle's ability to generate **tension** (force) and to **actively shorten**
  - **cardiac pump** – cardiac performance is measured through the heart capacity to generate **an intracavitary pressure** and to provide the **cardiac output (CO)**
- **Major determinants** – at the level of both cardiac muscle and pump:
  A. Preload
  B. Afterload
  C. Inotropism
  D. Heart rate

Observation: Increased **preload, inotropism** and **heart rate** lead to **increased cardiac output,** whereas an increased **afterload** causes[a **decrease** in **cardiac output**.

A. PRELOAD

1. PRELOAD of the CARDIAC MUSCLE

- **Definition** – the **tension** that determines the ***degree of stretch*** of the myocardial fibers **at rest** (the length of the sarcomeres before contraction).
- **Characteristics:**
  - the length of the muscle prior to stimulation (contraction) will increase the force of the contraction by:
    - ✓ optimizing the degree of overlap of the myofilaments with the increase of the number of *actin-myosin bridges* during the next systole
    - ✓ increasing the muscle filaments' sensitivity to Ca^{2+}
  - at a sarcomeres length between **1,6-2,2 µm**, the active tension is *directly proportional* to the preload
  - the optimal length of the sarcomere which determines *maximum force* is **2,2 µm**, any further increase in length will lead to a decrease in force

Observations:
The force generated by the muscle during contraction is directly proportional to the *number of actin-myosin bridges (interactions)* which in turn are conditioned by the concentration of Ca^{2+}in the *space between the muscle filaments*. This explains why medication that leads to an accumulation of Ca^{2+} in the *intracellular space of the myocardial fibers* (inotropic drugs) or works by *increasing the sensitivity of myofilaments to* Ca^{2+} (*levosimendan*) leads to an increase in the force of contraction; these drugs are called **calcitropic inotropes**. The classic inotropic drugs include: *digitalis* – sodium-potassium pump inhibitor; *dopamine, dobutamine* – beta agonists and *milrinone* – phosphodiesterase inhibitor.
However, the excess of calcium at the interfilament level causes unfavorable effects by: *altering myocardial relaxation, increasing* O_2 *consumption* and *arrhythmogenic risk*, therefore these drugs are not indicated in chronic heart failure (HF) (except digitalis) but only in **acute HF**.

2. PRELOAD of the CARDIAC PUMP

- **Definition** – the **tension** within the ventricular wall at the **end of DIASTOLE,** approximated by the ***telediastolic / end-diastolic volume (TDV / EDV)*** or ***telediastolic / end-diastolic pressure (TDP / EDP)*** which determines the length of the sarcomeres at rest.

- **Major preload determinants** – Tab. 10.1.

Table 10.1. Determinant factors of the cardiac pump's PRELOAD.

Determinant factor	Effect on preload
1. Venous tone	▪ Increased venous tone leads to an increased venous return and EDV
2. Volemia	▪ Increased volemia leads to increased venous return and EDV
3. Atrial contraction	▪ Contributes by approximately 20% to the EDV
4. Intra- *vs.* extrathoracic distribution of blood volume	▪ Clinostatism, inspiration and physical effort determine a higher EDV
5. Ventricular compliance	▪ EDV decreases due to a deficit in relaxation in: – Concentric ventricular hyperthrophy (e.g. arterial hypertension and aortic stenosis) – Restrictive and hyperthorphic cardiomyopathy – Myocardial fibrosis after extensive myocardial infarction

- **Characteristics:**
  - the **relationship between EDV and myocardial performance** was described by the physiologists Frank and Starling and is known as the **Frank-Starling law** or as the **cardiac function curve**, which shows that:
    - ✓ at rest the normal heat functions at an intermediate length of the sarcomers (the point which represents normal cardiac function at rest which corresponds to an EDV of 135 ml that provides a systolic stroke volume of 70 ml)
    - ✓ the ascending part of the curve (from the function point at rest till the top of the curve) is known as the **cardiac reserve,** which is high in the normal heart and progressively decreases in heart failure.

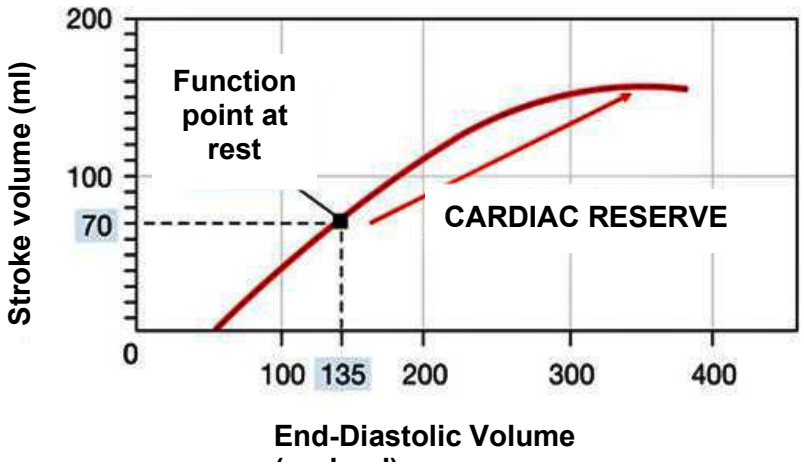

Figure 10.1. The CARDIAC FUNCTION CURVE (explanations in text).

- **The cardiac output** can be increased by **2 mechanisms:**
  - **Increase in contractility** and **heart rate** (via β_1*-adrenergic stimulation*), which ***will shift the curve upwards*** – *the adaptation of the normal heart during exercise*
  - **Increase in the EDV** according to the *Frank-Starling mechanism*, which ***will shift the heart's function point on the ascending part of the cardiac function curve*** with a decrease in cardiac reserve – the adaptation of the *failing heart to the decrease in cardiac output*, occurring initially upon exertion but subsequently at rest as well

Observation: During ventricular filling, EDP slightly increases for EDV values that determine lengthenings of the sarcomeres between 1,6 - 2,2 μm, after which EDP increases exponentially (the cardiac muscle becomes rigid) and retrograde stasis/congestion phenomena appear. This represents the long term disadvantage of adaptation through increased EDV because pulmonary capillary stasis will lead to the exit of liquid from the vessel into the interstitium => acute pulmonary edema.

B. AFTERLOAD

1. AFTERLOAD of the CARDIAC MUSCLE

- **Definition -** the **resistance** which the heart muscle must overcome **during contraction**

2. AFTERLOAD of the CARDIAC PUMP

- **Definitions:**
  - the ***tension*** *within the ventricular walls* ***during systole*** *or the systolic parietal tension*
  - the ***resistance*** that the ventricular myocardium must overcome ***during systole***, approximated by ***systolic arterial blood pressure****:*
    - from the aorta for the left ventricle (LV)
    - from the pulmonary artery for the right ventricle (RV)
- **Characteristics:**
  - Afterload (systolic wall tension) is classically defined as the ***wall-stress*** (σ) and is expressed as the ratio *force (tension)/surface unit*
  - According to Laplace's equation for a spherical cavity (T = P x r), left ventricular parietal stress (σ) is:

$$\sigma = P \times r/2h$$

where: *P = intraventricular pressure*
r = radius of the cavity
h = wall thickness

  - σ increases either by increasing ***P*** (in pressure overload) either by increasing ***r*** (in volume overload which leads to ventricular dilation and an increased cavity radius)

Observation: In pathological conditions with **chronic hemodynamic overload due to pressure or volume**, increasing ***h*** represents a **compensatory mechanism** aimed at reducing wall stress (by increasing ventricular mass the amount of force distributed to the unit of surface will decrease).

C. INOTROPISM (CONTRACTILITY)

- **Definition** – the intrinsic property of the cardiac muscle to **contract** and which can change under the action of **pharmacological agents or neuro-humoral changes,** for a given value of pre- and afterload
- **Significance** – the modifications of the contractile state are reflected in the Frank-Starling curve by the change in its *position*:
  - **Increased inotropism due to pharmacological agents** (e.g. digitalis) – moves the cardiac function curve *upwards*, causing an increase in systolic volume and cardiac output for any value of the preload

– **Decreased inotropism** (e.g. heart failure) – moves the cardiac function curve *downwards*, causing a decrease in systolic volume for any value of the preload

D. HEART RATE

Represents the **major mechanism** through which cardiac output is increased during exercise (as a response to an increase in O_2 demand)

- **For the CARDIAC MUSCLE** – an increase in the stimulation rate shortens the time available for the Ca^{2+} pump from the sarco-endoplasmic reticulum (SERCA, „*sarco-endoplasmic reticulum calcium ATP-ase*") to reuptake Ca^{2+}, which will lead to the increase of free [Ca^{2+}] in the space between the filaments, with **2 consequences:**
  - positive inotropic effect in the *short term*
  - alteration of cardiac muscle relaxation in the *long term*
- **For the CARDIAC PUMP** (CO = SV x HR)*:*
  - HR up to 140 - 160 b/min – CO increases based on the higher HR
  - HR > 160 b/min – CO decreases due to lower systolic volume (SV) because of a shorter diastole and shortened ventricular filling time

HEART FAILURE (HF)

DEFINITIONS:

- **Pathophysiological definition** – clinical syndrome caused by the **heart's inability to fulfill its function as a pump** which determines the:
  - **decrease of CO under the metabolic needs of the body**, which causes the **antegrade manifestations** *and/or*
  - preservation of the CO at the expense of a **symptomatic increase in heart filling pressures**, which causes the **retrograde manifestations**
- **Universal definition – clinical syndrome** characterized by the current or past existence of the following elements:
  - **signs and/or symptoms** caused by a structural or functional cardiac abnormality associated with **at least one** of the following criteria:
    - ✓ **increased serum level of HF biomarkers, natriuretic peptides**
    - ✓ **imaging or hemodynamic evidence of pulmonary or systemic congestion**, of cardiac origin, at rest or during physical exertion

SYMPTOMS of HF:

- *Left HF* – dyspnea on exertion or at rest, paroxysmal nocturnal dyspnea, orthopnea, cough, weakness/fatigue, reduced exercise tolerance
- *Right HF* – hepatalgia, bloating, anorexia

SIGNS of HF:

- *Left HF* – tachycardia, pallor, sweating, symmetrical subcrepitant pulmonary crackles, lateral displacement of the apexian shock
- *Right HF* – jugular turgor, hepato-jugular reflux, peripheral edema, painful hepatomegaly, pleural effusion, ascites

HF should **never** be the solely diagnosis of a patient but must be accompanied by the **diagnosis of the underlying disease** that led, in evolution, to the occurrence of HF.

TERMINOLOGY:

① **Acute** *versus* **Chronic HF:**

- **Chronic, congestive HF** – corresponds to the above mentioned definition and is the most commonly found form in clinical practice
- **Acute HF** – describes:
  - ✓ **de novo HF**, with acute onset (in case of a severe cardiac disease)
  - ✓ **decompensation of a chronic HF** caused by *precipitating factors* (see below) and can be complicated by *acute pulmonary edema* (APE) or *cardiogenic shock*

② **Left** *versus* **right/global HF:**

- **Left HF** – corresponds to a predominant dysfunction of the left ventricle and signs of *pulmonary stasis/congestion*
- **Right HF** – corresponds to a predominant dysfunction of the right ventricle and signs of *systemic stasis/congestion*
- **Global HF** – corresponds to signs of *both pulmonary and systemic stasis/congestion*

CLASSIFICATIONS:

1. FUNCTIONAL NYHA (New York Heart Association) classification

- **Class I (asymptomatic HF)** – patients with structural disease/functional abnormalities *WITHOUT limitation of physical activity* = no symptoms: dyspnea, fatigue, palpitations
- **Class II (mild HF)** – **slight** limitation of regular physical activity (no symptoms at rest but with symptoms during *ordinary physical activity*: climbing stairs, gardening, sweeping, dancing)
- **Class III (moderate HF)** – patients with **marked** limitation of physical activity = symptoms appear at *lower than usual efforts*: getting dressed, making the bed
- **Class IV (severe HF)** – symptoms occur at **rest** and the slightest exertion worsens the symptoms

2. PATHOPHYSIOLOGICAL classification – according to the ejection fraction (EF) value

EF is calculated as the ratio **SV/EDV x 100** and has **a normal value = 50-70%.**
According to the EF values we can differentiate:

- **HF with reduced EF (HFrEF)** – characterized by abnormal ***contraction*** responsible for:
  - EF ≤ 40%
  - *systolic dysfunction of the left ventricle*
  - *eccentric* hypertrophy
- **HF with mildly reduced EF (HFmrEF)** – characterized by:
  - EF = 41 – 49%
  - *mild systolic dysfunction* associated with *diastolic dysfunction of the left ventricle* and, usually, normal dimensions of the LV
- **HF with preserved EF (HFpEF)** – characterized by abnormal ***relaxation*** responsible for:

- EF ≥ 50%
- *diastolic dysfunction* of the left ventricle
- *concentric* hypertrophy

ETIOLOGY:

Heart failure represents the **final evolutive stage** of all chronic structural cardiovascular diseases/functional cardiac anomalies - these being the **determining causes of HF**.
Once HF has occurred, a series of conditions can lead to its **aggravation/decompensation** - **precipitating factors of HF.**

A. The DETERMINING causes of HF are presented in Tab. 10.2.

Table 10.2. The DETERMINING causes of HF.

<table>
<tr><th>HFrEF with SYSTOLIC dysfunction
= HF due to reduced CONTRACTILITY</th><th>HFpEF with DIASTOLIC dysfunction
= HF due reduced VENTRICULAR FILLING</th></tr>
<tr><td>1. PRIMARY decrease in myocardial contractility in:
– Coronary heart disease:
✓ Myocardial infarction
✓ Chronic myocardial ischemia
– Dilated cardiomyopathy
– Myocarditis (viral, bacterial, parasitic)</td><td rowspan="3">1. Pathological hypertrophy:
– Primary: hypertrophic cardiomyopathy
– Secondary: HT
2. Restrictive cardiomyopathy
3. Infiltrative myocardial diseases:
amyloidosis, hemochromatosis, sarcoidosis
4. Pericardial diseases - e.g., constrictive pericarditis, cardiac tamponade
5. Comorbidities associated with low-grade chronic inflammation:
– obesity/metabolic syndrome
– diabetes
– chronic kidney disease
– COPD
– chronic hepatopathy
– sleep apnea
– cancerous disease
– gout
6. Ageing and associated cardiac fibrosis
7. Physical deconditioning</td></tr>
<tr><td>2. SECONDARY decrease in contractility by hemodynamic overload:
a) PRESSURE overload = ↑ afterload:
✓ HT
✓ Valvular stenosis - eg, severe aortic stenosis
b) VOLUME overload = ↑ preload:
✓ Valvular insufficiency - eg, mitral or aortic insufficiency
✓ Intracardiac shunts - eg, uncorrected septal defects</td></tr>
<tr><td>3. Comorbidities:
– diabetes mellitus
– chronic kidney disease
– neuromuscular diseases with damage to the myocardium - eg, Duchenne muscular dystrophy, Friedreich's ataxia
– cardiac toxics - e.g., alcohol, anticancer chemo- (especially with anthracyclines, typical e.g. doxorubicin) and radiotherapy</td></tr>
</table>

B. The PRECIPITATING factors of HF are presented in Tab. 10.3.

Many patients that suffer from HF are asymptomatic for a very long time due to to *compensatory mechanisms*. A series of *precipitating factors* determine an aggravation of HF, therefore the compensated HF becomes decompensated.

Table 10.3. PRECIPITATING factors of HF decompensation.

Precipitating factor (*cardiac* and *extracardiac* causes)	**The mechanism that causes HF decompensation**
1. RHYTHM AND CONDUCTION DISORDERS	
▪ Atrial Fibrilation/Flutter	▪ The atrial contraction is hemodinamically inefficient ▪ Decreased EDV by aprox. 20% causes a decrease in CO
▪ Supraventricular paroxystic tachycardia	▪ Shortening of the diastole decreases the ventricular filling time ▪ The decrease of systolic volume at a HR > 160 b/min causes a decreased CO
▪ Severe bradicardia (HR under 40b/min) ▪ Third degree A-V block (A-V dissociation)	▪ Decreased HR causes a decrease in CO (even though the diastole is very long and ventricular filling is well accomplished, respectively systolic volume is normal)
2. HYPERTENSIVE CRISIS	▪ The sudden increase in the *left* ventricle afterload leads to a decreased CO
3. MYOCARDIAL INFARCTION	▪ In a patient with coronary heart disease, cardiac contractility is further decreased due to necrosis of a certain portion of the myocardium which leads to decreased CO
4. INFECTIOUS DISEASES	▪ In all infectious diseases *fever* causes: – Increased tissue metabolic demands – Compensatory tachycardia and increased CO
▪ **CARDIAC infections (endocarditis, myocarditis)**	▪ Endocarditis leads to the aggravation of valvular lesions with a higher risk of valvular rupture with sudden increase of the preload and acute volume overload ▪ Myocarditis determines a further decrease in myocardial contractility
▪ **PULMONARY infections (pneumonia, bronchopneumonia)**	▪ Pulmonary infections determine an alteration in respiratory gas exchange which leads to hypoxia and alters the supply and demand of O_2 in the myocardium
5. PULMONARY EMBOLISM	▪ The sudden increase in the *right* ventricle afterload leads to a decreased CO

6. HYPERKINETIC conditions (chronic anemias, hyperthyroidism, pregnancy, arteriovenous fistulae)	▪ Increased tissue metabolic demands require a proportional increase of the CO
7. HYPERVOLEMIA (kidney failure, excessive salt or fluid intake)	▪ Increased volemia and preload
8. Increased ETHANOL consumption	▪ Decrease of myocardial contractility
9. OMISSION of prescribed HF MEDICATION	

HEART FAILURE STAGES:

According to the consensus document published in 2021, HF presents 4 evolutionary stages (Tab. 10.4.).

