

Disturbances of local and systemic
circulation.

Pathophysiological mechanisms of
shock.

Multiple organ dysfunction syndrome
(MODS)

Lecture content

- **Function of the circulatory system**
- **Regulation of circulation**
- **Local circulation disorders**
- **Disorders of systemic circulation**
- **Multiple organ dysfunction syndrome**

Function of circulatory system

- **The delivery** of oxygen and nutrients to all cells and **disposal** of metabolic products

- **Blood pressure** (*tensio arterialis* - TA)

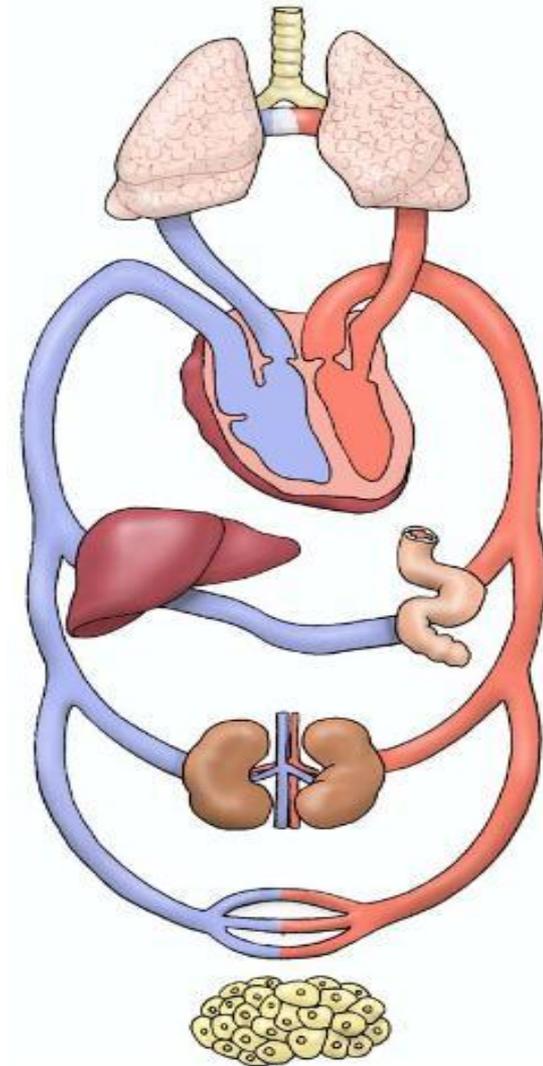
TA = MV multiplied by PR

MV (cardiac output in one minute)

PR (periphery resistance)

- **Pulmonary circulation**

- **Systemic circulation**



Function of the circular system

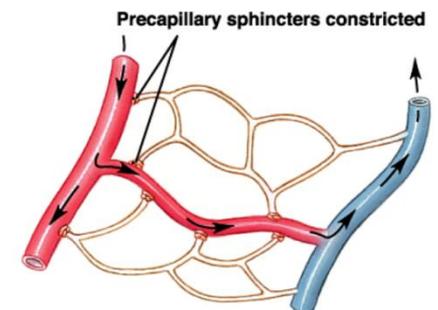
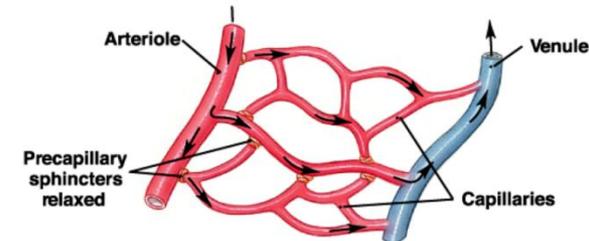
- In physiological condition **blood moves only in one direction only forward** 
- **The biggest blood supply** have important vital organs like **heart and brain**
- In situations of **vital threats some organs** (such as intestines, skin, and kidneys) **can stay without enough (normal amount) blood**

Regulation of local circulation

Local circulation depends on the:

- **Conditions of systemic circulation** (TA, MV, CF, viscosity and composition of blood, condition and integrity of blood vessels...)
- **Control** achieved **by central** (nervous and humoral) and **peripheral** (local) regulatory mechanisms

- **Precapillary sphincter** (important anatomical **sites of blood flow regulation** due to their strategic placement **at branch points of proximal arterioles**, where they reduce pressure and blood flux into the downstream capillary and regulate perfusion)



Nervous (central) regulation

- **Vasomotor center** for maintaining **blood vessel tone** (sympathetic, adrenal medulla, Renin-Angiotensin-Aldosterone system)
- **n. Vagus effects** (M1, M3 receptors, nitric oxide)

Humoral factors

- **Vasoconstrictors:**
 - noradrenaline and adrenaline (alpha and beta receptors),
 - angiotensin (AT1 receptors),
- **Vasodilators:**
 - bradykinin,
 - histamine (H1 receptors),
 - prostaglandins

Other factors affecting the level of local circulation

- local hypoxia,
- hydrogen ions,
- carbon dioxide (CO₂),
- endothelins (ETA receptors),
- High and low temperature,
- ions (sodium, potassium and calcium),
- vitamins (thiamine, riboflavin, niacin)

Local circulation disorders

- Arterial hyperemia
- Venous hyperemia
- Local ischemia syndrome
- Thrombosis
- Embolism
- Disorder of the lymphatic system

Arterial hyperemia

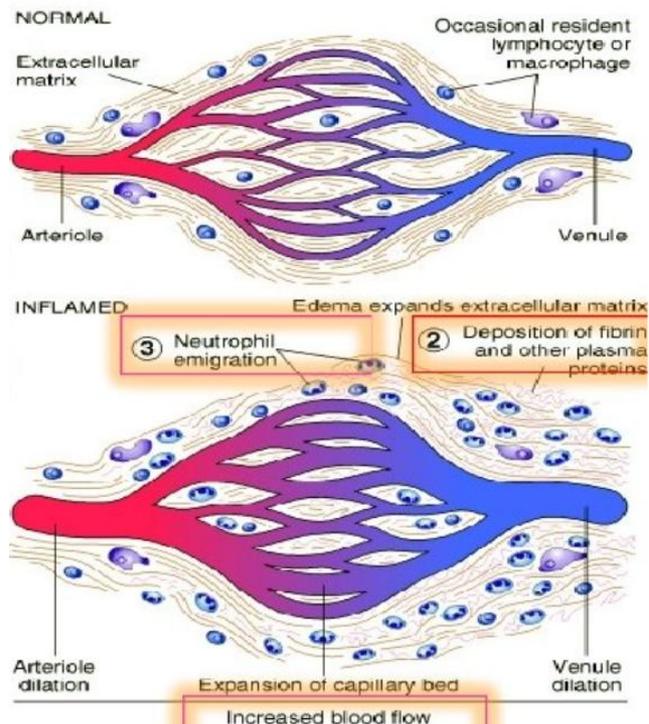
- It is characterized by **increased arterial blood flow** with normal outflow from the tissues
- Etiological factors: metabolic, biological, neurogenic
- Pathogenesis:
 - myoparalytic theory (decreased muscle tone),
 - neuroparalytic theory (decreased sympathetic tone),
 - neurotonic theory (increased parasympathetic tone)

Types of arterial hyperemia

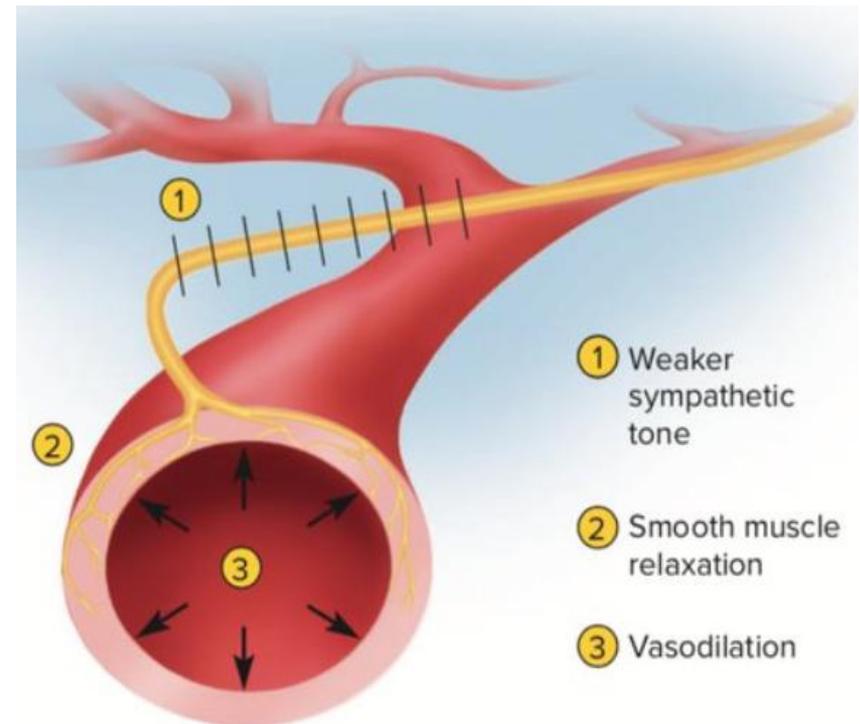
- In physiological conditions
 - during training
- In pathological conditions
 - during inflammation,
 - hyperemia caused by sympathectomy,
 - *ex vacuo*,
 - *vicar* hyperemia,
 - in the "steal syndrome"

Examples of arterial hyperemia

- **During inflammation**
after the release of mediators (histamine) and pro-inflammatory cytokines (IL-1, IL-6, TNF- α) from the tissue penetrated by microbes



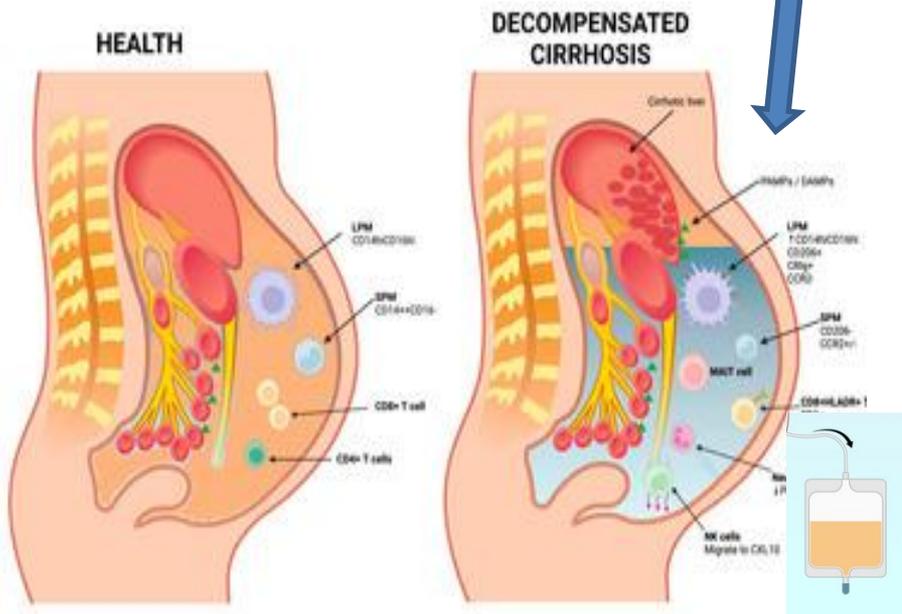
- **Caused by sympathectomy**
the termination of sympathetic innervation leads to vasoconstriction



Examples of arterial hyperemia

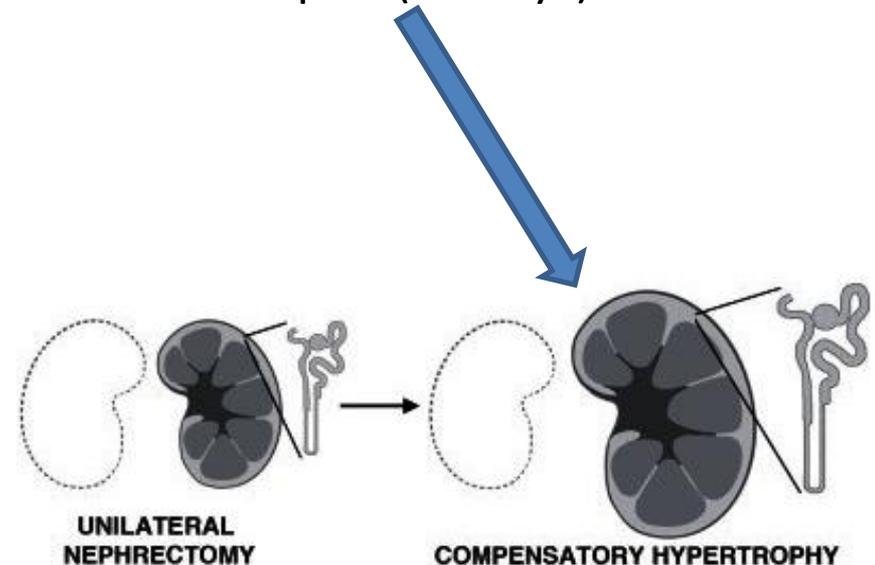
- **Ex vacuo**

after evacuation of an excessive amount of liquid (ascites) from the abdominal cavity - vasodilation in interstine blood vessels occurs