Table 10.4. Stages of HF evolution.

Stage A (*patient at high risk of developing HF*)	**Stage B** *(pre-heart failure)*	**Stage C** *(heart failure)*	**Stage D** *(advanced heart failure)*
• Patients **WITH risk factors for HF**: HT, DM, obesity, ATS, exposure to cardiac toxic substances, family history or genetic predisposition to cardiomyopathies • **NO** signs, symptoms, structural changes or biomarkers of HF.	• Patients **WITHOUT signs or symptoms, but displaying ONE of the following changes:** – ***Structural* cardiac anomalies** (LV hypertrophy, kinetic ventricular wall anomalies, myocardial edema or fibrosis, valvular system damage); – ***Functional* cardiac abnormalities** (decreased ventricular systolic function, diastolic dysfunction, increased filling pressures); – increased serum **HF biomarkers**	• Patients **WITH signs and/or symptoms AND cardiac structural/ functional abnormalities**	• Patients **WITH severe signs/ symptoms, *at rest*,** who: – Require frequent hospitalization, despite optimal treatment; – Are refractory or intolerant to optimal treatment; – Require heart transplant, mechanical circulatory support or palliative care.

Observations:

Although this staging includes 4 individualized categories, the authors of the consensus document draw attention to the fact that HF involves a pathophysiological continuum, and its evolution can be bidirectional, being influenced by therapy. Thus, it is also proposed to introduce a category of patients with *HF with*

improved EF – the initial EF of the patient was below 40%, but the treatment led to an increase of at least 10%, and the value at subsequent controls is over 40%.
In addition, stages A and B, of the presence of risk factors or of asymptomatic heart disease, account for almost half of heart failure cases. The aim is to define these stages that precede overt HF and contribute to a preventive approach to cases, in order to control the evolution towards the stages of symptomatic (stage C) and advanced (stage D) HF.

COMPENSATORY MECHANISMS in HF:

- HF evolves in **2 stages:**
  - **Compensated HF** – the compensatory mechanisms manage to *maintain CO at adequate levels* for the tissue metabolic demands at rest and adapt to exercise by using the cardiac reserve
  - **Decompensated HF**– the cardiac reserve is exhausted and the heart can *no longer meet the tissue metabolic needs*, not even at rest

- **The COMPENSATORY MECHANISMS in HF** are:
  A. The Frank-Starling mechanism
  B. Neurohumoral mechanisms
  C. Cardiac hypertrophy and remodeling

Compensatory mechanisms are **"double-edged swords":**
- ✓ have an **adaptive role** in the **short term - favorable effects**
- ✓ become **maladaptive** in the **long term - adverse effects**

Chronic HF medication is currently aimed at reducing the adverse effects of the functioning of compensatory mechanisms.

A. The FRANK-STARLING mechanism

a) The FAVORABLE (compensatory) effect of the Frank-Starling mechanism consists in **increasing the CO** by **increasing the preload (EDV)**.

- **Mechanisms for increasing the PRELOAD:**
  In HF decreasing the CO leads to:
  ① **An increase in residual/end-systolic volume** (RV, ESV)
  ② **A decrease in arterial pressure at the level of baroreceptors** (in the carotid sinus and the aortic arch) which determines an increase in sympathetic tone and a decrease in parasympathetic tone with **3 consequences:**
    – Increased HR
    – Increased inotropism
    – Vasoconstriction (through the stimulation of α-receptors in the arteries and the veins) with a *"centralization of circulation"* via the redistribution of blood towards *vital organs* (heart and brain), where vasodilation is predominant in the detriment of the *skin, kidneys and other organs* where vasoconstriction is predominant
  ③ **The decrease in renal blood flow** (which alongside renal vasoconstriction induced by sympathetic stimulation) causes **the activation of the RAA system**:

- AII determines an increase in the tubular reabsorption of Na and H_2O in the proximal convoluted tubule and systemic vasoconstriction
- ALDO determines the primary reabsorption of Na and secondarily of H_2O in the distal convoluted tubule and collecting duct
- both of these effects are responsible for hydrosaline retention with an increase in venous return and preload

- The Frank-Starling mechanism is based on the **cardiac function curve**:

1. In the **normal** heart the function point is set on the ascending part of the curve (**point A**) where EDV ensures **CO at rest.**

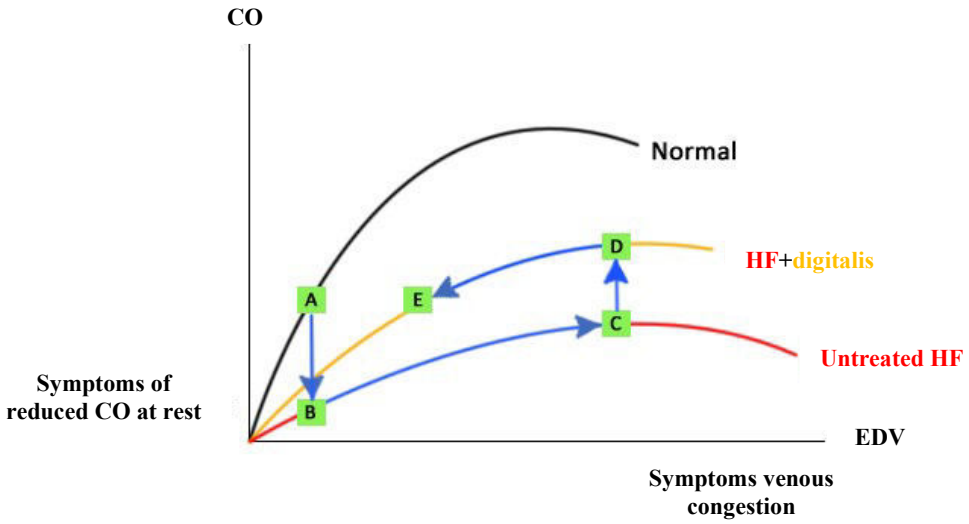

Figure. 10.2. Compensatory FRANK-STARLING mechanism and the DIGITALIS effect in HF (explanations in text).

2. In case of **HF** the function curve is moved *downward* with the reduction of CO (**point B**) and the heart performs its CO at rest (and adapts to effort) by **increasing the EDV.** The cardiac function point is moved *upward and to the right* (**from B to C**) on the ascending part of the curve, but this is done with the reduction of the cardiac reserve.
3. The excessive increase in EDV is counteracted by the administration of **positive inotropic agents** (classical e.g.: digitalis) - indicated in patients with HF with systolic dysfunction and reduced EF. Digitalis causes:
   - a positive inotropic effect via Na^+/K^+-ATPase inhibition (blocking its extracellular portion); increase in intracellular Na^+ concentration will cause activation of its exchange with Ca^{2+} with secondary accumulation of calcium available to activate contraction
   - *upward* displacement of the cardiac functional curve **- from C to D**
   - the increase in CO and tissue perfusion under the action of digitalis causes an increase in the rate of glomerular filtration, increased elimination of sodium and water, a decrease in volemia and venous return and, respectively, a decrease in EDV with the *downward and leftward displacement* of the functioning point on the curve of the heart treated with digitalis - **from D to E**

⇒ the heart treated with digitalis ensures the CO at rest due to the *moderate increase in EDV* with the *reduction of congestive phenomena*

b) The UNFAVORABLE effects of the Frank-Starling mechanism in *LONG TERM*

- **Stasis and retrograde congestion (symptoms of VENOUS CONGESTION)** – caused by the excessive rise of EDP which will be transmitted **retrogradely** to:
  - *the left atrium and pulmonary circulation in left HF with risk of* ***PULMONARY edema***
  - *the right atrium and systemic circulation in right HF with risk of* ***PERIPHERAL cardiac edema***
- **Alteration of the O_2 supply/demand ratio at myocardial level** – due to:
  - a decrease in O_2 supply due to the increase of EDP and diastolic wall tension, with the decrease of the coronary diastolic perfusion pressure gradient
  - an increase in O_2 demand due to ventricular distension, with the increase of the cavity radius and wall stress.

B. NEUROHUMORAL (NEURO-ENDOCRINE) compensatory mechanisms

- **Characteristics:**
  - consist in **excessive activation of nervous and endocrine systems:**
    - ✓ Sympathetic nervous system
    - ✓ Renin-angiotensin-aldosterone system (RAAS)
    - ✓ Release of ADH
    - ✓ Release of endothelins
    - ✓ Release of natriuretic peptides (ANP, BNP, CNP)
    - ✓ Release of proinflammatory mediators (cytokines such as TNF-α, IL-1, IL-6)
  - they are characterized by **high plasma levels of the above mentioned substances**

1. Increased SYMPATHO-ADRENERGIC STIMULATION (S-A)

- **Characteristics** – it is the normal heart's adaptive mechanism during physical effort and is **activated during HF by the decrease of CO.**

a) FAVORABLE effects of increased S-A stimulation in *SHORT TERM*:

- Locally released catecholamines from the sympathetic nerve endings (norepinephrine) and from the chromaffin tissue of the adrenal medulla (epinephrine and norepinephrine) activate the following receptors:

  ① **cardiac - β_1** – determine:
  - ***positive inotropic and chronotropic effect*** with the increase of CO
  - ***positive lusitropic effect*** with the acceleration in myocardial relaxation

  ② **vascular - α_1** – determine:
  - **arteriolar constriction** (increased tone in the resistance vessels) at *cutaneous, splanhnic and renal level* with the short term increase in PVR and BP in the context of CO decrease (BP = CO x PVR)
  - **venous constriction** (increased tone of the capacity vessels) determines increased venous return and EDV with the increase in CO

③ **coronary and cerebral arteries - β_2** – induce **vasodilation** preserving **vital organ perfusion (heart and brain)**

④ **juxtaglomerular apparatus - β_1** – induce the increase in **renin release** with the **activation of the RAA system**

The redistribution of blood flow due to increased arteriolar tone in the *skin and organs* (through α_1-adrenergic receptors) and decreased arteriolar tone in the *brain and heart* (through β_2-adrenegic receptors) is called **centralization of circulation**.

b) UNFAVORABLE effects of the increased S-A stimulation in *LONG TERM*:

- **Chronic tachycardia** – determines an increased myocardial O_2 demand and beyond a certain HR it shortens the diastole and decreases O_2 supply - coronary perfusion of cardiomyocytes
- **Proarrhythmogenic effect** – increased excitability of ectopic ventricular pacemakers which are responsible for a high risk of malignant ventricular tachyarrhythmias and sudden cardiac death in HF
- **Direct toxic effect of catecholamines oxidation end-products** – it appears in the presence of the excess of reactive oxygen species generated by the chronic inflammation associated with atherosclerosis
- **Proapoptotic effect** – cardiomyocyte apoptosis is increased due to the excess of catecholamines
- **Remodeling of the extracellular matrix**
- **Alteration of intracellular calcium signaling homeostasis:**

① **Normally:**

- norepinephrine released from the cardiac adrenergic nerve endings binds to β1-adrenergic membrane receptors coupled to Gs (stimulatory) proteins and causes *stimulation of adenylate cyclase and increase in cAMP*
- the cAMP increase causes the activation of protein kinase A responsible for the positive inotropic/lusitropic effect through:
  - ✓ *phosphorylation of slow Ca^{2+} channels in the sarcolemma* and increased Ca^{2+} influx in phase 2 (plateau) of the action potential with *increased systolic performance*
  - ✓ *phosphorylation of Ca^{2+} channels at the level of the sarcoplasmic reticulum* and increased Ca^{2+} release in the cytoplasm with *increased systolic performance*
  - ✓ *phosphorylation of phospholamban* (which inhibits SERCA in its dephosphorylated form) and SERCA, once activated, will increase *Ca^{2+} reuptake in the sarcoplasmic reticulum,* **with 2 effects**:
    - – *acceleration of relaxation* with improvement of *diastolic performance*
    - – *increase of Ca^{2+} stores available for the next systole* with the improvement of *systolic performance*

②**Pathologically** – during the progression of HF a **decrease in the membrane expression of β_1-adrenergic receptors *(down-regulation)*** occurs and the remaining ones are **desensitized at the level of cardiomyocytes** (alteration of intracellular signal transmission by uncoupling them from the Gs proteins with a decrease in cAMP

generation) responsible for reducing the favorable effects of sympathetic stimulation on the background of a *decrease in the adrenergic reserve of the heart* and the impairment of calcium homeostasis.

Observation: High plasma levels of catecholamines were inversely correlated with HF patient survival rate. Beta-blockers are administered in *chronic HF with reduced EF due to systolic dysfunction* in order to reduce the adverse effects of increased sympathetic stimulation and they elicit: i) an increase in coronary blood flow (by lengthening the diastole due to HR decrease), ii) a reduction in the arrhythmias incidence, iii) a decrease of the left ventricular remodeling progression and iv) a decrease in hospitalizations.

2. Activation of the RENIN-ANGIOTENSIN-ALDOSTERON SYSTEM (RAAS)

a) FAVORABLE effects of RAAS activation in *SHORT TERM*:

- **Hydrosaline retention** – increased EDV and CO through the Frank-Starling mechanism:
  - **sodium and water retention** – via a *direct* (the effect of AII on the PCT) and *indirect* (the effect of ALDO on the DCT) mechanism
  - **water** retention via thirst center stimulation and the release of ADH (vasopressin)
- **Systemic vasoconstriction** – increased PVR and BP via *direct* (effect of AII) and *indirect* (effect of S-A stimulation and ADH excess) mechanism

b) UNFAVORABLE effects of RAAS activation in *LONG TERM*:

- **Hydrosaline retention –** progressive increase in EDV and ventricular dilation cause **increased diastolic parietal tension** and **oxygen consumption** with subsequent *chronic ischemia and reduced inotropism*
- **Continuous vasoconstriction** (via AII, ALDO, ADH action) – determines the *increase in afterload* and the *decrease of CO*
- **Stimulation of proinflammatory cytokine production** (e.g. TNF-α, IL-1, IL-6) – aggravates *ventricular hypertrophy, cardiomyocyte apoptosis and patient cachexia*
- **Stimulation of fibroblast activationin the interstitium with collagen deposits** (through AII and ALDO stimulation) – causes *myocardial fibrosis* with **maladaptive remodeling**

All the **unfavorable effects of RAAS activation** in HF are tied to **AT-1 receptor stimulation.**

Observations:

Pharmacological antagonists of the RAA system: AII conversion enzyme inhibitors – ACEi or the "*prils*"; AII receptor blockers – ARB or the "*sartans*" and the mineralocorticoid receptor antagonists – MRA, e.g. *spironolactone and eplerenone* represent nowadays the main classes of drugs utilized in the treatment of *chronic HF with reduced EF and systolic dysfunction*. Their effects consist in: *prevention of cardiovascular remodeling, improvement of O_2 supply/demand ratio and reduced mortality especially in HF due to myocardial infarction*.

In the therapy of ***chronic HF*** **(NYHA classes II-IV) with reduced EF and systolic dysfunction** the European Society of Cardiology Guideline 2021 recommends the use of the following 2 classes of pharmacological agents, in order to **reduce the risk of hospitalization and death**:

i) Angiotensin Receptor Neprilysin Inhibitor (ARNI), the drug in clinical use being *sacubitril/valsartan*. Sacubitril is a prodrug that, upon activation, acts as a neprilysin inhibitor, preventing the degradation of natriuretic peptides and thus prolonging their beneficial effects. Valsartan is an angiotensin receptor blocker and works by blocking the RAA system. Because neprilysin breaks down angiotensin II, inhibition of neprilysin will lead to an accumulation of AII. For this reason, a

neprilysin inhibitor cannot be used alone but must always be combined with an ARB to block the effect of excess AII. The drug is recommended as a replacement for ACEI along with other standard treatments for HF (beta-blocker, mineralocorticoid receptor antagonists - MRA).

ii) **Sodium-GLucose coTransporter 2 (SGLT2) inhibitors** – e.g., *empagliflozin, dapagliflozin*, antidiabetic drugs used in patients with type II diabetes mellitus (DM), are currently indicated to be added to ACEI/ARNI/beta-blocker/MRA therapy in patients with **HFrEF**, regardless of whether they have or not diabetes, due to their pleiotropic (partially elucidated) cardioprotective effects.

Last but not least, in 2023 a *Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure* was issued and, in order to reduce the risk of HF hospitalization or cardiovascular death, an **SGLT2 inhibitor** (dapagliflozin or empagliflozin) is now recommended also in patients with:

- **HFmrEF** regardless of whether they have or not diabetes
- **HFpEF** regardless of whether they have or not diabetes
- **Type 2 DM and chronic kidney disease,** along with ***finerenone***, a selective, non-steroidal MRA

3. ANTIDIURETIC HORMONE (ADH, vasopressin) release

- **Characteristics** - its secretion is stimulated by *hypovolemia and hyperosmolarity* against the background of CO decrease

- **Effects:**
  a) **Volemia increase** - via *renal* V2 receptors it increases the reabsorption of WATER at the level of the DISTAL NEPHRON (collecting ducts)
     - **FAVORABLE effect**: by increasing venous return, it causes a short-term increase in EDV and CO
     - **ADVERSE EFFECT: WATER RETENTION**
  b) **Systemic vasoconstriction** - via *vascular* V1 receptors:
     - **FAVORABLE effect**: by increasing the PVR, it causes a short-term increase in BP
     - **ADVERSE effect**: the **increase in AFTERLOAD** causes the **decrease of CO** in the long term

- **Clinical significance:**

– ADH increases in severe chronic HF, especially in patients treated with diuretics, and the increased concentration of ADH precipitates hyponatremia, which is an unfavorable prognostic indicator

Observation: Selective V2 receptor antagonist (tolvaptan) may be indicated in acute HF with cardiogenic shock (especially if it is accompanied by septic shock).