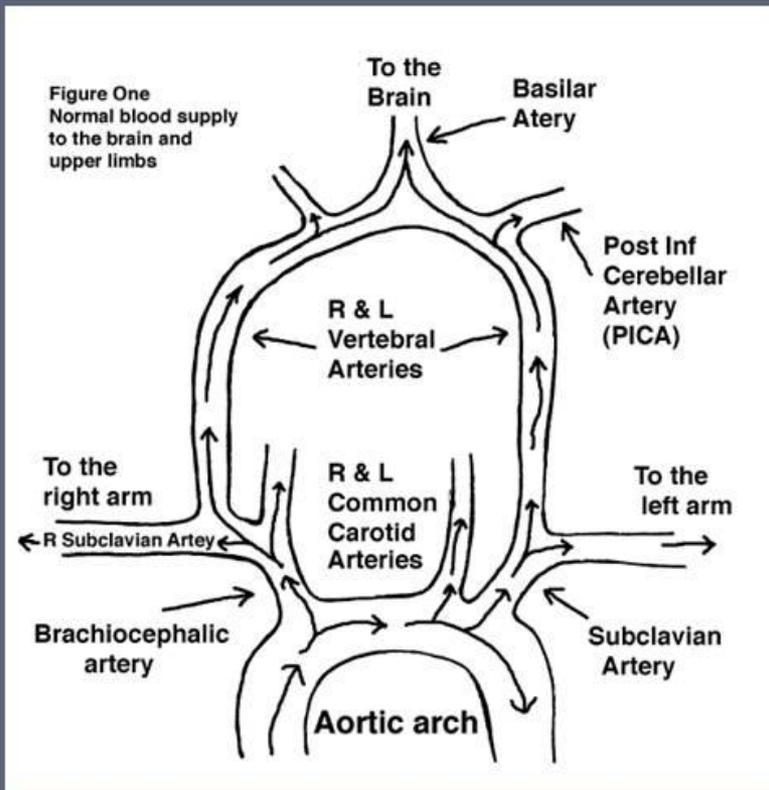


- **Vicar hyperemia**

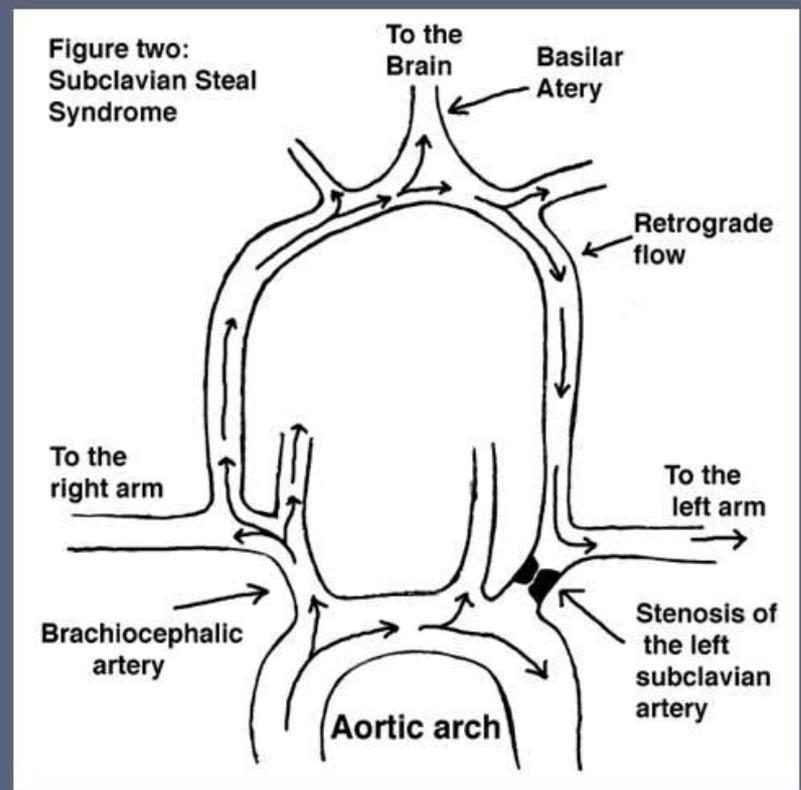
paired organs after the termination of the function of one of the pair (kidneys)



the "steal" syndrome



Normal



Subclavian steal pnenomenon

Clinical picture

- open red color of the region/organ/tissue,
- increase in volume and turgor of organs,
- increased tissue or organ temperature,
- locally increased metabolism,
- increase in tissue sensitivity,
- increase in tissue or organ function

Venous hyperemia

- It is characterized by normal delivery with weakened blood flow from capillary (like some kind of a dam there)
- Pathological processes at different levels blood vessels :
 - In the lumen
 - In the wall
 - Outside from the blood vessel
 - During right sided heart failure
([video 2:09](#))
- As a result disturbance of pressure balance at the capillary level with **prolonged blood retention in the capillary**

Clinical picture

- cyanotic color organs/tissues,
- an increase volume and turgor organs,
- reduction temperature of organs/tissues,
- locally reduction of metabolism,
- an increase sensitivity of tissues and pain,
- reduced function of tissues/organs or necrosis