4. ENDOTHELIN release

- **Characteristics:**
  – endothelins (ET-1, 2, 3, 4) are synthetized by *endothelial cells* and *cardiomyocytes* and interact with 2 types of receptors (ET-A and ET-B)
  – serum ET-1 is increased in patients with HF due to AII, NE, ADH and parietal distention and is responsible for **the progression of the left ventricle dysfunction**

- **Effects** – ET-1 binds to *ET-A receptors,* which have an increased expression in HF and induces:

- negative inotropic effects
- proarrhythmic effect
- fibroblast and vascular smooth muscle cells proliferation with **cardiovascular remodeling**
- increased ALDO release and hydrosaline retention
- systemic vasoconstriction with the increase in PVR
- pulmonary vasoconstriction with **secondary pulmonary hypertension**

Observation: Elevated plasma ET-1 levels correlate with the severity of hemodynamic disturbances, such that in patients with congestive HF acute intravenous administration of ET antagonists improved hemodynamic disturbances.
However, clinical trials using ET-1 receptor antagonists (bosentan) in chronic HF therapy were not associated with a beneficial effect on patient survival.

5. NATRIURETIC PEPTIDES release

- **Types:**
  - **ANP** (*Atrial Natriuretic Peptide*) secreted by the **atria**
  - **BNP** (*Brain Natriuretic Peptide*) and its precursor, **NT-proBNP** (N-terminalproBNP) secreted by the **ventricles**
  - **CNP** (*C type Natriuretic Peptide*) secreted by the **vascular endothelium**
- **Characteristics:**
  - secretion is stimulated by *atrial and ventricular distension* (increased wall stress) and by the activation of neurohumoral mechanisms (S-A, RAAS stimulation and ET-1 increase)
  - their role is to *counteract the effects of NE, AII, ADH and ET-1*
- **Effects:**
  - stimulation of natriuresis/diuresis by increasing glomerular filtration rate and decreasing sodium/water tubular reabsorption
  - arteriolar vasodilation by blocking vasoconstriction elicited by AII, NE, ET-1 and ADH
  - antiproliferative effect on cardiomyocytes and vascular smooth muscle cells
  - inhibition of ADH release
- **Clinical significance:**
  - The serum level of ANP correlates with the functional class, with the prognosis and with the hemodynamic status.
  - Serum levels of BNP and NT-proBNP correlate with ventricular parietal stress and with the severity of heart failure, thus being predictive markers of cardiovascular events and mortality; however, monitoring their serum levels is not currently routinely used to guide heart failure treatment.

6. PROINFLAMMATORY CYTOKINE release

- **Caracteristici:**
  - in HF, the serum concentration of some cytokines produced by cardiomyocytes and activated monocytes/macrophages increases: **TNF-α, IL-1, IL-6**

– high levels of **TNF-α and of soluble type 1 and type 2 TNF-α receptors** in the serum of patients with chronic HF are responsible for **persistent chronic inflammation** and have been associated with a poor prognosis due to:
  ✓ aggravated *maladaptive hypertrophy*
  ✓ persistent *apoptosis*
  ✓ worsening of *endothelial dysfunction and muscle hypoxia*
  ✓ *anorexia and **cachexia*** in the terminal stages of HF

Observation: Administration of the anticytokine therapies such as TNF-alpha inhibitors (etanercept, infliximab), IL-1 inhibitors (anakinra) or IL-6 inhibitors (canakinumab) resulted in mild clinical benefits in patients with chronic HF despite the decrease in serum levels of inflammatory markers.

C. CARDIAC HYPERTHROPHY AND REMODELING

DEFINITIONS:

- **Hypertrophy =** increased **ventricular wall thickness** due to increased:
  ✓ *cardiomyocyte size (higher number and greater size of sarcomeres)*
  ✓ *number of non-cardiomyocyte cells (fibroblasts) in the interstitium*
- **Remodeling** = progressive process by which ventricular size, shape and function are modified following the influence of mechanical, neurohormonal and possibly genetic factors from various diseases, including myocardial infarction, cardiomyopathy, hypertension and valvular diseases.
  – The defining elements of remodeling are **hypertrophy, loss of myocytes** and **increased myocardial fibrosis.**
  – The remodeling process continues for months after the initial injury, and the change in the shape of the ventricle can cause a consequent decrease in global cardiac function.

a) FAVORABLE (compensatory) effects of VENTRICULAR HYPERTHROPHY

– it is the compensatory mechanism of **chronic HF**
– hypertrophy is determined by the **increased parietal tension per surface unit** (σ, wall-stress) in the ventricular myocardium and its role is to **reduce parietal stress** according to the following equation $\sigma = P \times r/2h$
– **the increase in parietal stress** (σ = T/unit of surface, where T = P x r, according to the law of Laplace) can be achieved by:
  ✓ pressure overload (higher P) with *concentric hypertrophy*
  ✓ volume overload (higher r) with *eccentric hypertrophy*
– **the increase of h** (wall thickness) will **return σ to normal in the first phase** (phase of *adaptive hypertrophy*) after which the increase in pressure or volume will no longer be able to be compensated by increasing ventricular wall thickness (*maladaptive hypertrophy and remodeling*)

1. CONCENTRIC hypertrophy

- **Characteristics:**
  – is triggered by **pressure overload** from: arterial hypertension, aortic stenosis, hypertrophic cardiomyopathy
  – **systolic** wall tension or afterload is **increased**

- new sarcomeres are formed **in parallel** with the existing ones
- ventricular compliance is **decreased**
- diastolic performance is **decreased** because of ventricular wall stiffness
- congestive phenomena, backward stasis and the risk of pulmonary edema occur ***early*** in the evolution of the disease

2. ECCENTRIC hypertrophy

- **Characteristics:**
  - is triggered by **volume overload** from: aortic regurgitation, dilative cardiomyopathy
  - **diastolic** parietal tension or preload is **increased**
  - new sarcomeres are formed **in series** with the existing ones and a despiralization process of the myocardial fibers and bands occurs, which accentuates the ventricular cavity dilation
  - ventricular compliance is **normal** or **increased**
  - diastolic performance is **increased**
  - congestive phenomena, backward stasis and the risk of pulmonary edema occur ***later*** in the evolution of the disease

b) UNFAVORABLE effects of VENTRICULAR HYPERTHROPHY, particularly evident in case of concentric hypertrophy

- **Increased parietal systolic tension** (afterload) will decrease the fiber shortening and lower the ejection fraction, and thus CO will progressively decrease
- **Increased O_2 demand (consumption)** – due to a higher contractile mass
- **Decreased O_2 supply** – due to the impaired O_2 diffusion
- **Uncontrolled proliferation of fibroblasts with increased collagen synthesis – diffuse fibrosis** which makes ventricular walls more rigid with:
  - impaired lusitropism and further decrease in diastolic compliance with the aggravation of venous stasis/congestion
  - altered impulse conduction responsible for the desynchronized contractile function
- **Apoptosis stimulation** – due to the action of proinflammatory citokines, especially TNF-α
- **Complex changes in ventricular geometry with maladaptive hypertrophy and progressive cardiac remodeling**

CLINICAL FORMS OF HEART FAILURE

- According to the diseased ventricle – **3 types**:
  - Left HF
  - Right HF
  - Global (biventricular) HF

I. LEFT HEART FAILURE

- **Definition** – decreased *left ventricle (LV)* performance
- **Classification** – **2 main types** in clinical practice according to the **EF** (Tab. 10.5.).

- ✓ **HF with reduced EF (≤ 40%)** – HFrEF
- ✓ **HF with preserved EF (≥ 50%)** – HFpEF

to which **HF with mildly reduced EF – HFmrEF (41-49%)** was added.

Table 10.5. Pathophysiological characteristics of left HF with reduced vs. preserved EF.

HF with <u>REDUCED</u> EF (HfrEF)	HF with <u>PRESERVED</u> EF (HFpEF)
Systolic ventricular dysfunction and ***altered pump function***	***Diastolic*** ventricular dysfunction and ***decreased ventricular filling***
Primary/secondary decreased ***contractility*** (inotropism)	*Decreased ventricular* ***relaxation*** (lusitropism)
Eccentric ventricular hypertrophy	***Concentric*** ventricular hypertrophy
Mechanisms: **① Sustained activation of neuro-humoral mechanisms with structural changes consisting of *eccentric* ventricular remodeling and *dilation* of the LV cavity:** – apoptosis and necrosis responsible for the loss of cardiomyocytes – abnormal contractile protein synthesis through fetal gene activation – ventricular fibrosis with collagen deposits	**Mechanisms:** **① Increased extracellular matrix** through increased production of stiff type I collagen and reduced degradation (deficiency of matrix metalloproteinases) **② Cytoskeleton protein abnormalities -** predominance of the *stiff isoform of titin* **③ Vascular dysfunction associated with stiffness of the arterial walls** **④ Inability of SERCA to remove Ca^{2+} from the interfilament space** - reduced compliance, abnormal relaxation of the LV and increased EDP

- **Manifestations – 2 main types:**
  - *anterograde* caused by the decreased left ventricle SYSTOLIC performance
  - *retrograde* caused by the decreased left ventricle DIASTOLIC performance

a) ANTEROGRADE manifestations

- **Cause** – the *decreased EF and systolic output* of the left ventricle causes the decrease of the effective arterial volume (the volume that fills the arterial system)
- **Pathomechanism** – decreased **tissue perfusion**
- **Consequences:**
  - Decreased skeletal muscle perfusion – causes *fatigue during exercise*
  - Decreased renal perfusion – causes activation of the RAAS with *oliguria*
  - Decreased cerebral perfusion – increases S-A stimulation with *tachycardia, agitation and confusion*

b) RETROGRADE manifestations

- **Cause** – *increased EDV of the left ventricle* due to increased venous return

- **Pathomechanism** – increased **intraventricular pressure which is retrogradely transmitted** to the **left atrium, pulmonary veins and capillaries**
- **Consequences** – **pulmonary** stasis/congestion elicits **clinical manifestations of left HF:**
  - Effort dyspnea
  - Orthopnea
  - Paroxystic nocturnal dyspnea or nocturnal cough
  - Cardiac asthma
  - **Acute pulmonary edema** - the most severe form, occurring in acute left HF or chronic decompensated HF

ACUTE PULMONARY EDEMA

- **Causes:**

  1. DETERMINING factor – the increased **hydrostatic pressure** in **pulmonary capillaries**

  2. FAVORING factors:
  - Decreased plasma oncotic pressure due to hypoalbuminemia
  - Increased interstitial oncotic pressure due to increased capillary permeability
  - Decreased pulmonary lymphatic drainage

- **Evolution – 2 phases:**

  ① INTERSTITIAL edema phase
  - Is triggered by **the increase of hydrostatic pressure in the pulmonary circulation > 20 mmHg** (normally cca. 7 mmHg)
  - Liquid accumulation in the interstitium stimulates the "J" distension receptors that trigger *reflex tachypnea* in order to increase the lymphatic drainage
  - Edema is constituted when liquid filtration in the interstitium outweighs the lymphatic drainage capacity
  - The liquid accumulates in the pericapillary spaces and then moves upward towards the peribronchovascular spaces
  - Interlobular edema determines the *Kerley B lines* to appear on the X-ray (infiltration of pulmonary interlobular septa and their thickening due to pulmonary edema)

  ② ALVEOLAR edema phase
  - Is triggered by tears in the tight junctions between alveolar epithelial cells, which allows the fluid to enters into the alveoli, gradually replacing the respiratory gasses
  - Perialveolar capillary rupture in the advanced stages allows the passage of red blood cells into the alveoli which explains *hemoptysis* - pink aerated sputum

- **Consequences – 2 main types**:

  ① HEMODYNAMIC consequences
  - Pulmonary blood flow redistribution with **decreased perfusion of the basal areas** and **increased perfusion of the apical areas** due to the compression of the basal blood vessels by the interstitial edema and the reflex arteriolar constriction caused by hypoxia

② **RESPIRATORY consequences**

- **Pulmonary ventilation impairment** via the: i) obstruction of the small bronchi by the interstitial edema, ii) reduced pulmonary compliance and iii) increased ventilatory workload
- **Gas exchanges impairment** due to abnormal **diffusion:**
  - ✓ in the interstitial edema phase: PaO_2 decreases (hypoxemia) and $PaCO_2$ decreases (hypocapnia) with *respiratory alkalosis*
  - ✓ in the alveolar edema phase: PaO_2 decreases (hypoxemia) and $PaCO_2$ increases (hypercapnia) with *respiratory acidosis*

II. RIGHT HEART FAILURE

- **Definition** – decreased *right ventricular* performance
- **Causes:**

1. Cardiac

- Congestive left heart failure - **the main cause**
- Pulmonary stenosis
- Right ventricle infarction
- Pericardial diseases, e.g., constrictive pericarditis

2. Pulmonary – PARENCHIMAL diseases

- Chronic pulmonary diseases (COPD) and *cor pulmonale*
- Interstitial pulmonary diseases (e.g. sarcoidosis)
- Acute respiratory distress syndrome

3. Pulmonary – VASCULAR diseases

- Pulmonary embolism
- Severe pulmonary hypertension

In COPD, alveolar hypoventilation causes hypoxia, which in turn elicits reflex arteriolar constriction (to adapt perfusion to ventilation). Increased resistance in the pulmonary circulation will increase the right ventricle afterload with **chronic pressure overload** of the right ventricle, which in time, will fail, and **cor pulmonale (right HF due to pulmonary diseases)** will occur.

- **Manifestations – 2 main types:**
  - *anterograde* caused by the decreased right ventricle SYSTOLIC performance
  - *retrograde* caused by the decreased right ventricle DIASTOLIC performance

a) ANTEROGRADE manifestations

- **Cause** – *decreased right ventricle EF* will result in right heart dilation; the interventricular septum bulges to the left, impairing LV filling, which subsequently reduces the left ventricle output leading to **peripheral ischemia** (muscular, renal and cerebral)
- **Consequences** – anterograde manifestations are *identical* to those of left HF, frequent *fatigue, low energy, dizziness, difficult concentration and confusion*

b) RETROGRADE manifestations

- **Cause** – *increased EDV of the right ventricle*

- **Pathomechanism** – increased **intraventricular pressure which is retrogradely transmitted** to the **right atrium** and the **two venae cavae**
- **Consequences – systemic** stasis/congestion with **clinical manifestations of right HF:**
  - Swelling of the neck veins with the elevation of the jugular venous pressure
  - Shortness of breath, especially when lying flat
  - Liver distension with: *congestive hepatomegaly, right hypochondrial pain* and *hepato-jugular reflux*
  - Stasis in mesenteric veins with: *abdominal discomfort or swelling (ascites)*, *loss of appetite* and rarely, *malabsorption* (bowel edema)
  - Stasis in renal veins with: *oliguria, hematuria and proteinuria*
  - Stasis in the veins of the lower limbs with: *peripheral edema* (swollen ankles) and *cyanosis*
  - General stasis with: *edema of the legs, ascites and hydrothorax*

The elevated pressure is transmitted from the right ventricle to the suprahepatic veins and sinusoid capillaries lead to intrahepatic edema, decreased perfusion and injury to the hepatocytes (elevation of liver enzymes: ALT, AST, LDH), remodeling of the lobule architecture due to collagen deposition and fibrosis, responsible for the **cardiac cirrhosis** of the liver.

PERIPHERAL CARDIAC EDEMA

- **Pathomechanisms – 2 major processes:**
  - Increased sodium and water retention in the body
  - Impaired water distribution between the intravascular and the interstitial space with the accumulation of water in the interstitium

1. SODIUM and WATER retention

- **Cause** – decreased effective arterial volume with renal and cerebral ischemia (increased S-A stimulation), both responsible for RAAS activation
- **Pathomechanisms:**
  - Decreased glomerular filtration (due to renal vasoconstriction)
  - Increased tubular reabsorption (in the PCT and the loop of Henle)
  - Secondary aldosterone hypersecretion (due to RAAS activation)
  - ADH hypersecretion (induced reflex by the decrease of the left atrial filling pressure)

2. WATER DISTRIBUTION impairment with its accumulation in the INTERSTITIUM

- **DETERMINING factor** – increased **hydrostatic pressure** in the **systemic capillaries**
- **FAVORING factors:**
  - Decreased plasma oncotic pressure due to hypoalbuminemia determined by **3 factors:**
    - ✓ Hepatic lesions with decreased albumin synthesis
    - ✓ Renal albumin loss due to renal capillary hyperpermeabilization elicited by hypoxia
    - ✓ Decreased intestinal absorption of aminoacids due to interstitial edema (which also explains the decreased absorption of oral medication and the need for increased doses in these patients)

- Increased interstitial oncotic pressure due to capillary endothelium hyperpermeabilization caused by hypoxia and acidosis
- Decreased lymphatic drainage due to stasis in the venae cavae with increased central venous pressure and impeded lymphatic drainage
- The gravitational factor favors the dependent and symmetrical localisation of the edema

Observation: Due to gravitational effects, edema is more pronounced in the lower limbs in orthostatism and in the presacral area in clinostatism. Even in the absence of visible edema, the patient gains weight therefore patients with congestive heart failure should be weighed daily to correctly adjust diuretic therapy.