Syndrome of local ischemia

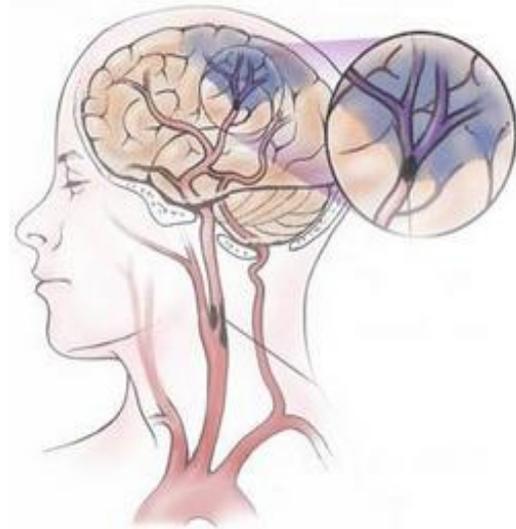
- One of the **most common disorders** in the population
- **An imbalance** between the **needs** of tissues/organs for arterial blood and **the ability** of blood vessels **to supply it** (disorder at the level of arteries)
- Anaerobic **metabolism**... This can result in damage which depends on the cell type and the duration of ischemia
- The causes are pathological processes:
 - in the blood vessel (in the lumen, wall or outside)
 - vasoconstriction of smooth muscle layer of the arterial wall (Prinzmetal's angina pectoris)

Syndrome of local ischemia

- Pathophysiological events
- In front of the narrowing point, there is an **increase in pressure**, and after the narrowing point, the **hydrostatic pressure and perfusion drops sharply**
- **Acute** or **chronic condition** (collaterals)
- Symptoms and clinical picture depend on the presence and degree of development of collateral blood flow.

Clinical picture

- **pallor** and **cyanosis** distal to the narrowing site,
- **drop in temperature** of the region,
- **weakened pulsations**,
- **reduced tissue volume and turgor**,
- **pain and atrophic changes**,
- **in sensitive cell types and necrosis**



Thrombosis

- Lifelong formation of a blood clot that reduce the lumen of the blood vessel and compromises distally circulation
- **During the physiological process** of hemostasis, after an injury, coagulation process ends with **melting the formed clot** (by the activity of the **fibrinolytic** system) so the **lumen** of the blood vessel **is fully passable** (like before the formation of the clot)
- When the formed thrombus **is not melted**, his presence carries a **significant risk** of breaking off and resulting **of embolism** distally

Causes of thrombus formation

"Virchhoff's Triad"

- The central place in the formation of thrombus is occupied by three groups of factors that trigger the formation of thrombosis - Virchhof's triad
 - 1. Factors that promote endothelial damage (wall damage)**
 - 2. Changes in blood composition**
 - 3. Factors that disrupt normal circulation**

Factors that promote endothelial blood vessel damage

- Disturbance of endothelial function which leads to loss of fibrinolytic activity (hypoxia, autoAb, bacterial toxins, mechanical lesions of the endothelium, increase in carbon dioxide concentration)
- Expression of subendothelial tissue (after damage of blood vessel) where platelets adhere and form a white thrombus (mainly in arteries and heart cavities)

Changes in blood composition

- Cellular changes in blood composition (increased blood viscosity):
 - thrombocytosis, erythrocytosis
- Humoral changes in blood composition:
 - increased concentration of coagulation factors,
 - increase in antifibrinolytic factors,
 - reduction of anticoagulants,
 - reduction of fibrinolytic factors,
 - hyperlipidemia

Factors that disrupt normal circulation

- **Factors that disrupt normal circulation:**
 - shock, hypovolemia, heart diseases with small MV, arrhythmias,
 - varicose veins, the part behind the narrowing of the blood vessel,
 - long-term immobilization or sitting in the same place for several hours
- Primarily, a white (soft) thrombus is formed, and after the addition of erythrocytes, a red or mixed thrombus is formed

The outcome of the thrombus

- growth and enlargement of the thrombus,
- thrombus embolization,
- softening,
- thrombus organization with recanalization or calcification

Embolism

- Represent the state in which the circulation is completely compromised by a particle that has completely closed the blood vessel.
- Embolus - particles carried by the bloodstream lead to embolism
- Embolus: exogenous or endogenous origin
- Embolism can involve an arterial or venous blood vessel
- Embolus:
 - **solid** (parts of bone, tumor cells, bacterial colony),
 - **liquid** (fat droplets),
 - **gaseous** (nitrogen, air)

Types of embolism

- **Thrombous** (a particle is part of a thrombus that broke and go away)
- **Fatty** (insoluble fats in the blood, during long bone fractures)
- **Aerial** (insoluble gases that are artificially introduced into the blood (during intravenous injection))
- **Gaseous** (in divers, during rapid decompression, nitrogen does not dissolve in the blood)
- Embolism by **tumor cells, bacterial colony...**

Types of embolism

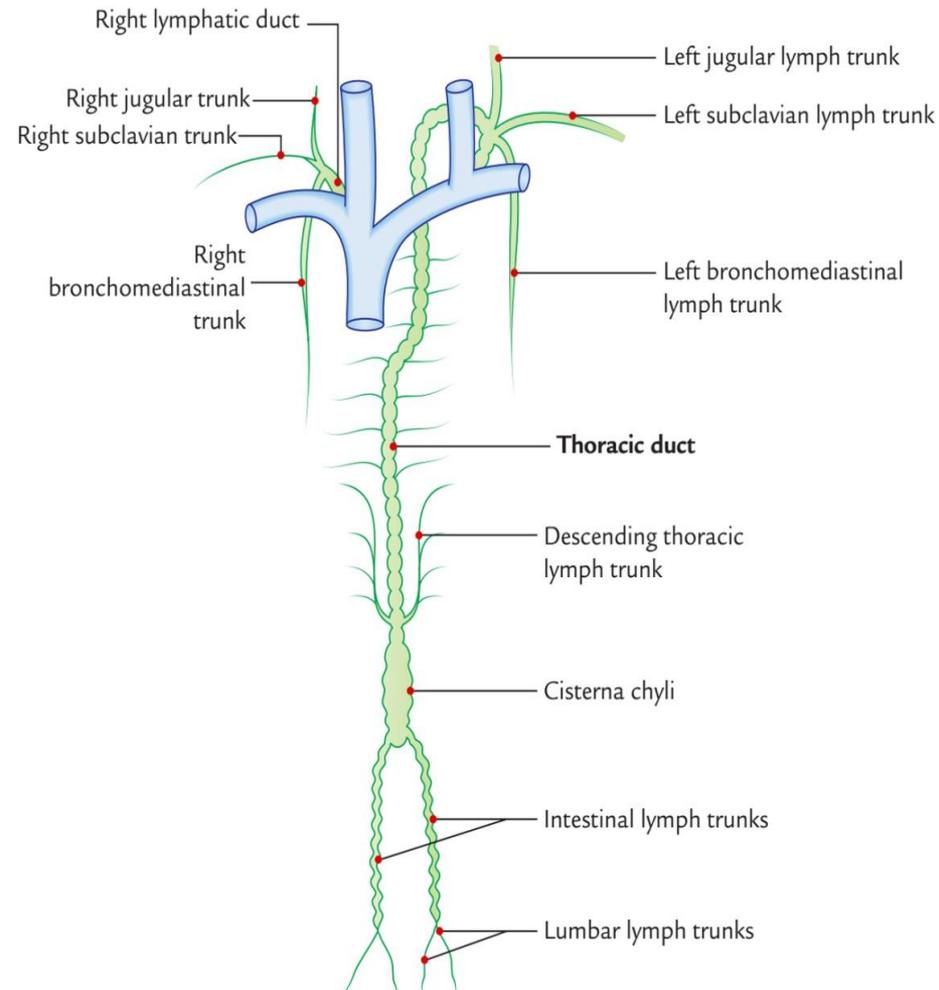
- According to the direction:
 - orthograde embolism (in the direction of blood or lymph flow - forward),
 - retrograde embolism (in the opposite direction to the movement of blood or lymph - when the pressure in the right atrium is higher than the pressure in the systemic veins),
 - paradoxal embolism - two preconditions must be met:
 - communication between left and right side of heart
 - right-left shunt.

Clinical picture

- **State of emergency**
- **Paleness** : pallor and later cyanosis distal to the site of obstruction;
- **Pulsness** : pulsations are absent,
- **Pain** : pain and later trophic tissue changes,
- **Paresthesia** : an unusual feeling of pricking, tingling, tingling,
- **Paralysis** : absence of active movements,
- **Prostration** : if a large part of the body is affected
- general malaise

Disorders of lymphatic circulation

- **Two terms**
- **Lymphostasis**
accumulation of lymph
in the lymphatic system
- **Lymphedema**
edema caused by disorders
of the lymphatic system



Disorders of lymphatic circulation

- **Lymphostasis**, is caused by a **disturbed structure** of lymphatic vessels or **increased central venous pressure**
- **Lymphedema** can be
 - **primary** (congenital disorders in the structure of lymphatic vessels)
 - **secondary** (damage to lymphatic vessels during surgery, trauma, radiation)

Clinical presentation



Lecture content

- **Function of the circulatory system**
- **Regulation of circulation**
- **Local circulation disorders**

Lecture content

- **Disorders of systemic circulation - Shock syndrome**
- **Multiple organ dysfunction syndrome - MODS**

Shock syndrome

- **Definition**
- **Shock syndrome etiology**
- **Specific mechanisms**
- **Stages**
- **Specific types**

Shock syndrome

Definition:

- **Acute, generalized disorder of perfusion of all organic systems** followed by a significant disorder of cell metabolism.
- During the perfusion disorder **cells remain without enough oxygen and nutrients**, with **accumulation of different products of metabolism** that further deteriorate the microenvironment in tissues

Development of shock syndrome

1. Initial disorders (that can cause shock syndrome)
2. Specific mechanisms during the development of shock syndrome
3. The final, common pathway of shock syndrome

Initial disorders

- **Cardiogenic disorders:** malignant heart rhythm disorders, disorders of the mechanical function of the heart, myopathic lesions (1)
- **Obstructive disorders:** cardiac tamponade, constrictive pericarditis, pulmonary embolism (1)
- **Hypovolemic disorders:** bleeding, loss of fluid from the body, transfer of volume to the "third" space (2)
- **Distributive disorders:** anaphylaxis, sepsis, neurogenic, and metabolic causes (3)

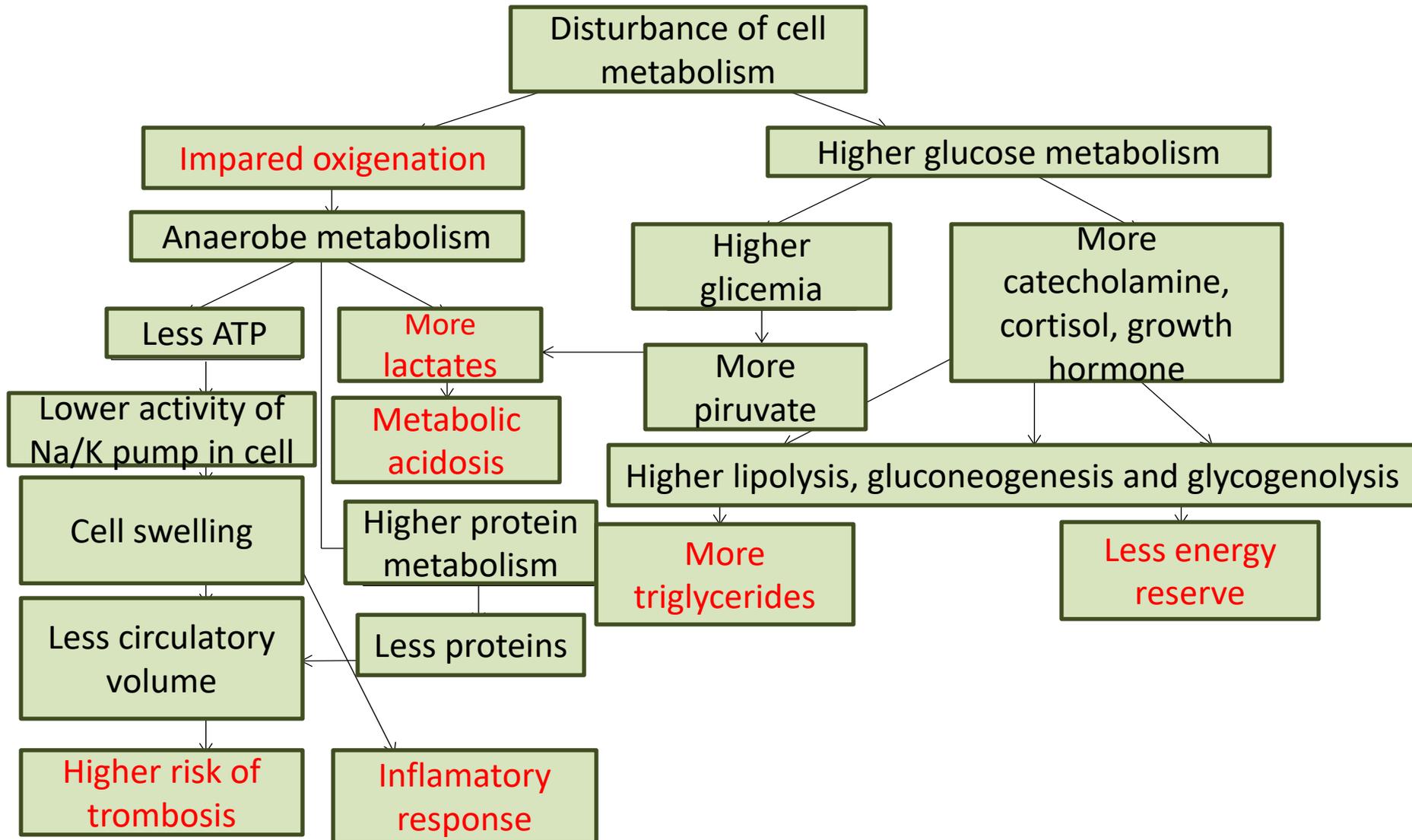
Specific mechanisms

- 1. Cardiogenic mechanism (1 and 2)**
- 2. Oligemic mechanism (3)**
- 3. Distributive mechanism (4)**