11. PATHOPHYSIOLOGY OF ENDOCRINE DISORDERS

THE HORMONES – BRIEF PHYSIOLOGY OVERVIEW

The classical endocrine glands include: the *pituitary gland* (integrated into the hypothalamic-pituitary system) and *the peripheral glands* (thyroid, parathyroids, adrenals, gonads, and endocrine pancreas) whose secretion is regulated by the pituitary gland. The secretory product of the endocrine glands are the **hormones.** They are released directly into the *bloodstream* and transported towards *'target' cells*, where they exert their action by binding to *specific receptors.*

a) HORMONAL SECRETION – is controlled by *3 mechanisms:*

- **Endocrine** (hormone feed-back) – the secretory activity of a peripheral endocrine gland is controlled by the *hypothalamic-adenohypophyseal axis*. Within it, the middle nuclei of the **hypothalamus** secrete *Releasing Hormones (RH) or **'liberins'*** which stimulate secretion of „***tropic"*** hormones by the **adenohypophysis.** These in turn stimulate the secretion of the peripheral endocrine glands, according to the following sequence:
  - **TRH (thyroliberin)** stimulates the release of **TSH (thyrotropin hormone)**, and this stimulates the secretion of **thyroid hormones** - hypothalamic-pituitary-thyroid axis
  - **CRH (corticoliberin)** stimulates the release of **ACTH (corticotropin)**, and this stimulates the secretion of **cortisol** and **androgenic sex hormones** by the **adrenal cortex** - hypothalamic-pituitary-adrenal axis
  - **GnRH (gonadoliberin)** stimulates the release of **FSH** and **LH (gonadotropins)**, and these stimulate the secretion of **sex hormones** in the **gonads** - the hypothalamic-pituitary-gonadal axis

Observation! In case of the negative feed-back control mechanism, the level of the hormone in the blood regulates the hypothalamic secretion of 'liberin' (long feed-back) and the pituitary secretion of 'tropic' hormone (short feed-back), while the level of the 'tropic' hormone in the blood regulates the hypothalamic secretion of 'liberin' (ultrashort feed-back). Increased levels of hormones in the periphery (endogenous or therapeutically administered) will result in reduced hormone release at the pituitary and hypothalamic levels, respectively.

- **Chemical** (humoral feed-back) – the level of a biochemical constant in the peripheral blood regulates the secretory activity of an endocrine gland (e.g., **blood glucose** level controls the **insulin** secretion of the endocrine pancreas, **calcemia** level controls the **PTH** secretion of the parathyroid glands).
- **Nervous** – the level of activity of the vegetative nervous system controls the secretory activity of a peripheral endocrine gland (e.g., the level of sympathetic activity controls the secretion of catecholamines from the adrenal medulla).

b) BLOOD TRANSPORT of hormones – depends on their structure:

- **Water-soluble hormones:** are *peptides* (STH, insulin, PTH), *polypeptides* (liberins, ACTH, calcitonin, glucagon, ADH, oxytocin), *glycoproteins* (TSH, FSH, LH) or *amines* (catecholamines) that circulate in plasma in *free form*, acting on *membrane* receptors with short-lasting effects.
- **Fat-soluble hormones**: are *amines* (thyroid hormones) or *steroids* (adrenal cortex and gonadal hormones) that circulate in plasma mainly *bound to carrier proteins* (specific globulins, albumin) and to a lesser extent in *free form*, acting on *nuclear* (thyroid hormones) and *intracytoplasmic* (adrenal cortex and gonadal hormones) receptors with long-lasting effects.

The ***free fraction*** is the ***biologically active fraction*** responsible for hormonal effects. This fraction is subsequently inactivated via hepatic metabolism or renal elimination.

c) The RESPONSE of the "target" cells to the action of hormones – can be:

- **Direct:** changes in cellular function resulting from the action of the hormone on specific cell receptors and activation of post-receptor signalling mechanisms such as:

  - activation of intracellular signalling pathways, with production of secondary messengers
  - activation of intracellular enzymes
  - altered activity of nuclear transcription factors and gene expression
  - synthesis of specific cellular proteins
- **Permissive:** facilitating maximal response from a cell (e.g. insulin promotes intracellular glucose transport in skeletal striated muscle).
- **Biphasic:** dependent on hormone concentration (e.g. ADH in physiological doses stimulates renal water reabsorption and in increased concentrations has a vasoconstrictive effect).

GENERAL PATHOGENIC MECHANISMS OF ENDOCRINE DISEASES

A. Altered SECRETORY FUNCTION of endocrine glands

Alteration of the secretory function may be the consequence of: i) *direct* damage to the endocrine gland and/or ii) impairment of the *feed-back* mechanism controlling hormonal secretion.

1. PRIMARY disorders – are caused by altered secretion of **blood hormones through DIRECT damage to a peripheral endocrine gland**

- **PRIMARY endocrine hypofunction = hormone deficiency:**
  - **Causes:**
    - *damage/destruction of the gland:* autoimmune mechanism, infection/inflammation, ischemia/hypoxia, malignant proliferation, trauma
    - *decrease in the number of secretory cells:* degeneration secondary to ageing, post-radiation therapy, drug-induced or idiopathic causes
    - *genetic defects*: lack/defective development of the gland, deficiency of one of the enzymes involved in hormone synthesis
  - **Consequence:** negative feed-back mechanism **increases** the level of the *pituitary "tropic" hormone* and of the *"hypothalamic liberin"*, but the peripheral endocrine gland *cannot respond* to the action of the feed-back control mechanism.

- **PRIMARY endocrine HYPERfunction = hormonal excess:**
  - **Cause:** *glandular hyperplasia* (aberrant increase in the number of secretory cells), most commonly in adenomas
  - **Consequence:** negative feed-back mechanism **decreases** *pituitary "tropic" hormone* and *hypothalamic "liberin"* levels, but the peripheral endocrine gland *does not respond* to the feed-back control mechanism (glandular secretion becomes autonomous)

2. SECONDARY disorders – are caused by alterations in the secretion of **pituitary "tropic" hormones,** resulting in either **hyperstimulation - SECONDARY endocrine HYPERfunction,** or **hypostimulation - SECONDARY endocrine hypofunction** of the peripheral endocrine gland

3. TERTIARY disorders – are the consequence of **hypothalamic dysfunctions,** in which both the pituitary and peripheral glands are **hypostimulated - endocrine TERTIARY hypofunction**

Observation:
Secondary functional endocrine impairment can also occur in **the absence of endocrine disease** itself, as is the case of *chronic kidney disease*, *liver failure* or *heart failure*. For example, in chronic kidney disease, deficiency of renal vitamin D activation (caused by decreased number of functional nephrons) and hyperphosphatemia (caused by decreased glomerular filtration rate) are responsible for *hypocalcaemia*, which will eventually lead to *secondary hyperparathyroidism*.

B. Altered BLOOD TRANSPORT of hormones

- **Endocrine HYPERfunction** – is the consequence of *an increase in the free hormone fraction* due to:
  - *decreased levels of transporter protein* through decreased protein synthesis (e.g. liver cirrhosis, malnutrition) or loss of transporter protein via the kidney (e.g. nephrotic syndrome)
  - *hormone inactivation deficiency* through decreased hepatic degradation (e.g., in liver failure) or decreased renal clearance (e.g., in renal failure)
- **Endocrine hypofunction** – is a consequence of *the presence of circulating hormone inhibitors* (e.g. circulating auto-Ab).

C. Altered RESPONSE OF "TARGET" CELLS to the action of hormones

- **Endocrine HYPERfunction** - is due to:
  - an ectopic *tumour* secretion that is not subject to the negative feed-back control mechanism
  - presence of anti-receptor Auto-Ab with a *stimulatory* role in hormone secretion
- **Endocrine hypofunction** - is due to decreased response of "target" cells by:
  - decrease in the number of receptors
  - hormone-receptor binding deficit (decreased affinity for a particular hormone)
  - post-receptor signalling defects

PATHOPHYSIOLOGY OF THYROID DISEASES

The THYROID and THYROID HORMONES – BRIEF PHYSIOLOGY OVERVIEW

The morpho-functional unit of the thyroid gland is the **thyroid follicle.** Its outer limit is represented by a layer of ***follicular epithelial cells*** called ***thyrocytes*** which synthesise thyroid hormones under the action of **TSH**. Thyrocytes take up and concentrate **plasma iodide** (I^-) intracellularly and synthesise a glycoprotein rich in thyroxine residues called ***thyroglobulin*** (TG). Both are then secreted at the apical pole of the thyrocyte into the lumen of the thyroid follicle containing *the* ***follicular colloid***. At the level of the follicular colloid the following occur:

- the oxidation reaction of iodide in the presence of the enzyme ***thyroid peroxidase*** (**TPO**)
- iodination of TG thyroxine residues with the formation of thyroid hormones: ***T4 - thyroxine*** (97%) and ***T3 - triiodothyronine*** (3%), respectively.
- uptake of follicular colloid at the apical pole and release of circulating T4 and T3 at the basal pole of thyrocytes

TSH is the tropic hormone synthesized and stored by the adenohypophysis that binds to TSH receptors (TSH-R) on thyrocytes causing:
- release of thyroid hormones stored in the follicular colloid
- increased synthesis of thyroid hormones
- hypertrophy of the thyroid gland (with the appearance of the goiter) in case of chronic stimulation

TSH release is stimulated by **TRH** (produced and stored in the hypothalamus, released into the hypothalamic-pituitary portal system and transported to the adenohypophysis).
Thyroid hormones circulate in the plasma under **2 forms**:
- **protein-bound:** mainly bound to *Tyroxine-Binding-Globulin* (TBG)
- **free form** (free, F): comprises FT4 and FT3, but at tissue level the free form FT4 is converted by **deiodinase** into the **FT3 form. FT3** is the **biologically active fraction** that:
  - binds to **nuclear receptors** and is responsible for the **effects of thyroid hormones**
  - provides *negative feed-back* control of thyroid hormone secretion within the *hypothalamic-pituitary-thyroid axis*

CLASSIFICATION OF THYROID DISORDERS

1. According to the PLASMA LEVEL OF HORMONES:
- **INCREASED hormone levels**:
  - *Hyperthyroidism:* increased synthesis of thyroid hormones, with increased plasma levels of T3, T4
- **LOW hormone level:**
  - *Hypothyroidism:* deficiency of thyroid hormone synthesis, with decreased plasma levels of T3, T4

2. According to the TYPE of GLANDULAR HYPERTROPHY:
- **Thyroid GOITER** – **diffuse** glandular hypertrophy caused by the *prolonged action of TSH,* which may be associated with hypo-, hyper- or euthyroidism
- **Thyroid NODULE** – hypertrophy **located** in a portion of the gland, caused by a *benign or malignant tumor*

3. According to the ETIOLOGY– thyroid disorders can be:
- **PRIMARY thyroid disorder:** primary alteration of ***thyroid hormone*** levels, with negative feed-back effect on TSH secretion
  - PRIMARY hyperthyroidism: increased T4, T3 and low TSH
  - PRIMARY hypothyroidism: decreased T4,T3 and high TSH
- **SECONDARY thyroid damage**: primary alteration of ***pituitary TSH*** levels
  - high TSH with SECONDARY hyperthyroidism (increased T4, T3)
  - low TSH with SECONDARY hypothyroidism (decreased T4,T3)
- **TERTIARY thyroid damage:** primary alteration of ***hypothalamic TRH*** levels
  - low TRH with low TSH and TERTIARY hypothyroidism (decreased T4,T3)

HYPERTHYROIDISM

DEFINITIONS:
- **HYPERTHYROIDISM** – HYPERFUNCTION of the thyroid parenchyma (as a whole or limited to a portion) responsible for **EXCESSIVE secretion of THYROID hormones**

- **THYROTOXICOSIS – clinical syndrome** caused by **EXCESS of thyroid hormones in PERIPHERY** and characterized by a **HYPERMETABOLIC state**

ETIOPATHOGENESIS of hyperthyroidism and common causes of thyrotoxicosis – Tab. 11.1.

Table 11.1. HYPERTHYROIDISM & THYROTOXICOSIS etiopathogenesis.

Causes	PATHOGENIC mechanisms
A. PRIMARY HYPERTHYROIDISM - thyroid	
1. Graves-Basedow Disease	▪ **Mechanism: AUTOIMMUNE, production of autoAb against TSH receptors (TSH-R) with stimulatory effect on secretion of T4, T3** (TSH-like effect)
2. Single toxic adenoma (solitary thyrotoxicosis)	▪ **Mechanism: AUTONOMOUS THYROID SECRETION of thyroid hormones** T4, T3
3. Toxic *multinodular* goiter (multinodular thyrotoxicosis)	
4. Infectious thyroiditis E.g. subacute viral thyroiditis (De Quervain disease, transient thyrotoxicosis)	▪ **Mechanism: ACUTE glandular GRANULOMATOUS INFLAMMATION,** frequently triggered after a viral respiratory infection
B. SECONDARY HYPERTHYROIDISM - pituitary	
1. Pituitary adenoma	▪ **Mechanism:** TSH hypersecretion by the adenohypophysis
C. IATROGENIC THYROTOXICOSIS (of EXOGENOUS cause)	
1. Drug-induced thyroiditis (e.g. interferon, amiodarone, antineoplastics)	▪ Various mechanisms dependent on drug class
2. Thyrotoxicosis factitia	▪ Increased ingestion of thyroid hormones (levothyroxine: *Euthyrox)*

GRAVES-BASEDOW disease

DEFINITION: diffuse thyroid hypertrophy **(goiter)** of **autoimmune** cause induced by the production of **anti-TSH receptor (TSH-R) autoantibodies (autoAb)** with **stimulatory** effect**,** responsible for:

- **primary HYPERthyroidism** – characterized by:
  - increased T4 and T3 (high plasma levels of hormones due to increased hormone synthesis)
  - decreased TSH (suppression by negative feed-back)
- **goiter:** diffuse, homogeneous
- **thyrotoxicosis:** a HYPERmetabolic condition caused by excess thyroid hormones

It is **the most *common clinical form of hyperthyroidism*** (50-80% of cases).

It is **5 times more common in women than in men** and can occur at any age, with a **peak incidence between 20-40 years.**

ETIOLOGY: multifactorial, being determined by the combined effects of genetic and environmental factors

- **GENETIC factors** - play the major role in susceptibility to developing the disease:
  - **Genetic susceptibility** - proven by:
    - familial clustering of the disease
    - the presence in patients and/or their relatives of other *endocrine* (e.g. Addison's disease, type I diabetes mellitus) or *non-endocrine* (e.g. *myasthenia gravis*, pernicious anaemia, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome) autoimmune diseases
  - **Female gender** – estrogens favour the development of autoimmune disease by *stimulating B lymphocytes* (whereas androgens inhibit it)
- **ENVIRONMENTAL factors** - contribute to disease onset:
  - **smoking** – is associated with the presence of the disease in male heavy smokers
  - **psychological stress** (emotional shocks)
  - **iodine excess:** taking **iodine-containing drugs** (e.g. amiodarone), interferon, anti-retroviral treatment
  - **pregnancy, postpartum period**

PATHOGENESIS: it is a **type II hypersensitivity reaction** in the thyroid gland characterized by the **defect of regulatory T lymphocytes** that allow **Th2 lymphocytes** to induce **activation** and **proliferation of self-reactive B lymphocytes** and thyroid gland infiltration with B lymphocytes that secrete **anti-TSH receptors autoantibodies.**

CLINICAL MANIFESTATIONS:

1. **Goiter:** diffuse, homogeneous, encompasses both thyroid lobes, hypervascularized
2. **Ophthalmopathy - exophthalmia:**
   - **Cause** - a ***local autoimmune reaction*** mediated by the:
     - **self-reactive cytotoxic T lymphocytes** directed against antigens expressed by **fibroblasts and extrinsic muscle fibres of the eyeballs**, which release *proinflammatory cytokines* responsible for *inflammation/oedema* of retroorbital tissues
     - **self-reactive B lymphocytes** producing **anti-TSH-R auto-Ab** against TSH receptors expressed on retroorbitally located **fibroblasts**, with the *proliferation of retroorbital connective tissue* with protrusion of the eyeballs
   - **Consequences:**
     - inflammation and proliferation of retroorbital connective tissue with **exophthalmia**
     - inflammation and a lymphocytic infiltrate in the extrinsic muscles causes **diplopia**
     - in severe forms, occur the:
       - permanent upper eyelid retraction with **photophobia and corneal ulcerations**
       - optic nerve compression with **blindness**
   - is aggravated by **smoking** (banned in Graves disease) and **radioactive iodine therapy**

- corresponds with the highest serum levels of **anti-TSH-R autoAb**, with a *direct correlation* between the *antibody level* and *severity of ocular damage*

3. CARDIOVASCULAR manifestations:

- **Cause:** increased number of cardiac beta-adrenergic receptors and/or their affinity for catecholamines, with the potentiation of cardiac effects of catecholamines
- **Consequences:**
  - **Rhythm disorders:**
    - ✓ persistent **sinus tachycardia** (100-130 b/min)
    - ✓ **tachyarrhythmias:** premature atrial contractions, and frequently **atrial fibrillation**, when **conversion to sinus rhythm is achieved by controlling the thyroid function**
  - **Increased CO** and heart failure with increased CO (due to the hyperkinetic state)
  - **Secondary hypertension** with increased differential BP:
    - SBP increases via the increased CO (positive chronotropic and inotropic effect)
    - DBP decreases via the decreased PVR (vasodilation induced by thermolysis activation)

4. DERMATOPATHY – manifested with:

- **warm and moist skin** caused by the:
  - *increased basal metabolism, high* skin temperature & thermophobia (heat intolerance)
  - *activation of thermolysis mechanisms* with cutaneous vasodilatation and increased sweating
- **thin hair, diffuse alopecia**
- **pretibial edema** (localized pretibial myxedema)
  - connective tissue deposition at the pretibial level with thickened, erythematous skin and an "orange peel" appearance
  - is associated with *increased serum levels of anti-TSH-R autoAb*

5. NERVOUS manifestations:

- *behavioural disorders*: irritability, insomnia
- *neuromuscular hyperexcitability:* fine tremors of the extremities

6. BONE manifestations: osteopenia, osteoporosis

7. DIGESTIVE manifestations:

- weight loss with preserved appetite (due to increased metabolic rate)
- accelerated intestinal transit (diarrhoea)

8. Impaired FERTILITY:

- abnormal menstruation (oligomenorrhoea or amenorrhoea) in women
- impotence in men

9. Thyroid CRISIS („thyroid storm")

- **Definition**: **life-threatening** manifestation of **untreated hyperthyroidism**
- **Etiology:** psychological stress (emotional trauma), childbirth, infections, surgery (overactive thyroid surgery), poorly controlled diabetes, acute myocardial infarction, radioactive iodine therapy
- **Clinical manifestations:**

- *cardiovascular*: tachycardia, angina, hypertension
- *neurological*: extreme agitation, delirium, coma
- *digestive*: nausea, vomiting, diarrhoea
- *fever > 38 C and heat intolerance*

HYPOTHYROIDISM

DEFINITIONS:

- **HYPOTHYROIDISM** – hypofunction of the thyroid parenchyma (as a whole) responsible for REDUCED secretion of THYROID hormones
- **MYXEDEMA** – clinical syndrome caused by **PERIPHERAL** thyroid hormone **DEFICIT** and characterized by a **hypometabolic** state leading to peripheral tissue infiltration

ETIOPATHOGENESIS of hypothyroidism and myxedema – Tab. 11.2.