Compensatory mechanisms during shock syndrome

- Significant compensatory hormonal answer (nonspecific - always the same) includes:
 - **Activation sympathetic nervous system to maintain BP (TA)** (vasoconstriction, autotransfusion and autoinfusion)
 - **Increased creation glucagon, corticosteroids and catecholamines to maintain glycemia** (enable increased glucose production)
 - **Secondary hyperaldosteronism** (with increased retention of sodium and chlorine) **and increase release of vasopresin/ADH** (water retention) to maintain volume

The final path of shock syndrome



Stages in the development of shock syndrome

- 1. Compensated shock** - early stage in which compensatory mechanisms are activated (the patient is usually euphoric, active, knows what happened and asks for help)
- 2. Decompensated shock** - the body's compensatory response fails to maintain normal perfusion and blood pressure (the patient is quiet, calm, does not ask for help, you have the impression that he is not seriously injured - torpid phase)
- 3. Irreversible shock** - the occurrence of irreversible changes in cell/tissues/organs (changes in cell morphology occur)

Specific types of shock syndrome

- Hypovolemic shock
- Cardiogenic shock
- Obstructive shock
- Septic shock
- Anaphylactic shock
- Neurogenic shock

Hypovolemic shock

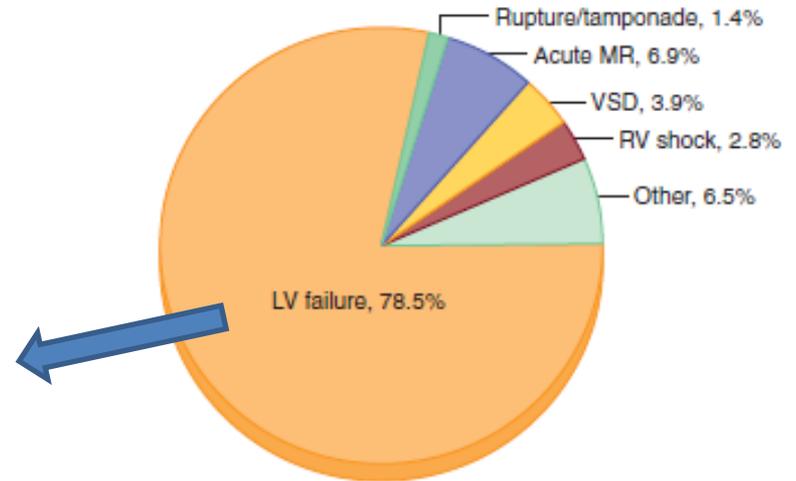
- Etiology:
 - Bleeding (internal or external)
 - Severe dehydration
 - Loss through the GIT (significant diarrhea)
 - Urine loss (*polyuria*)
 - Transition to the "third space" (ascites)
- Occurs when circulating volume decreases by 15%

Hypovolemic shock

- Compensatory response:
 - Activation of catecholamines with increased peripheral resistance and cardiac activity
 - Centralization and redistribution of blood flow
 - Secondary hyperaldosteronism
- Relative maintenance of perfusion in vital organs and blood pressure
 - If the loss continues, the decompensated and then the final phase of shock with tissue damage occurs
- Mortality from traumatic hemorrhagic shock ranges from 10-30%

Cardiogenic shock

- Etiology:
 - Heart attack (>40%)
 - Congestive heart failure
 - Cardiomyopathy
 - Arrhythmia
 - Severe cardiac defects
(valve stenosis and insufficiency)



Cardiogenic shock

- Compensatory response:
 - Activation of catecholamines with increased peripheral resistance and cardiac activity
 - Secondary hyperaldosteronism
 - Increases in preload and frequency, which **additionally burdens the myocardium and increases the oxygen requirements**
- As the underlying problem is localized in the heart itself (not in other organs), **the additional load reduces cardiac output, blood pressure, and tissue perfusion**
- Ischemia, cellular changes, and additional dysfunction of the heart occur – an vicious circle (*circolo vizioso*)

Cardiogenic shock

- How basic issue represents the impossibility of the heart to pump out enough blood volume, clinical **signs of congestive heart failure can be seen such as :**
- lungs oedema with tachycardia,
- swollen jugular veins,
- swelling of the lower extremities,
- oliguria,
- white and cold extremities.

Obstructive shock

- Etiology:
 - 1. Impaired diastolic right ventricular (blood) filling**
 - constrictive pericarditis
 - pericardial tamponade
 - 2. Impaired left ventricular (blood) filling**
 - tension pneumothorax
 - tumors in thorax
 - 3. ↑ afterload** (obstruction of left and right ventricular output)
 - massive pulmonary or systemic embolism
 - acute pulmonary hypertension
 - aortic dissection

Distributive shock

- Disturbance of the blood distribution due to dilation of arterioles localized in one part of the body
- Etiology:
 - Anaphylaxis (response to the presence of an allergen)
 - Neurological injuries (sympathetic and parasympathetic disorders)
 - Sepsis (response to certain microorganisms)
 - Hypo/hyperthermia
 - Medicine (sodium nitroprusside (antihypertensive) or bretylium (antiarrhythmic))

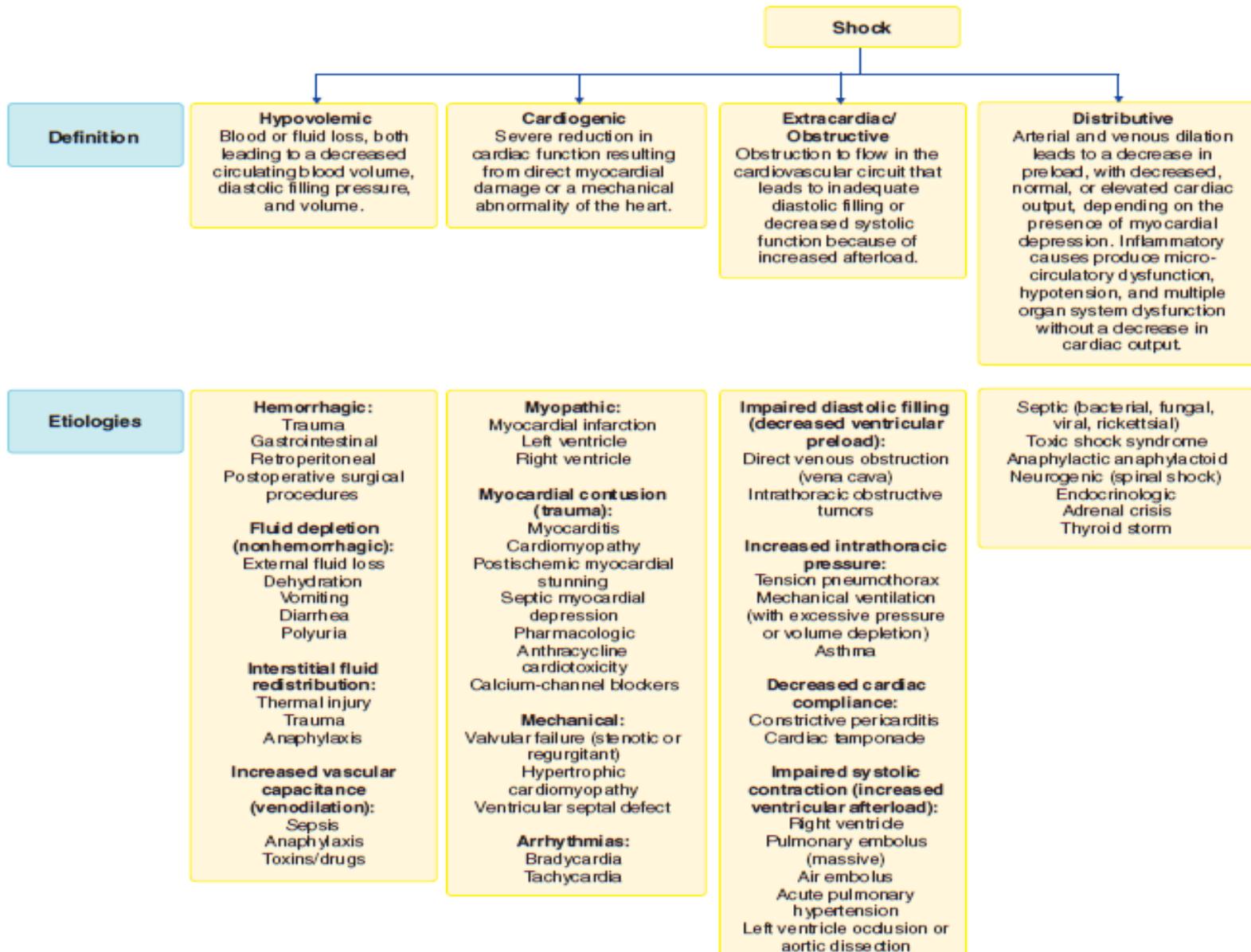
Distributive shock

- In **anaphylactic shock** because of actions of **mediators** which produce relative hypovolemia which is followed by falling of blood pressure and collapse
- In **neurogenic shock** head or CNS injury **result in lower activities of sympathetic** or **higher activities of parasympathetic** system which leads to a significant fall of peripheral resistance and massive peripheral vasodilatation (same volume in larger area)
- **Septic shock** represents a final stage of progressive dysfunction of different organ system provoked by microorganisms

Septic shock

- **Sepsis + hypotension/lactates over 2 mmol/l**
- Bacteremia (**Gr+ or Gr- bacteria**) activate immune system cells to produce
- Release of **pro-inflammatory cytokines** such as IL-1, IL-6 , TNF- α
- Activation of the complement system, coagulation system
- **Endothelial cell dysfunction** with capillary permeability disorder, increased adhesion, hypoxia, apoptosis and increased risk of thrombosis

Summary



Changes during shock syndrome

- **Microcirculation** - fluid extravasation, haemoconcentration
- **Lungs** - generalized interstitial pneumonitis
- **Kidneys** - hypoperfusion, renal insufficiency
- **Gastrointestinal tract** - ulcers and bleeding in the stomach, necrosis of the intestinal wall, decrease in liver function
- **Central nervous system** - quantitative disorders of consciousness
- **Heart** - decrease in contractility, diastolic dysfunction

Multiple organ dysfunction syndrome

- It is defined as **progressive dysfunction of two or more organ systems** after an **acute, life-threatening systemic homeostasis disturbance**.
- **The leading cause of death** in intensive care units
- Multiple organ dysfunction syndrome is **the most severe manifestation of uncontrolled systemic inflammation**, i.e. disturbed inflammatory immune response (**↑**pro , **↓**anti)
- Potentially reversible

Multiple organ dysfunction syndrome

- **Two types - primary and secondary**

1. **Primary** - direct effect of one etiological factor

(occurs **when an etiological factor independently leads to damage to two or more organs** (for example, massive tissue damage in traffic trauma or mesenteric necrosis in mesenteric artery embolism or extensive burns). Then as a consequence of extensive tissue damage, due to the action of the etiological factor itself and the progressive loss of organ function, there is a primary uncontrolled response of the immune system and the production of pro-inflammatory cytokines, which lead to endothelium damage and further consequences. Primary MODS develops in a very short time interval of a few hours or days.)

Multiple organ dysfunction syndrome

- **Two types**

1. **Secondary** - two etiological factors

(In the body we already have one etiological factor that predisposes to the occurrence of uncontrolled inflammation (which arms immune cells) and after the action of second etiological factor, there is the occurrence of massive uncontrolled inflammation that leads to damage to the endothelium of other pathological processes, damage to two or more organs or death (for example, the initial disorder is diabetes in which the cells of the immune system are armed due to the presence of meta-inflammation, and as a secondary factor it can be an infection with the Covid 19).