Table 11.2. Etiopathogenesis of HYPOTHYROIDISM and MYXEDEMA.

Causes	PATHOGENIC mechanisms
I. PRIMARY hypothyroidism - thyroid (95% of cases)	
1. Hashimoto's chronic autoimmune thyroiditis	▪ AUTOIMMUNE mechanism: destruction of the thyroid gland
2. Thyroid ablation	▪ Surgical (postthyroidectomy) ▪ Postradiotherapy in throat cancers ▪ Postradiation with radioactive iodine in hyperthyroidism
3. IATROGENIC hypothyroidism (lithium, amiodarone, antineoplastics)	▪ Inhibition of thyroid hormone synthesis/release
II. SECONDARY hypothyroidism - pituitary	
1. Pituitary disorders	▪ Isolated TSH secretion deficiency or hypopituitarism
III. TERTIARY hypothyroidism	
1. Hypothalamic disorders	▪ Isolated TRH secretion deficiency

HASHIMOTO'S chronic autoimmune thyroiditis

DEFINITION: thyroid hypofunction of **autoimmune** cause characterized by **progressive** destruction of the thyroid gland by **anti-thyroglobulin (anti-TG)** and **anti-thyroid peroxidase (anti-TPO) autoantibodies** resposible for:

- **primary hypothyroidism:** low T4 , low T3, high TSH
- **goiter:**
  - **initially:** diffuse goiter due to glandular hyperplasia induced by ↑TSH
  - **in advanced stages:** atrophic, fibrous gland (firm and irregular)
- **myxedema**: hypometabolic state with decreased basal metabolism

FAVORING factors:

- **genetic:** presence of HLA DR3, DR4, DR5

- **female gender (10 times more frequent):** through the stimulatory effect of oestrogens on selfreactive lymphocyte clones
- **viral infections** (e.g. rubella): through molecular mimicry
- **iodine excess:** by triggering the autoimmune process and/or direct thyroid toxicity

PATHOGENESIS – type IV and II hypersensitivity:

- **defective regulatory T-lymphocytes** allow:
  - **T helper 1** (Th_1) **lymphocytes** to induce activation and proliferation of **autoreactive cytotoxic T lymphocytes** capable of inducing necrosis (via perforins) & apoptosis (via cytokine release - TNFα, IL1, IFN γ) of thyrocytes expressing *non-self* antigens
  - **T helper 2 (**Th_2) **lymphocytes** to cause proliferation of **autoreactive B lymphocytes** and **differentiation into plasma cells** secreting AutoAb that are directed against antigens released by injured thyrocytes→ **anti-TG autoAb and anti-TPO autoAb**
- **chronic inflammatory infiltrate** causes **chronic lymphocytic thyroiditis** with progressive glandular destruction:
  - **glandular destruction flare-ups** are manifested by **transient thyrotoxicosis** caused by the release into the circulation of thyroid hormones stored in the follicular colloid
  - there is a **preclinical stage** when **T4, T3 have normal values, TSH is high, and anti-TG and anti-TPO autoAb are positive** → very important for **early diagnosis of the disease!**
  - **hypothyroidism** becomes **clinically manifest** when **90% of the thyroid gland is destroyed**

CLINICAL MANIFESTATIONS:

- **Characteristics:**
  - **hypometabolic** state induced by hormone deficiency → cold intolerance and decreased sweat secretion
  - **myxedematous** infiltration of connective tissue by accumulation of **mucopolysaccharides and water:**
    - *peripheral edema* (hands, feet) → non-pitting, hard, painful edema
    - *periorbital, palpebral edema* → „puffy" face
    - *tongue edema* → macroglossia

1. NEUROLOGICAL manifestations:

- lethargy, drowsiness

2. MUSCULAR manifestations:

- muscle weakness (peripheral myopathy)

3. CARDIOVASCULAR manifestations:

- myxedematous heart - cardiomegaly with reduced contractility and HR
- myxedematous pericarditis
- arterial hypotension - by decreased CO

4. DIGESTIVE manifestations:

- constipation by reduced gastrointestinal motility
- weight gain despite the reduced appetite

5. Impaired FERTILITY: menorrhagia, anovulatory cycles

6. MIXEDEMATOUS coma:

- **Definition**: **life-threatening event** in advanced stages of **chronic hypothyroidism**
- **FAVORING factors:** elderly, exposure to cold, acute cardio-respiratory diseases, drugs - anesthetics, sedatives, hypnotics, analgesics (accumulation due to drug metabolism deficiency), ascites
- **CLINICAL manifestations:**
  - hypotension → *cardiovascular collapse*
  - global hypoventilation → *hypoxemia and hypercapnia*
  - metabolic imbalances → *lactic acidosis, hypoglycemia*
  - *hypothermia*

PATHOPHYSIOLOGY OF ADRENAL CORTEX DISORDERS

The adrenal cortex and ADRENOCORTICAL HORMONES – BRIEF PHYSIOLOGY OVERVIEW

The adrenal cortex (AC) has 3 areas that secrete: **mineralocorticoids (aldosterone), glucocorticoids (cortisol) and androgenic sex hormones (dehydroepiandrosterone)** - Tab. 11.3.

Cortisol circulates in plasma 96% bound to a transporter globulin ("Corticosteroid-Binding-Globulin", CBG or transcortin). The remaining 4% is free, being the physiologically active fraction.
Serum levels are controlled by the *hypothalamic-adenohypophyseal-adrenal axis*. **ACTH** controls both basal and stress-induced cortisol secretion. In turn, ACTH is released under the action of **CRH.** Increased serum cortisol levels exert a negative feed-back on ACTH and CRH release.

Table 11.3. Hormones secreted by the AC.

Area (zone)	Hormone type	Secretion control
GLOMERULOSA	**Aldosterone** *Role:* – Electrolyte balance – BP adjustment	Angiotensin II and III
FASCICULATA	**Cortisol** *Role:* – Catabolic effect – Adapting to chronic stress	ACTH
RETICULATA	**Dehydroepiandrosterone** *Role:* – Anabolic effect – Secondary sexual characteristics	ACTH

CLASSIFICATION of AC disorders:

1. According to the LEVEL of HORMONES:

- **Hypercorticism** – includes:
  - *Hypercortisolemia:* excess cortisol in the blood
  - *Hyperaldosteronism:* excess ALDO in the blood
- **Hypocorticism** – includes:

- *Hypocortisolemia:* cortisol deficiency in the blood
- *Hypoaldosteronism:* deficiency of ALDO in the blood

2. According to the <u>AREAS AFFECTED</u>:

- **Global impairment** – all AC areas
- **Partial impairment** – limited to one area of the AC

HYPERFUNCTION of the ADRENAL CORTEX

CUSHING syndrome

DEFINITION: Cushing syndrome is the clinical expression of **chronic CORTISOL excess no matter the cause**

CLASSIFICATION:

- **ACTH-<u>independent</u> Cushing syndrome:**
  - **Tumoral**: benign (adenomas) or malignant (carcinomas) tumours of the AC
  - **Iatrogenic**: prolonged corticosteroid therapy
- **ACTH-<u>dependent</u> Cushing's syndrome**
  - **Cushing's disease:** ACTH-hypersecreting pituitary adenoma - *the most common clinical form* (80% of cases)
  - **Ectopic ACTH syndrome:** caused by malignant tumors (lung, bronchial, gastric, pancreatic, thymic cancers) secreting "ACTH-like" substances

PATHOGENESIS:

- increased **cortisol** secretion (Tab. 11.4) is associated with:
  - loss of physiological circadian rhythm of ACTH and cortisol secretion (maximum at 8 am, minimum at midnight)
  - lack of ACTH and cortisol secretion in the presence of a stressor stimulus
  - ± alteration of the negative feed-back control mechanism

Table 11.4. Cortisol and ACTH secretion levels in Cushing syndrome types.

Cushing syndrome	Cortisol secretion level	ACTH level
Tumoral Cushing syndrome	Autonomic cortisol hypersecretion	↓↓
Iatrogenic Cushing syndrome	Decreased secretion of endogenous cortisol	↓
Cushing **disease**	Hypersecretion of cortisol and androgenic sex hormones by bilateral hyperplasia of the AC	↑
Ectopic Cushing syndrome (ectopic ACTH syndrome)	Hypersecretion of cortisol and androgenic sex hormones	↑↑

CLINICAL MANIFESTATIONS:

1. METABOLIC effects

a) PROTEIN metabolism: cortisol is a **PROTEOLYTIC hormone** that *mobilizes amino acids from extrahepatic tissues*

- **Consequences:**
  - **skeletal muscles** → *atrophy of proximal limb muscles (proximal myopathy), muscle weakness*
  - **bones** → *osteoporosis*
  - **skin**: inhibition of *fibroblasts* causes loss of collagen and connective tissue → *purple stretch marks on abdominal flanks* (rupture of cutaneous collagen fibres allows skin vessels to be seen through the thin tegument)*, purpura and ecchymosis* at minimal trauma (loss of perivascular connective tissue), *delayed wound healing*
  - **lymphatic tissue** → *depressed immunity, increased risk of fungal infections*

b) CARBOHYDRATES metabolism: cortisol is a **HYPERGLYCEMIC hormone** that stimulates **neoglucogenesis** *starting from amino acids released from extrahepatic tissues.*

- **Consequences:**
  - **insulin secretion stimulation** by increasing blood glucose (cortisol is a blood glucose counter-regulatory hormone)
  - **insulin resistance** through decreased insulin affinity of the receptors in muscles and adipose tissue → **Adrenal type 2 diabetes**

c) LIPID metabolism: cortisol is a **LIPOLYTIC hormone** that *mobilizes lipids from their stores* **and** determines the **redistribution of adipose tissue** according to the ratio between the density of receptors for cortisol (which increase lipolysis) and insulin (which stimulate lipogenesis), respectively.

- **Consequence:** Cushing obesity characterized by:
  ① **In the areas with a high number of insulin receptors** – **lipogenesis** predominates
    - face → *round, "full moon" appearance*
    - abdomen (perivisceral) → *abdominal obesity*
    - thorax → *accumulation of fatty tissue in the posterior cervical region* ("buffalo hump")

  ② **In the areas with a high number of cortisol receptors** – **lipolysis** predominates
    - upper and lower limbs → *thin limbs*

2. Osteoporosis:

- **PATHOGENIC mechanisms:**

① Increased BONE RESORPTION and decreased OSTEOID MINERALISATION by inhibition of hepatic vitamin D hydroxylation cause:
  - **hypocalcaemia + hypophosphatemia** through decreased digestive absorption and renal reabsorption
  - **hyperparathyroidism secondary to hypocalcaemia**

② Decreased OSTEOID PRODUCTION
  - *directly* via increased bone protein catabolism
  - *indirectly* through decreased estrogen secretion

3. CARDIOVASCULAR manifestations:

- **Secondary hypertension** through:

- hydrosaline retention (cortisol stimulates ADH secretion and has mineralocorticoid properties)
- increased reactivity to catecholamines
- stimulation of the RAA system

4. NEUROLOGICAL manifestations:
- emotional lability

5. SEXUAL abnormalities:
- **in females**: *virilizing effect (excess of androgens)***:** hirsutism, acne, seborrhoea

HYPOFUNCTION of the ADRENAL CORTEX

DEFINITION: decreased synthesis of AC hormones with **AC insufficiency**

CLASSIFICATION:

a) **PRIMARY insufficiency -** damage at the level of the **AC** with:
decreased secretion of cortisol and aldosterone due to one of the following causes:
   - **autoimmune = Addison's disease**, most common form in the F gender
   - **infectious = TB (Tuberculous adrenalitis)**, the most common form in the M gender

b) **SECONDARY insufficiency - pituitary** lesion with:
decreased ACTH secretion responsible for decreased cortisol secretion in the following conditions:
   - pituitary adenoma surgery
   - global pituitary hypofunction
   - prolonged corticosteroid therapy - which suppresses pituitary ACTH secretion and leads to atrophy of the AC

c) **TERTIARY insufficiency** - lesion at hypothalamic level (rarely), with:
decreased CRH secretion responsible for decreased ACTH and cortisol secretion

ADDISON disease

DEFINITION: primary **GLOBAL autoimmune** deficiency of **glucocorticoid** (hypocortisolism) and **mineralocorticoid** (hypoaldosteronism) secretion

PATHOGENESIS:
- activation of **self-reactive cytotoxic T lymphocytes** directed against Ag from the AC $\rightarrow$ necrosis/apoptosis of AC cells
- activation of **self-reactive B lymphocytes** directed against Ag from the AC $\rightarrow$ production of **anti-AC autoAb** and **anti-21 α -hydroxylase autoAb**
- **chronic inflammatory infiltrate** contributes to the destruction of the AC by the release of *pro-inflammatory cytokines*:
  - there is a **preclinical stage** when **serum cortisol and aldosterone have normal values, ACTH is elevated, and anti-AC** and **anti-21 alpha-hydroxylase autoAb are positive** $\rightarrow$ very important for **early diagnosis of the disease!**
  - Addison disease becomes **clinically manifest** when **90% of the AC is destroyed**

CLINICAL MANIFESTATIONS:

1. Effects of HYPOCORTICISM:

- **General symptoms:** asthenia, adynamia
- **Melanodermia:** generalized on the skin and mucous membranes, caused by excess ACTH
- **Arterial hypotension** accentuated by orthostasis → lipothymic states, vascular collapse (low, rapid pulse, sometimes arrhythmias)
- **Digestive manifestations:** anorexia, weight loss
- **Metabolic disorders**: hypoglycemia through decreased gluconeogenesis
- **Sexual abnormalities**:
  - sexual asthenia in men
  - disturbed menstrual cycle in women

2. Effects of HYPOALDOSTERONISM: impairment of fluid and electrolytes homeostasis with:

- hypovolemia and hypotension
- hyponatremia
- hyperkalemia

3. ADDISONIAN crisis:

- **Definition:** life-threatening manifestation of **ACUTE AC failure in a patient with Addison disease**
- **Causes:**
  - final stage of the evolutionary course of the disease
  - abrupt discontinuation of treatment
  - decompensation in conditions of stress, dehydration and severe infections, post-surgery
- **Clinical manifestations:**
  - asthenia and severe adynamia
  - severe dehydration with oligoanuria
  - arterial hypotension → vascular collapse
  - hyponatremia
  - hyperkalemia
  - vomiting and diarrhea

12. PATHOPHYSIOLOGY OF CALCIUM, PHOSPHATE AND MAGNESIUM METABOLISM

I. PHOSPHATE and CALCIUM BALANCE – BRIEF PHYSIOLOGY OVERVIEW

- **The regulation of phosphate and calcium metabolism** has as **role** the maintenance of **calcemia** and **phosphatemia** within normal limits as a *balance* between: i) *digestive intake*, ii) *distribution between the extracellular sector and the intracellular sector* and iii) *renal excretion* of calcium and phosphate.
- **Regulatory mechanisms:**
  - ***Endocrine mechanisms:*** calcemia and phosphatemia levels are regulated by: **parathormone, calcitonin and vitamin D** (acting as a hormone) through their action on the: **bone, kidney and intestine**
  - ***Renal mechanisms*****:** calcium and phosphate excretion is regulated by calcemia and phosphatemia levels

1. PARATHORMONE (PTH)

a) Source: PTH is secreted by the *chief cells* of the **parathyroid glands** which have receptors that are sensitive to calcium and vitamin D.

b) Effects: PTH causes HYPERCALCEMIA and **hypoPHOSPHATEMIA by acting at bone, kidney and intestinal level.**

- **At BONE level (PTH action requires a normal serum Mg^{2+} level):**
  - increases **osteoclast number and activity** (increases resorption of mineralised bone) - rapid response
  - increases the **release of Ca^{2+} from the bone**
  - increases **phosphate release from the bone** (followed by increased renal excretion in order to prevent formation of insoluble tricalcium phosphate complexes that precipitate in tissues)
- **At RENAL level (PTH action is enhanced by vitamin D):**
  - increases **calcium** and **magnesium reabsorption**
  - increases **phosphate excretion**
  - stimulates hydroxylation and activation of **vitamin D** (PTH activates 1α -hydroxylase)
- **At INTESTINAL level (PTH action requires a normal level of vitamin D):**
  - increases calcium and phosphate absorption via vitamin D - slower response

c) Secretion regulation – is dependent on the following factors:

- **Calcemia: is the main factor that rapidly (seconds) regulates PTH secretion**
  Mechanism: parathyroid chief cells have **calcium-sensing receptors** (CaSR) and regulate the release of PTH into the plasma by a **negative feed-back mechanism**:
  - *increased plasma Ca^{2+} concentration:* activates CaSR and decreases PTH release into the plasma
  - *decreased plasma Ca^{2+} concentration:* reduces CaSR activation and increases PTH release into the plasma
- **Magnesemia:** regulates PTH secretion in a similar manner to that of Ca^{2+}, i.e. by acting on CaSRs which have a low affinity for plasma Mg^{2+} as well $\Rightarrow$ Hypomagnesemia can suppress the normal PTH response to hypocalcaemia.
- **Active vitamin D:** *inhibits* PTH synthesis by *increasing calcemia*
- **Hyperphosphatemia:** *stimulates* PTH secretion by the *decrease of calcemia* (formation of inactive tricalcium phosphate complexes)

2. VITAMIN D

a) Sources:

- **synthesis at skin level:** ultraviolet rays convert 7-dehydrocholesterol into cholecalciferol (inactive product)

- **diet:** intake in the form of *vitamin D_2* (ergocalciferol) from plant sources and *vitamin D_3* (cholecalciferol) from animal sources

Vitamin D activation requires 2 processes:

I. Cholecalciferol is transported by plasma albumins and stored in the liver where the *first hydroxylation* takes place under the action of *25-hydroxylase* and generates **25-hydroxycholecalciferol (calcidiol)**

II. In the **kidney (PCT**), the *second hydroxylation* is due to the activity of *1-α -hydroxylase* which:

– generates **1,25 dihydroxycholecalciferol (calcitriol) or the active vitamin D**

– is subject to a **negative feed-back control mechanism** by 1,25-dihydroxyvitamin D3 (limitative stage)

b) Effects: active vitamin D causes **HYPERCALCEMIA and HYPERPHOSPHATEMIA** by acting at intestinal (mainly), renal and bone level:

- **At INTESTINAL level:** increases calcium and phosphate absorption
- **At RENAL level:** increases calcium and phosphate reabsorption
- **At BONE level:** the action of vitamin D depends on calcemia levels:

– *under normocalcemic conditions* – ensures bone mineralisation in the process of bone growth/development in children and bone remodeling in adults

– *under hypocalcemic conditions* – "sensitizes" the bone to the action of PTH, causing bone demineralisation

c) Production regulation: is stimulated by **PTH, hypocalcemia** and **hypophosphatemia** which activate the renal *1-α -hydroxylase*.

3. CALCITONIN (reduced role in adults)

a) Source: polypeptide hormone secreted by thyroid *parafollicular cells*

b) Effects: calcitonin causes hypoCALCEMIA and **hypoPHOSPHATEMIA** by acting on the bone and kidney:

- **At BONE level:**
  – stimulates calcium deposition in the bone
  – decreases bone resorption through osteoclast inhibition (induced by PTH and vitamin D)
- **At RENAL level:**
  – decreases calcium and phosphate reabsorption

4. FIBROBLAST GROWTH FACTOR 23 (FGF-23) - is an important regulator of serum phosphate concentration, along with PTH.

a) Source: secreted by *osteocytes* in response to hyperphosphatemia

b) Effects – at RENAL level:

– ***decreases phosphate reabsorption*** (independently of PTH) in the proximal convoluted tubules (PCT) with ***phosphaturia***

– ***reduces the synthesis of 1,25(OH)$_2$D*** by *inhibiting 1 α-hydroxylase*

In patients with **chronic kidney disease** (CKD) phosphate retention leads to *increased synthesis of FGF-23* with consequent decrease in 1,25(OH)$_2$D concentration and altered calcium absorption; hyperphosphatemia and hypocalcemia are responsible for the development of *secondary hyperparathyroidism* in CKD.

II. IMPAIRED CALCIUM METABOLISM

CALCIUM METABOLISM – BRIEF PHYSIOLOGY AND BIOCHEMICAL OVERVIEW

- **Calcium distribution in the body**

Calcium is *the most abundant mineral* in the body and has the following **distribution:**

- **99% at bone level** (free calcium and in the form of hydroxyapatite crystals) – is the main source of Ca^{2+} which can be mobilised to maintain extracellular calcium within normal limits
- **~1% intracellular** – participates in cellular functions
- **0.1-0.2% in the plasma** – represents the calcemia

- **Calcemia** – total amount of calcium in plasma
  - normal value: **8.5-10.5 mg/dL (2.2-2.6 mmol/L)**
  - exists in **3 forms:**
    1. **Non-diffusible calcium** – bound to plasma albumins - 45%
    2. **Complexed calcium** – **bound to plasma anions, especially** phosphate, sulfate and citrate - 5%
    3. **Ionized calcium (Ca^{2+}) – biologically active fraction** - 50%:
       - can **freely** leave the vascular compartment, fulfilling the roles of calcium in the body
       - participates in exchanges with the **bone**, **kidney** and **digestive tract** and contributes to the maintenance of calcemia

The distribution of plasma calcium in the 3 forms depends on **3 factors:**
- **Plasma albumin level:** a decrease in plasma albumin causes a *decrease in albumin-bound calcium* (non-diffusible calcium) and *calcemia,* but does NOT change the level of ionized calcium.
- **Plasma pH**: an increase in pH - **alkalosis** causes a *decrease in ionized calcium* by **enhancing calcium binding to proteins**, but does NOT change calcemia levels
- **Plasma phosphate levels**: increased phosphatemia causes *decreased ionized calcium* and *increased complexed calcium* (tricalcium phosphate) that precipitates in tissues

- **Calcium balance in the body depends on:**
  1. **Dietary intake**: 800-1000 mg/day (mostly under the form of milk and dairy products)
  2. **Digestive absorption:** occurs in the *duodenum* and *upper jejunum* (30-50% of the daily calcium intake) and is:
     - stimulated by vitamin D
     - inhibited by calcitonin
     - favoured by the acidity of the gastric juice (especially for calcium carbonate)
     - impeded by increased phosphate intake (formation of non-absorbable complexes)
  3. **The removal of calcium from the body** – occurs via **2 pathways:**
     - **digestive** – through the secretions of the digestive glands and faeces
     - **renal** = calciuria (100-300 mg/day). Ca^{2+} filtered at glomerular level is reabsorbed into:
       - PCT (65%): passively, paracellularly
       - Henle loop (15-20%): passively, paracellularly, depending on the electrical gradient created by $Na^+/K^+/2Cl^-$ co-transport **– inhibited by loop diuretics** which decrease Ca^{2+} reabsorption with **hypocalcemia**
       - DCT (5-10%): actively, transcellularly, depending on $3Na^+/1Ca^{2+}$ exchanger **– stimulated by thiazide diuretics** which increase Ca^{2+} reabsorption with **hypercalcemia** (under PTH and vitamin D control)

- **Roles of Ca^{2+} in the body:**
  - Regulation of neuromuscular excitability - extracellular Ca^{2+} level influences the value of the threshold potential
  - Regulation of cardiac activity - extracellular Ca^{2+} levels influence the duration of phase 2 of the action potential
  - Muscle contraction
  - Bone mineralisation
  - Blood clotting factor
  - Intracellular messenger

HYPOCALCEMIA

DEFINITIONS:

– **Hypocalcemia** – decreased calcemia < **8.5 mg/dL** in the presence of **normal albuminemia,** which is **symptomatic** because the **ionized fraction** of calcium is **low.**

– **Pseudohypocalcemia** – decreased calcemia < **8.5 mg/dL** in the presence of **low albuminemia,** which is **asymptomatic** because the **ionized fraction** of calcium is **normal.**

ETIOLOGY:

1. Chronic kidney disease (CKD defined as GFR < 60 ml/min/1,73 m^2) **– MAIN CAUSE of hypocalcemia**

- **Pathomechanisms:**
  - **decreased renal elimination of phosphates with hyperphosphatemia** causes *hypocalcemia* by binding of plasma Ca^{2+} in the form of insoluble complexes
  - **inhibition of 1 α-hydroxylase** with **hypovitaminosis D** causes *hypocalcemia* by decreased intestinal absorption and renal reabsorption of Ca^{2+}
- **Consequences:**
  - hyperphosphatemia and hypocalcemia cause **secondary hyperPTH**
  - hyperPTH and hypovitaminosis D cause **renal osteodystrophy**

Administration of vitamin D in CKD corrects hypocalcemia, hyperPTH and ameliorates renal osteodystrophy.

2. Reduced Ca^{2+} MOBILIZATION from BONES – in**:**

- **Primary hypoparathyroidism (hypoPTH):**
  - *accidental removal or trauma to* the parathyroid glands during surgery, e.g. parathyroid adenoma removal, thyroidectomy - causes **frequent but transient hypocalcemia**
  - *autoimmune diseases*: production of *antiparathyroid autoantibodies* in patients with other autoimmune endocrinopathies, such as *type 1 diabetes mellitus* or *Graves-Basedow disease*
- **Pseudo-hypoparathyroidism: PTH resistance syndrome** due to PTH recognition deficiency by peripheral receptors (mutation of Gs1 protein coupled to PTH receptors)
- **Severe hypomagnesemia (hypoMg):**
  - hypoMg induces a ***functional hypoPTH*** by increasing *"bone resistance*" to PTH action (although PTH is increased, it does not cause hypercalcemia)
    Pathomechanism: Mg^{2+} is a cofactor of *adenylate cyclase* coupled to the PTH receptor, and in conditions of hypomagnesemia, the activity of *adenylate cyclase decreases* $\rightarrow$ the bone becomes *"resistant"* to the action of PTH

3. Deficiency of active VITAMIN D (calcitriol)

- **Characteristics:** it is an *important* cause of hypoCa affecting mainly bone deposits, with significant effects on the *bone, i.e.* rickets in children and osteomalacia in adults
- **Causes:**
  - **reduced food intake**: exclusively vegetarian diets
  - **insufficient exposure to ultraviolet radiation**
  - **lipid malabsorption**: obstructive biliary disorders, pancreatic insufficiency

- **altered hepatic vitamin D metabolism:**
  - *deficiency of liver activation*: liver cirrhosis
  - *inhibition of liver activation*: anticonvulsant medication (e.g. phenytoin), corticosteroid therapy
  - *increased liver catabolism*: chronic alcoholism
- **renal activation deficiency**: chronic kidney disease (CKD)

4. Formation of INACTIVE COMPLEXES with decreased ionized fraction – due to**:**

- **Binding to plasma albumin under conditions of increased plasma pH** (alkalosis)
- **Combination with chelating agents:**
  - *phosphates in increased concentrations* (e.g. CKD)
  - *free fatty acids (FFA) in increased concentrations*:
    - *chronic alcohol consumption:* increases liver production of free fatty acids
    - *acute pancreatitis:* inflammation of the pancreas causes the release of lipolytic enzymes that increase the concentration of FFA in the pancreas and cause "sequestering" of Ca^{2+} in the pancreas.
  - *blood citrate in massive transfusions*

CLINICAL MANIFESTATIONS:

- In **ACUTE** hypocalcemia**, neuromuscular** and **cardiovascular manifestations predominate**, and are precipitated by:
  - *the presence of alkalosis:* vomiting, bicarbonate administration, hyperventilation
  - *increased renal Ca^{2+} excretion*: administration of loop diuretics
- In **CHRONIC** hypocalcemia, **bone manifestations** and **trophic changes predominate**

1. NEUROMUSCULAR manifestations – TETANY

- **Definition:** clinical and electrical syndrome characterized by ***neuromuscular hyperexcitability*** due to **decreased Ca^{2+} levels in plasma, nerve and muscle cells**
- **Pathomechanism: low threshold potential value** with the possibility of triggering a response to subthreshold intensity stimuli
- **Consequences:** depend on cause, severity, swiftness of onset, associated electrolyte imbalances and pH and consist of:
  a. **SENSORY manifestations:** paresthesia of lips, tongue, fingers
  b. **SPONTANEOUS MUSCLE cramps/spasms:**
     - **SOMATIC muscles:**
       - *manifest tetany*: painful carpopedal spasm
       - *latent tetany*: positive Chvostek and Trousseau signs
     - **VISCERAL muscles:**
       - pharyngoesophageal spasm (lump in the throat sensation)
       - laryngospasm (laryngeal stridor in children)
       - bronchial spasm (pseudo-asthmatic crises)
       - coronary artery spasm (angina attacks)
       - pyloric or gastric spasm (epigastric pain)
       - spasms in the small intestine and colon (abdominal colic)
  c. **CONVULSIVE seizures:** in severe hypocalcemia

2. CARDIOVASCULAR manifestations

- **Pathomechanism:** prolongation of phase 2 of the action potential of the working myocardium
- **Consequences:**
  - **ECG change:** *prolongation of the QT interval* with the risk of rhythm disturbances, most commonly *premature contractions and paroxysmal supraventricular tachycardia* (manifested by palpitations and precordial mild pain)
  - the following may occur in **severe acute hypoCa:**
    - **severe arrhythmias**: blocks, ventricular fibrillation
    - **negative inotropic effect:** arterial hypotension, signs of heart failure
    - **lack of response to calcium-dependent inotropic medication** (e.g., norepinephrine, dopamine)

3. BONE manifestations: correspond to bone manifestations of *vitamin D deficiency* (rickets in children, osteomalacia in adults) with **bone pain**, **deformities**, **fractures**

4. TROPHIC changes: brittle nails and hair, leukonychia, periodontitis and early edentulism

HYPERCALCEMIA

DEFINITION: increased calcemia > **10.5 mg/dL** in the presence of **normal albuminemia.**

ETIOLOGY:

1. Increased Ca^{2+} MOBILIZATION from BONES (BONE RESORPTION) – in:

- **primary hyperPTH:** parathyroid adenoma (> 80% of cases), hyperplasia (15 - 20% of cases), carcinoma (< 1% of cases)
- **paraneoplastic hypercalcemia**: characterizes *terminal stages of malignant diseases* that produce bone metastases (in the presence of hypercalcemia the prognosis is reserved) and is caused by *increased bone resorption* (increased osteoclast activity) under the action of:
  - **PTH related proteins (PTHrP**) – PTH-like proteins secreted by *solid tumors* (lung, esophageal, renal, breast cancer) and some *T-cell lymphomas/leukemias* in the adult
  - **osteolytic cytokines** (IL-17, IL-1, TNF-α) – secreted in **multiple myeloma**

2. Increased INTESTINAL ABSORPTION of Ca^{2+} – in:

- **hypervitaminosis D** – *which can be:*
  - *exogenous:* vitamin D intoxication
  - *endogenous:* granulomatous diseases (e.g. sarcoidosis, tuberculosis) due to increased production of 1-α -hydroxylase by activated macrophages in the granuloma structure
- **excess administration of calcium preparations:** most common in women during *osteoporosis* treatment
- **excess milk and absorbable antacid medication** (containing $CaCO_3$)

3. Decreased RENAL ELIMINATION of Ca^{2+} – in:

- **treatment with thiazide diuretics** – increase Ca^{2+} reabsorption in the distal convoluted tubule

- **treatment with lithium salts** (treatment of manic-depressive disorders) – stimulates PTH secretion

CLINICAL MANIFESTATIONS:

1. NEUROMUSCULAR manifestations:
- **Pathomechanism:** increased the *threshold potential value*
- **Consequences**:
  - *MUSCULAR manifestations*: muscle weakness, ataxia, muscle hypotonia, muscle atrophy
  - *NEUROLOGICAL manifestations*: lethargy, acute psychosis, stupor, coma
  - *GASTROINTESTINAL manifestations*: anorexia, nausea, vomiting, constipation

2. CARDIOVASCULAR manifestations:
- **Pathomechanism:** shortening of phase 2 of the action potential of the working myocardium
- **Consequences:**
  - *positive batmotropic effect:* ventricular arrhythmias, cardiac arrest
  - *increased sensitivity to digitalis*: increased risk of digitalis toxicity
  - *ECG change*: shortening of the QT interval

3. RENAL manifestations:
- **Decreased ability of the kidney to CONCENTRATE URINE** – causes **NEPHROGENIC diabetes insipidus** manifested by *polyuria*, *polydipsia*, *hypovolemia*
- **Ca^{2+} precipitation** – causes:
  - formation of kidney stones (oxalate, calcium phosphate) with **renal lithiasis**, which may be complicated by **renal colic**
  - generalized renal storage (parenchymal, tubular) with **nephrocalcinosis** and development of **CKD**

4. DIGESTIVE manifestations:
- **Reduced motility of the digestive tract** – causes anorexia, constipation, nausea, vomiting
- **Ca^{2+} excess** – causes:
  - increased gastrin secretion with risk for **peptic ulcer**
  - ectopic calcifications in the pancreatic ducts with risk for **acute pancreatitis**