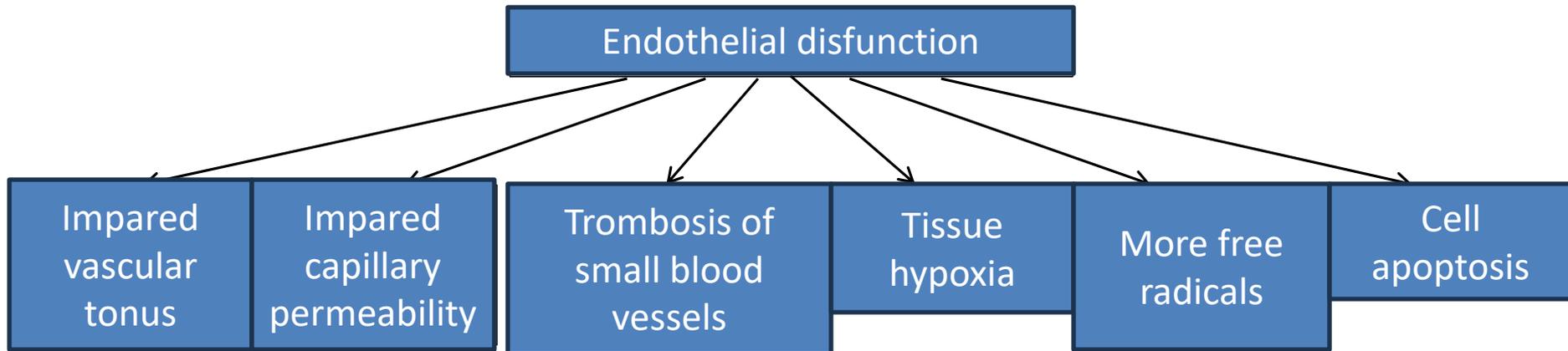
Multiple organ dysfunction syndrome

Etiology

- Infectious
 - Bacteria, viruses and fungi
- Non-infectious
 - Extensive trauma and/or necrosis
 - Massive burns
 - Shock
 - Mesenteric necrosis
 - Acute pancreatitis
 - Acute liver insufficiency
 - Acute respiratory distress syndrome (ARDS)
- Depending on the presence of gene polymorphism for certain molecules such as:
 - IL-6
 - TNF- α
 - TLR

Multiple organ dysfunction syndrome

- **Primary** - dominant activation of cells of non-specific immunity (macrophages and neutrophils)
- The primary target of the disturbed inflammatory response **is the endothelium**, and then the cells of all organs



Multiple organ dysfunction syndrome

- **Secondary**

1. **Massive systemic inflammatory response**

2. **Endothelial changes with activation of the coagulation and complement systems**

Development of hyperinflammatory and hypercoagulant state

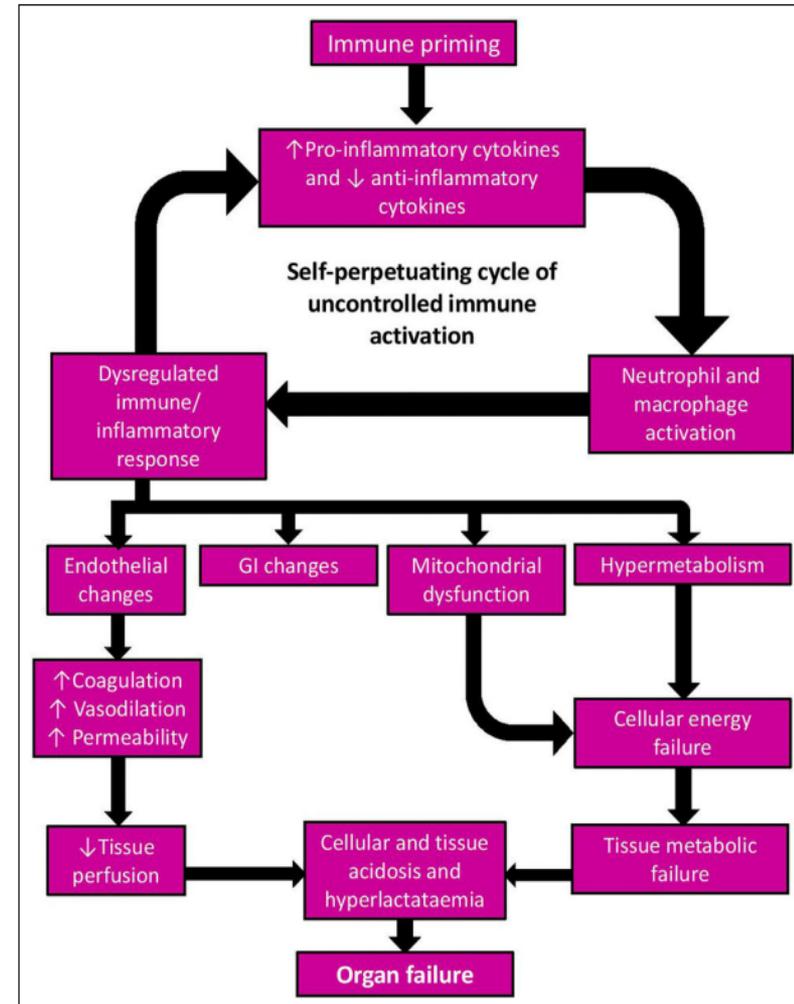
Plus

3. **Blood distribution disorder with tissue damage**

Changes in GIT like stress ulcers

4. **Hypermetabolic state (Intense neuroendocrine response)**

Increased secretion of stress hormones such as catecholamines, cortisol, glucagon, growth hormone



Multiple organ dysfunction syndrome - Clinical consequences

Organ	Disorder
Respiratory system	ARDS, pulmonary hypertension
GIT	Abdominal distension, ascites, paralytic ileus, bleeding, diarrhea, ischemic colitis
LIVER	Hyperbilirubinemia, liver necrosis, reduces ammonia detoxification, hepatomegaly
KIDNEYS	Ayotemia, oliguria/anuria or polyuria, acute tubular necrosis
KVS	Decrease in pulmonary capillary pressure, decrease or increase in systemic vascular resistance, increase or decrease in MV and FS, increase or decrease in oxygen demand
CNS	Decreased cognitive abilities, disorders of consciousness
Hematopoietic system	Anemia, thrombocytopenia, DIC
Immune system	Anergy, infection, lymphopenia

Lecture content

- **Disorders of systemic circulation - Shock syndrome**
- **Multiple organ dysfunction syndrome - MODS**