5. BONE manifestations:
- **Bone manifestations of primary hyperPTH – fibrocystic osteodystrophy** involving:
  - generalised demineralisation (osteoporosis) through increased osteoclast activity
  - loss of bone mass that is replaced by fibrous tissue (fibrosis) and multiple bone cysts (osteolysis)

6. HYPERCALCEMIC crisis:
  - occurs in **rapid** increases of calcemia in **malignant diseases** and **hyperPTH**
  - manifested by: polyuria, fever, volemic depletion (prerenal azotemia), cardiac arrhythmias (risk of cardiac arrest), altered consciousness

III. IMPAIRED PHOSPHATE METABOLISM

PHOSPHATE METABOLISM – BRIEF PHYSIOLOGY AND BIOCHEMICAL OVERVIEW

- **Phosphate distribution in the body:**
  Phosphates are the ***main intracellular anions*** and have the following distribution:
  – **85% in bone:** under the form of *hydroxyapatite crystals*
  – **1% in the extracellular fluid**: predominantly as *inorganic phosphate* (HPO_4^{2-} /$H_2PO_4^-$)
  – **14% intracellular:** predominantly in the form of *organic phosphorus* in the composition of ATP, nucleic acids, membrane phospholipids, etc.
- **Phosphatemia -** total phosphate in plasma
  – normal value in adults: **2.5-4.5 mg/dL (0,8-1,5 mmol/L)**
- **Phosphate balance in the body – depends on:**
  1. **Dietary intake**: 1200 mg/day, under the form of milk, meat, fruits, vegetables
  2. **Digestive absorption:** occurs in the jejunum (80% of food intake)
     – stimulated by vitamin D
     – diminished by increased intake of Ca^{2+}, Mg^{2+}, Al^{3+} (binds phosphates into complexes)
  3. **Renal elimination -** phosphaturia
     Glomerularly filtered phosphates are reabsorbed in the **proximal tubule** depending on the phosphatemia level:
     – vitamin D increases reabsorption (increases phosphatemia)
     – PTH and calcitonin inhibit reabsorption (decrease phosphatemia)
- **Roles of phosphates in the body:**

– *ATP synthesis with role in:*
  - neuromuscular activity
  - osmotic resistance of erythrocytes
  - normal function of leukocytes and platelets

– *Synthesis of organic compounds:*
  - nucleic acids, membrane phospholipids
  - enzymes required for the intermediate metabolism of carbohydrates, lipids and proteins
  - formation of 2,3-DPG (regulation of haemoglobin affinity for O_2)

– *Acid-base balance regulation*
  - plasma and urine buffer system

HYPOPHOSPHATEMIA

DEFINITION: decreased serum phosphate **< 2.5 mg/dL** in adults

ETIOLOGY:

1. Decreased INTESTINAL PHOSPHATE ABSORPTION:

– *excess administration of antacids* containing aluminium hydroxide and carbonate as well as calcium carbonate (can be used to reduce phosphatemia in CKD)
– *excess administration of laxatives* (with severe diarrhoea)
– *corticotherapy*
– *hypovitaminosis D*

2. RENAL loss of phosphates:

– *hyperPTH*

- corticotherapy

3. INTRACELLULAR migration of phosphates:

- **Parenteral glucose hyperalimentation** with increased phosphate requirement for intracellular glucose metabolism
- **Insulin administration in diabetic ketoacidosis** with increased intracellular glucose uptake and phosphate requirement for glucose metabolism

CLINICAL MANIFESTATIONS:

- **Main cause:** depletion of intracellular stores of ATP

1. NEUROMUSCULAR manifestations – occur in **acute hypophosphatemia** and comprise:

- *Peripheral neuropathy*: tremor, paresthesias, muscle weakness
- *Metabolic encephalopathy*: irritability, confusion, coma

2. HEMATOLOGICAL manifestations – occur in **severe hypophosphatemia (0.1-0.2 mg/dL)** and consist of:

- *Microspherocytosis, rigid erythrocytes* and *haemolytic anaemia*
- *Impaired leukocyte chemotaxis and phagocytosis* with *increased susceptibility to infection*
- *Platelet dysfunction* (impaired platelet aggregation) with *haemorrhagic syndrome*

3. BONE manifestations → occur in **chronic hypophosphatemia** and consist of bone mineralisation disorders (osteoporosis)

HYPERPHOSPHATEMIA

DEFINITION: serum phosphate increase **> 4,5 mg/dL** in the adult

ETIOLOGY:

1. Decrease in RENAL PHOSPHATE EXCRETION:

- advanced CKD (when the GFR drops < 30-50 ml/min)
- hypoPTH

2. INCREASED EXOGENIC phosphate intake:

- excess administration of laxatives containing phosphates
- vitamin D intoxication

3. EXTRACELLULAR migration of phosphates:

- *Massive cytolysis*: osteolytic metastases, massive trauma, rhabdomyolysis, tumor lysis syndrome

Tumor lysis syndrome occurs when tumor cells release their content into the bloodstream, either spontaneously or in response to cytostatic therapy, and includes 4 characteristic findings:

- *hyperkalemia* and *hyperphosphatemia* – due to acute release from the lytic cells
- *hyperuricemia* – due to degradation of purine nucleotides
- *hypocalcemia* – due to acute hyperphosphatemia

CLINICAL MANIFESTATIONS:

- **Caused by the consequences of the formation and precipitation of tricalcium phosphate complexes:**
  - *Hypocalcemia:* paresthesias, tetany and cardiac arrhythmias
  - *Ectopic calcifications:* precipitation of calcium phosphate in soft tissues or tissues with low turnover:
    - joints – causes arthralgia, limitation of movement
    - skin – causes pruritus
    - vessels – causes arteriosclerosis
    - cardiac – causes arrhythmias
- **Caused by inhibition of 1-α-hydroxylase:**hypovitaminosis D (osteoporosis, osteomalacia)

IV. IMPAIRED MAGNESIUM METABOLISM

MAGNESIUM METABOLISM – BRIEF PHYSIOLOGY AND BIOCHEMICAL OVERVIEW

- **Distribution of magnesium in the body:**
  Magnesium is the *second* most important *intracellular cation* after K^+ and has the following **distribution:**
  - 50-60% in bones
  - 40-50% in intracellular fluid
  - 1% in extracellular fluid
- **Magnesemia:** total amount of magnesium in plasma
  - normal value: **1.8-2.7 mg/dL (0,7 – 1,1 mmol/L)**
  - exists in **3 forms:**
    - *non-diffusible magnesium*: protein bound (20-30%)
    - *complexed magnesium*: complexed with phosphates or other anions (40-65%)
    - *ionized magnesium:* the biologically active fraction (15-30%) participating in exchanges with the **bone** and **kidney**
- **Magnesium balance in the body:**
  1. **Dietary intake**: 350 mg/day (green vegetables, cereals, nuts, meat, seafood, etc.)
  2. **Intestinal absorption:** jejunum (25-65% of Mg intake)
     - not regulated by hormones
     - reduced by excessive Ca^{2+} intake through competition at the level of their common carriers
  3. **Renal elimination:** glomerularly filtered magnesium is reabsorbed tubularly depending on the level of magnesemia and calcemia:
     - in the PCT (20%): passively, paracellularly
     - in the loop of Henle (70%): passively, paracellularly, depending on the electrical gradient created by the $Na^+/K^+/2Cl^-$ cotransporter activity (**loop diuretics** inhibit it and decrease Mg^{2+} reabsorption)
     - in the DCT (10%): by active mechanism stimulated by PTH
- **Roles of Mg^{2+} in the body:**
  - *Cofactor of intracellular enzymes involved in ATP generation* – Mg^{2+} is required for glycolysis activation
  - *Decreases conductance* of *membrane Ca^{2+} channels* (motor plate, myocardium) and *K^+ channels* (myocardium, renal tubular cells), respectively – Mg^{2+} is the natural Ca^{2+} and K^+ channel blocker
  - *Blocks brain NMDA receptors* – Mg^{2+} has anticonvulsant (used in the treatment of preeclampsia in pregnant women) and neuroprotective effects (used in the treatment of seizures in children)
  - *Regulates PTH secretion and bone "sensitivity" to PTH action* – Mg^{2+} deficiency is responsible for functional hypoPTH.

HYPOMAGNESEMIA

DEFINITION: decreased magnesemia **< 1,8 mg/dL**

ETIOLOGY:

1. Decreased EXOGENOUS INTAKE and DIGESTIVE ABSORPTION:
- malnutrition, chronic alcoholism
- diarrhea, laxatives abuse
- excessive Ca^{2+} intake (absorption: Ca-Mg competition at the level of their common transporters)

2. Increased RENAL Mg^{2+} LOSS:
- hypoPTH
- loop diuretics
- diabetic ketoacidosis
- nephrotoxic drugs: antibiotics, immunosuppressants

3. INTRACELLULAR Mg^{2+} migration
- **Parenteral glucose hyperalimentation, rapid i.v. administration of insulin** with the use of Mg^{2+} for glucose metabolism
- **Alkalosis**: increases H^+/Mg^{2+} exchange, similarly to H^+/K^+ exchange (H^+ leaves the cell, K^+ and Mg^{2+} enter the cell)

CLINICAL MANIFESTATIONS:

Occur in severe hypomagnesemia and are caused by associated hypocalcemia and hypokalemia.
- **Hypocalcemia (hypoCa)** – appears through:
  - decreased PTH release and functional hypoPTH (hypomagnesemia reduces the effect of PTH on bone)
  - intracellular migration of Ca^{2+} in exchange for Mg^{2+}
- **Hypokalemia (hypoK)** – hypomagnesemia reduces the kidney's ability to preserve K^+ (increases the conductance for K^+ of the renal tubular cells)

HypoCa and hypoK respond to treatment only **after the correction** of hypomagnesemia**.**

1. NEUROMUSCULAR manifestations:
- Hypomagnesemia reduces the presynaptic Ca^{2+} channel blockade and **increased ACh release** from the motor plate → *neuromuscular hyperexcitability* (tetany)

2. CARDIOVASCULAR manifestations:
- Hypomagnesemia decreases myocardial/vascular Ca^{2+} channel blockade – **intracellular Ca^{2+} increase** is responsible for the occurrence of ventricular arrhythmias and digitalis toxicity
- Hypomagnesemia decreases myocardial K^+ channel blockade – **decreased intracellular K^+** is responsible for the development of ventricular arrhythmias and digitalis toxicity

3. BONE manifestations:

- Risk factor for **osteoporosis/osteomalacia** in patients with *chronic alcoholism, diabetes mellitus and malabsorption syndrome*

HYPERMAGNESEMIA

DEFINITION: increased magnesemia **> 3 mg/dL**
- is **rare,** due to the ability of the kidney to excrete excess Mg
- the risk is higher in the **elderly**, due to *reduced kidney function* and *abuse of antacids, mineral supplements or laxatives*

ETIOLOGY:

1. Increased Mg^{2+} INTAKE:
- antacids, mineral supplements, laxatives
- treatment of toxemia gravidarum (pre-eclampsia) with **magnesium sulphate** i.v.→ spasmolytic action on the pregnant uterus, anticonvulsant and sedative

2. Reduced RENAL Mg^{2+} EXCRETION:
- kidney failure

3. EXTRACELLULAR Mg^{2+} migration:
- tissue damage in *burns*, *trauma* (associated with **hyperkalemia** and **hyperphosphatemia)**

CLINICAL MANIFESTATIONS: occur when hypermagnesemia is **severe**

1. NEUROMUSCULAR manifestations:
- increased blockade of presynaptic Ca^{2+} channels causes decreased ACh release from the motor plate → **neuromuscular hypoexcitability** (hyporeflexia, muscle weakness, muscle paralysis, respiratory muscle impairment)

2. CARDIOVASCULAR manifestations:
- increased myocardial/vascular Ca^{2+} channel blockade leads to **decreased intracellular Ca^{2+}** with risk of ventricular arrhythmias (prolonged QT interval) and cardiac arrest (at values > 15 mEq/L)

13. PATHOPHYSIOLOGY OF SHOCK

DEFINITION: pathological condition with **vital risk** characterized by a **severe and generalized decrease of tissue perfusion**, responsible for:

- ***cell hypoxia and cellular metabolic abnormalities***
- ***systemic inflammatory reaction***, in evolution

ETIOPATHOGENIC CLASSIFICATION:

According to the ***cause responsible for the decrease in tissue perfusion***, **3 main types** of circulatory shock are described (in the evolution of shock these may coexist):

- **CARDIOGENIC** shock – primary decrease of the **cardiac output (CO)**
- **HYPOVOLEMIC** shock – primary decrease of the **circulating volume (VOLEMIA)**
- **DISTRIBUTIVE** shock (vasogenic) – primary decrease of **peripheral vascular resistance (PVR)**

EVOLUTIVE STAGES – 3 stages, regardless of the etiology**:**

I. COMPENSATED or EARLY shock:

- **Cause** - the presence of the etiologic factor responsible for the reduction of tissue perfusion
- **Characteristics:**
  - the **EFFICIENT INTERVENTION** of **compensatory mechanisms**
  - **blood pressure and tissue perfusion are maintained** within normal limits
- **Clinical manifestations** - nonspecific symptoms due to the intervention of compensatory mechanisms: tachycardia, rapid and shallow breathing, cold skin, wet skin (except during septic shock), thirst, oliguria, agitation, confusion, anxiety, mydriasis

The compensatory mechanisms that maintain tissue perfusion in circulatory shock are:

- **Nervous** mechanisms - **sympatho-adrenergic (S-A) activation,** aimed at **restoring BLOOD PRESSURE**
- **Hormonal** mechanisms - **activation of the RAAS and increase ADH release**, aimed at **restoring VOLEMIA**

To the latter, **restoration of volemia is contributed by the redistribution of the extracellular fluid**. With the progressive decrease in tissue perfusion, the hydrostatic pressure (Ph) in the systemic capillaries also decreases with the subsequent decrease in the filtration pressure at the arteriolar end of the capillaries and increase in the reabsorption pressure at their venular end.

II. DECOMPENSATED or PROGRESSIVE shock:

- **Cause** – persistence of the etiological factor or inefficiency of compensatory mechanisms and/or of the therapy
- **Characteristics:**
  - the **FAILURE** of **compensatory mechanisms**
  - **arterial hypotension** with **tissue hypoperfusion** which induces:
    - ✓ the reduction of **renal** perfusion with the aggravation of *oliguria* and the risk of acute kidney injury (AKI) known as *shock kidney*
    - ✓ the reduction of **cerebral** perfusion with *altered mental status*
    - ✓ the reduction in **coronary** perfusion with signs of *myocardial ischemia*

  - **lactic metabolic acidosis**
- **Clinical manifestations:** aggravated tachycardia and tachypnea, reduction of pulse pressure (the difference between the SBP and DBP, normally = 40 mmHg, during shock it falls below 25% of the SBP), cyanotic skin and sensory disturbances, obnubilation, stupor, coma

III. IRREVERSIBLE or REFRACTORY shock:
- **Cause** – progression of shock, which can no longer be reversed
- **Characteristics:**
  - **diffuse tissue hypoxia** with **the FAILURE of MICROCIRCULATION**
  - the presence of ***positive feedback mechanisms*** of **worsening/perpetuating of the state of shock**:
    1. Lack of response of the vascular system to catecholamines (vasoconstriction is replaced by vasodilatation) with **hemodynamic disturbances** and **circulatory collapse** that aggravated the tissue hypoperfusion
    2. **Damage of vascular endothelium** and the release of proinflammatory mediators induce the **systemic inflammatory reaction**
    3. **Altered coagulation** with the risk for **disseminated intravascular coagulation (DIC)**
    4. Impairment of the **cellular metabolism** responsible for **irreversible** extensive tissue injury with the risk for the **multiorgan organ dysfunction syndrome (MODS)**
  - evolution towards death, despite therapeutic measures
- **Clinical manifestations:** marked hypotension, bradycardia, decrease in respiratory rate with the decrease of the tidal volume, cyanotic and cold skin, marked diaphoresis, risk of severe tachyarrhythmias, altered mental status and coma

MICROCIRCULATION FAILURE IN SHOCK

- **Pathogenesis:**
  1. **In the first stage of shock** – the intense S-A stimulation produces a ***generalized spasm of the microcirculation*** **(arterioles, pre- and postcapillary sphincters, venules)** which, in *short-term* has a compensatory effect (maintains tissue perfusion), but in *long term* leads to ischemia and cellular hypoxia, activation of anaerobic glycolysis and subsequent **lactic acidosis**
  2. **In the second stage of shock** - **acidosis causes precapillary sphincter relaxation** (which are more susceptible to acidosis), while **postcapillary/venular** sphincters (more resistant to acidosis) remain **contracted**. Thus, the blood enters the microcirculation and accumulates in the capillaries leading to the **microcirculation failure**.

     Stasis in the microcirculation (the "pooling" phenomenon) causes:
     - ***aggravation of the vascular endothelium injury***
     - ***hyperpermeabilization of capillaries*** with the formation of an *exudate* in the interstitium with the reduction of volemia, decreased venous return, cardiac output and blood pressure and the aggravation of shock

- **Consequences:**

Microcirculation failure leads to initiation of ***positive feedback mechanisms*** that are responsible for worsening of tissue hypoxia, impairment of cellular metabolism and progression towards MODS with vital risk.

There are **5 positive feedback mechanisms** that underlie the failure of mirocirculation:

1. Progressive decrease of the CIRCULATING VOLUME

- **Cause:** worsening of tissue hypoperfusion and capillary hyperpermeabilization
- **Effects:**
  - worsening of endothelial dysfunction with increased fluid extravasation in the interstitium, decreased venous return/preload and **aggravation of cardiac output decrease**
  - worsening of cellular hypoxia with decreased ATP synthesis, impairment of ATP-ases function and **cell death**

2. Activation of COAGULATION and FIBRINOLYSIS

- **Cause**: vascular endothelium injury and tissue destruction
- **Effects:**
  - **primary activation of coagulation** via:
    - ✓ platelet adhesion and aggregation with *thrombus formation,* which causes platelet consumption and **thrombocytopenia**
    - ✓ exposure of subendothelial structures, which activates the ***intrinsic*** pathway of coagulation
    - ✓ release of tissue factors, which activate the ***extrinsic*** pathway of coagulation that causes:
    - ✓ uncontrolled **generation of thrombin** in the bloodstream responsible for:
      - **fibrin deposition**
      - **consumption of coagulation factors** and **hypofibrinogenemia**
  - **secondary activation of fibrinolysis** responsible for:
    - **fibrin degradation**
    - **increased fibrin degradation products** (FDP, D dimers)
    - risk of **disseminated intravascular coagulation** (consumptive coagulopathy)

3. Ischemia of the INTESTINAL MUCOSA

- **Cause:** hypoperfusion of the digestive tract
- **Effects:**
  - sequestration of fluids in the intestinal lumen
  - increased permeability of the intestinal mucosa with:
    - ✓ translocation of bacteria and the absorption of their toxins
    - ✓ invasion of the body by the bacterial toxins and the onset of the **systemic inflammatory reaction,** which involves the release of mediators (cellular and plasmatic) of the inflammatory response

4. Release of LYSOSOMAL ENZYMES

- **Cause:** activation of phagocytes under the action of bacterial toxins (in septic shock)

- **Effects:**
  - activation of the transformation of *kininogen (inactive precursor)* into *bradykinin (vasoactive kinin)* which further causes vasodilation, increased capillary permeability, activation of coagulation
  - extensive tissue injury and cell death

5. SYSTEMIC INFLAMMATION

- **Causes:**
  - Endothelial dysfunction
  - Release of pro-inflammatory cytokines (TNF-α, IL-1)
  - Excessive generation of nitric oxide (NO)
  - Oxidative and nitrosative stress (the superoxide anion forms with NO the peroxynitrite anion with increased toxicity)
- **Effects:**
  - risk of progression towards **multiple organ dysfunction syndrome** (MODS)

IMPAIRMENT OF CELLULAR METABOLISM

Once installed, microcirculation failure causes severe impairment of oxygen and metabolic substrates use and a state of **increased catabolism** which contributes to shock progression.

1. Decreased OXYGEN supply and use:

Hypoxemia and tissue hypoxia are responsible for the **anaerobic metabolism**, therefore the **anaerobic glycolysis** becomes the main source of energy with **2 effects**:

a) **Energy (ATP) decrease** and the decline in the Na^+/K^+ pump activity with alteration of ionic gradients causes:
   - ✓ *entry of Na^+ (+ H_2O) into the cells* with osmotic cytolysis
   - ✓ *exit of K^+ from the cells* with partial depolarization of the myocardial cells/neurons and decreased resting potential

b) **Progressive lactic acidosis:**
   - ✓ *intracellular* with the decrease of activity/inhibition of cellular enzymes
   - ✓ *extracellular* with metabolic acidosis (primary decrease in plasma bicarbonate), reduced Hb affinity for O_2 (right shifht of the dissociation curve of oxyHb to provide tissue oxygenation)

2. Impaired GLUCOSE metabolism:

In the case of a severe decrease in tissue perfusion, **the reduction of glucose** at tissue level causes an **energy substrate deficit.**

In septic shock, **hyperglycemia** is initially caused by:

- decreased glucose utilization by the cells due to insulin resistance secondary to bacteremia and bacterial endotoxins
- increased production of glucose through glycogenolysis and gluconeogenesis due to increase level of the counter-regulatory hormones

Activation of **anaerobic glycolysis** results in **lactic metabolic acidosis**, which is:

- **compensated** via the **RESPIRATORY** mechanisms, i.e., hyperventilation with secondary decrease of $PaCO_2$

- **corrected** via the **RENAL** mechanisms, i.e., increased reabsorption and generation of bicarbonate
- **decompensated** with the progression of shock, being aggravated by the:
  - ✓ decrease of *hepatic lactate metabolism* („shock liver")
  - ✓ decrease of *renal excretion of lactate* („shock kidney")

3. Impaired LIPID metabolism:

- **Lipolysis activation in the adipose tissue** and hydrolysis of the triglycerides under the effect of catecholamines induces the **release of free fatty acids into the circulation.**

4. Impaired PROTEIN metabolism:

- Activation of **protein catabolism** under the effect of cortisol causes the **release of aminoacids;** alanine and glutamine are used for the activation of gluconeogenesis
- **In septic shock** there is the **preferential degradation** of:
  - *serum albumins* with hypoalbuminaemia, decreased plasma oncotic pressure and fluid reabsorption in the venous end of the capillaries with worsening of hypovolemia
  - *immunoglobulins* with reduced capacity for specific defence, increased infection risk and delayed wound healing
  - *muscle proteins* with extreme fatigue

MECHANISMS OF CELL DEATH IN SHOCK

1. MITOCHONDRIAL DYSFUNCTION

- **Cause:** inhibition of the electron transfer at the mitochondrial respiratory chain due to decreased oxygen availability
- **Effects**:
  - decreased energy stores (low ATP levels)
  - impairment of the transmembrane ion transport
  - inability to maintain structural integrity of cell membranes

2. Membrane injury induced by COMPLEMENT ACTIVATION

- **Cause**: activation of complement via the *classical* (by antigen-antibody complexes in anaphylactic shock) or via the *alternative pathway* (by bacterial toxins in septic shock)
- **Effects**: lysis of the cell membranes via the membrane attack complex

3. Release of LYSOSOMAL ENZYMES responsible for cellular autodigestion.

ETIOPATHOGENIC TYPES OF SHOCK:

I. CARDIOGENIC shock

DEFINITION: decreased tissue perfusion due to the **primary decrease of CO** due to:

- decreased myocardial contractile function in **non-mechanical** shock
- impaired ventricular filling or pump function deficit in **mechanical** shock

Observation: For the assessment of cardiogenic shock, the cardiac index (CI) is used, where CI = CO/BSA, and BSA represents the body surface area.
Normal CI values = 2.5 - 4 L/min/m^2; in cardiogenic shock, CI falls < 2.2 L/min/m^2.

ETIOLOGY:

1. **NON-MECHANICAL cardiogenic shock** occurs in**:**
   - **acute myocardial infarction (necrosis > 40%** of the **left ventricle) – main cause**
   - malignant tachyarrhythmias (ventricular tachycardia and fibrillation)
   - dilated and hypertrophic cardiomyopathies in advanced stages
   - prolonged cardiac surgery
   - severe sepsis (trelease of TNF-α, IL-1, IL-6 by inflammatory cells, NO by endothelial cells and a Myocardial Depressant Factor/MDF by the ischemic pancreas that further depresses myocardial function)

2. **MECHANICAL or OBSTRUCTIVE cardiogenic shock** may complicate:
   - massive pulmonary embolism or severe pulmonary HT $\rightarrow$ risk of acute right HF
   - restrictive cardiomyopathy in advanced stage
   - cardiac tamponade
   - constrictive pericarditis
   - tension pneumothorax

Observations:

Massive pulmonary embolism and severe pulmonary HT lead to ***pulmonary vascular OBSTRUCTIVE shock*** characterized by decreased right ventricular output due to a "barrier" to the passage of blood flow into the pulmonary circulation.

The other causes of mechanical obstructive shock present clinically as hypovolemic shock caused by low preload through reduced venous return to the right atrium or by insufficient right ventricular filling.

II. HYPOVOLEMIC shock

DEFINITION: decrease in tissue perfusion due to the **primary decrease in effective circulating volume (by > 15%)**.

ETIOLOGY:

- **BLOOD losses with HEMORRHAGIC shock** due to acute bleeding (internal/external) in:
  - polytrauma - contusions or penetrating trauma
  - vascular disorders - aortic aneurysm rupture
  - gastrointestinal disorders - upper or lower gastrointestinal bleeding
  - obstetrical disorders - ruptured ectopic pregnancy
  - intra- and postoperative hemorrhage
  - postpartum hemorrhage
- **EXTRACELLULAR FLUID losses with NON-HEMORRHAGIC shock** in:
  - gastrointestinal losses - diarrhea, vomiting
  - renal losses - polyuria in diabetes mellitus, diabetes insipidus
  - plasmorrhagia - severe burns (III and IV degree)
  - sequestration of fluids in the body cavities with the formation of the 3rd space - acute pancreatitis, peritonitis, intestinal obstruction

III. DISTRIBUTIVE or VASOGENIC shock

DEFINITION: decreased tissue perfusion due to the **primary decrease of peripheral vascular resistance (PVR)**, also known as **normovolemic shock or relative hypovolemia**.

ETIOLOGY:

1. **Septic shock – most frequent type of distributive shock**
2. **Neurogenic shock**
3. **Anaphylactic shock**

1. SEPTIC shock

DEFINITIONS:

- **SEPSIS**: the abnormal immune response of the host to infection that causes **organ dysfunction** with vital risk
- **SEPTIC SHOCK**: subtype of sepsis in which the host abnormal immune response to infection may lead to **multiple organ dysfunction** with increased vital risk

CHARACTERISTICS of septic shock:

- decreased tissue perfusion caused by the **primary decrease in PVR** as a result of the **SYSTEMIC inflammation**
- the presence of **HEMODYNAMIC disturbances** as seen by **persistent arterial hypotension** defined by a decrease in mean arterial pressure (MAP) $\leq$ 65 mmHg despite adequate volemic resuscitation and the need for vasopressor support
- the presence of **CELLULAR METABOLIC impairment** diagnosed by the increase of **serum lactate** > 2 mmol/L
- the presence in patients with known infection of 3 variables (quickly identifiable at the patient's bedside): respiratory rate ≥ 22 breaths/minute, altered mental status, SBP $\leq$ 100 mmHg
- **Multiple Organ Dysfunction Syndrome (MODS)**, which is the main cause of death

Observations:

Systemic inflammatory reaction has replaced the term "systemic inflammatory response syndrome (SIRS)" which was earlier defined by the presence of **two or more** of the following:

- Temperature > 38,5°C or < 36°C
- HR > 90 b/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
- No. leukocytes >12.000/mm^3 or < 4.000/mm^3 or > 10% immature forms (”band forms”)

These parameters were used in the definition of sepsis in the presence of a suspected or documented infection, but currently their use has been abandoned, the variables mentioned above being used.

ETIOLOGY:

A. CAUSATIVE factors:

1. Infectious causes:

- Bacterial infections:
  - **Gram (-)** bacterial infections - E. coli, Pseudomonas (release **endotoxins,** e.g., the membrane lipopolysaccharide)
  - **Gram (+)** bacterial infections - Staphylococcus aureus, Streptococcus (secrete **exotoxins**, e.g., the lipoteichoic acid, peptidoglycans)

- Viral, fungal, protozoal, rickettsiae infections

2. Non-infectious causes:

- Polytrauma
- Burns
- Acute pancreatitis
- Drug reactions
- Posttransfusion hemolytic reactions

B. RISK factors:

- **extreme ages** – neonates/infants, elderly (> 65 years)
- **patients with a personal history of sepsis**
- **pre-existing chronic pathology** - diabetes, chronic kidney disease
- **patients with medical conditions causing immunosuppression** - advanced cancers, AIDS, cyrrhosis, autoimmune disorders, splenectomy
- **iatrogenically immunosuppressed patients by immunosuppressive therapies**, including systemic corticosteroid therapy
- **the presence of a means of access for germs** - venous catheterization, urinary catheterization, tracheal intubation
- **alcohol or i.v. drug abusers**
- **pregnancy**

PATHOGENESIS

Septic shock of an infectious cause has as its starting point a localized site of infection (pulmonary, urinary, digestive) from where the bacteria can:

i) *proliferate locally* and release into the blood their **endo- or exotoxins** or

ii) *enter the blood stream*, causing **bacteremia** (documented by positive blood cultures)

”Pathogen-Associated Molecular Patterns” (PAMPs) include components of infectious agents (bacterial, viral, fungal) that are recognized by specific receptors located on the *surface* (e.g., Toll-like receptors) and in the *cytosol* (e.g., NOD-like receptors where NOD - Nucleotide-binding Oligomerization Domain) of native defence cells (macrophages/dendritic cells, microphages, natural killer lymphocytes). The effects consist in increasing the expression of the genes responsible for the synthesis of pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6, etc.) which induce:

i) the increase of the innate immune defence by activating phagocytosis and formation of *neutrophil extracellular traps (NETs)* in order to limit the spread of infection (include DNA fragments, proteins, antibacterial enzymes and bacteria). NETs are intended to protect the host by preventing the spread of microorganisms, but when excessive formed during sepsis, platelets become hyperactivated and the hemostatic balance may be shifted in favour of excessive coagulation, with increased formation of thrombi and risk of DIC. Of note, NETs were present in increased numbers in the pulmonary circulation at the autopsy of patients who died with COVID-19.

ii) the release of microparticles containing lipids and pro-oxidizing and pro-coagulant proteins and tissue factors that determine the occurrence of the *"immunothrombosis" phenomenon*, by which microbial agents are trapped in microthrombi favoring the

perpetuation of chemotaxis/activation of leukocytes, the self-maintenance of systemic hyperinflammation and finally, microcirculation failure, DIC and MODS.

The massive circulatory release of the cellular mediators (primary and secondary) and plasma mediators (the complement system, kinins, coagulation factors) is the central event in the occurrence of septic shock to which the acute phase reaction contributes via the stimulation of acute phase proteins synthesis by the liver under the action of IL-6.

An essential role in the **pathogenesis of marked vasodilation with severe hypotension** has been attributed to:

- proinflammatory cytokines **TNF-α** and **IL-1** with a direct toxic effect at endothelial level
- **nitric oxide (NO)** which, when released excessively, causes cell damage mediated by the formation of oxygen and nitrogen free radicals (the peroxynitrite anion)

In large quantities, **both cytokines and NO exert an effect of depressing myocardial contractility** (which is, however, reversible), paving the way towards irreversible shock.

2. NEUROGENIC shock

DEFINITION: decreased tissue perfusion due to **the primary decrease in PVR** caused by the **alteration of the autonomic nervous control of the vascular tone.**

ETIOLOGY:

- **Inhibition of sympathetic stimulation** in: spinal cord trauma
- **Increase of parasympathetic stimulation** in: cranio-cerebral trauma with damage to the vasomotor center, overdose in anesthesia, barbiturate poisoning

CLINICAL MANIFESTATIONS

- at variance from tachycardia and cold skin characteristic for the previously described types of shock, in neurogenic shock hypotension from the decompensated (progressive) shock may be accompanied by **signs of excessive parasympathetic activity**: *bradycardia, warm skin, hyperemia*.

3. ANAPHYLACTIC shock

DEFINITION: decreased tissue perfusion due to the **primary decrease of PVR** caused by the **massive release of inflammatory mediators into the bloodstream.**

ETIOLOGY:

- the most severe form of anaphylaxis (type I HS reaction), with vital risk (it is a medical emergency)
- occurs in the conditions of exposure of the patient who has been sensitized to allergens such as: *insect venoms, drugs (e.g., penicillin), food (seafood, peanuts)*

CLINICAL MANIFESTATIONS:

- the vital risk is associated to **upper airway obstruction with bronchospasm, stridor and risk of asphyxia by glottic edema**
- it also associates: **severe hypotension** (through severe vasodilation and fluid extravasation secondary to vascular hyperpermeability), **generalized urticaria with itching, anxiety, dizziness, nausea, vomiting and abdominal cramps**.

COMPLICATIONS OF SHOCK:

The main complications of shock are:

1. **Acute Respiratory Distress Syndrome** (**ARDS)** or the "**shock lung"**
2. **Acute Kidney Injury (AKI) - the prerenal type of AKI** or the **"shock kidney"**
3. **Stress ulcer**
4. **Multiorgan Dysfunction Syndrome (MODS)**

MULTIORGAN DYSFUNCTION SYNDROME (MODS)

DEFINITION: progressive dysfunction of at least two organs (lung, kidney, liver, heart, brain) that leads to acute organ failure.

ETIOLOGY:

- **septic shock - the main cause, including the one associated with COVID-19**
- severe trauma that associates prolonged arterial hypotension
- major surgery
- severe burns
- acute pancreatitis

RISK factors:

- elderly (over 65 years)
- chronic alcoholism
- malnutrition
- chronic/severe pre-existing diseases: diabetes mellitus, renal failure, hepatic dysfunction, cancer
- severe tissue damage: large hematomas, extended tissue necrosis, severe burns
- coma upon admission into hospital or late cardio-pulmonary resuscitation

PATHOGENESIS: is a condition associated with hyperinflammation and a pro-coagulant state

MODS represents the most frequent cause of death in Intensive Care Units, with a mortality rate between 30-70%, depending on the number of affected organs.

Observations:

In recent years, one of the most intensively studied mechanisms in sepsis/septic shock is represented by the mitochondrial dysfunction. Thus, in mechanically ventilated patients, there is an association between the decrease in the energetic function and alteration of mitochondrial dynamics (with an increased fragmentation through the predominance of fission process over the one of mitochondrial fusion); in addition, the presence of hyperglycemia induces a mitochondrial "toxicity" that has been associated with increased mortality in these patients in intensive care units.

Currently, restoring/preserving mitochondrial function in critically ill patients represents a new therapeutic target and a hot research topic.

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