VASCULAR PATHOLOGY
Types of vessels: according to function and location:

**Arteries**
- large elastic
- large distributive (muscular)
- small (under 2 mm)
- arterioles (under 0.1 mm)

**Capillaries** (+postcapillary venules)

**Veins**

**Lymphatic vessels**
Cells in the vessel wall

**Endothelium**

multifunctional tissue:
- semipermeable membrane
- hydrophobic/antithrombotic surface
- regulator of vascular tonus and flow
- metabolism of hormones
- regulates inflammatory and immunological processes
- modification of lipoproteins
- regulation of other cells growth (SMC)

**Stimulation of endothelium** - fast reversible response (minutes) to histamin, serotonin, thrombin… permeability↑, NO↓

**Activation of endothelium** - synthesis of adhesion molecules, cytokines, vasoactive substances - response to cytokines, bacterial products, lipoproteins, viruses, complement, hypoxia...
Cells in the vessel wall

Smooth muscle cells
function:
- contraction/relaxation
- synthesis of collagen, elastine, proteoglycans
- synthesis of growth factors (VEGF)
- migration/prolifertion  (+ PDGF, bFGF, IL-1;
  - heparan sulphate, NO, INFγ, TGFβ )

Intimal thickening
Reaction to vascular wall injury (healing)- neointima formation :
- migration of SMCs from media to intima
- multiplication of intimal cells
- synthesis of intercellular substance
SMC - acquire „synthetic phenotype“
(→ stenosis, restenosis after angioplasty, transplantation, resulting from AS)
Diseases of blood vessels

- arteries are more often affected (AS !, hypertension, vasculitis)
- veins (varices, flebothrombosis)

Inborn anomalies

- berry aneurysm (brain arteries)
- arterio-venous fistulae (rare, lead to heart overload)
- arterio-venous malformations
Atherosclerosis

= vessel sclerosis/hardening
Include 3 different morphologies:
- atherosclerosis
  fibrous plaques with central lipid deposits
- calcification of media
  usually over 50 y., frequently combined with atherosclerosis
- arteriolar sclerosis
  usually in connection with DM or hypertension

Atherosclerosis
- causes >50 % death
  since 1970 slow decrease of deaths related to AS
  - therapy of hypertension, DM,
  - improved therapy of IM, CNS infarction
  - prevention: nutrition (lipids), smoking
Atherosclerosis

Morphological manifestations
- principal change is thickening of intima and lipid accumulation (in children lipid streaks, later lipid plaques)
- atheromatous/atherosclerotic plaque - thickened, protruding intima with fibrous cap and a lipid center (cholesterol), frequently softened and decomposed.
- abdominal aorta, coronary and iliac arteries, carotic a., Circulus arteriosus Willisi; bifurcations.
- excentric position
- cellular components: 1. SMCs, Mf, leukocytes, T ly.
  2. Extracellular matrix + collagen and elastic fibres.
  3. Intra- and extracellular lipid deposition.
- at edges neovascularisation.
- fibrous plaque - atherosclerotic with low lipid content
  - scarring healing of atheromatous lesion
Atherosclerosis
Morphologic manifestations
Atherosclerosis - complications

- **calcification** – in advanced disease, focal/massive; unfavourable prognosis

- **rupture/ulceration** of atherosclerotic plaque
  - thrombosis
  - atheromatous (“cholesterol”) embolism

- **hemorrhage in the plaque** – frequently in coronary aa. (tiny capillaries at the edge of the plaque…rupture.

- **thrombosis** – incorporated into the lesion
  - occlusion partial/complete

- **aneurysmatic dilatation**
  - process weakens the media, with destruction of elastic fibres and SMCs
Atherosclerosis - risk factors

- **age:** between 40 - 60 y. upto 5x increased incidence of MI
- **sex:** women upto 55 r. 1/5 MI in men. After 60 y. equal incidence.
- **genetic factors:** familial predisposition to atherosclerosis is polygenic; usually several risk factors combine (DM, hypertension, hyperlipoproteinemia)
- **hyperlipidemia:** = most important risk factor, especially *hypercholesterolemia*, less important - hypertriglyceridemia. LDL/HDL, obesity, smoking, physical (in)activity.
- **hypertension:** BP over 170/95 - 5x risk of AS
- **smoking:** increases risk of AS 2x
- **Diabetes mellitus:** leads to hypercholesterolemia
- **plasma homocysteine:** increases oxidative stress of ECs, thus their dysfunction, also in folic acid, vit. B6 a 12 carency.
- **coagulation factors:** - e.g. ↑ plasminogen activator inhibitor, ↑ CRP,...
Atherosclerosis - pathogenesis

- proliferative response of cells in/into intima to insudation of plasma proteins and lipids
- repeated mural thrombi formation with consecutive organisation

-present concept – combination of both as an inflammatory response of the vascular wall to endothelial injury:

• chronic endothelial damage - ↑permeability, ↑leukocyte adhesion
• lipid deposition into vessel wall, especially LDL, VLDL, oxidized forms of LDL
• adhesion of monocytes (and leukocytes), migration and transformation to foamy cells.
• platelet adhesion to damaged surface or leukocytes
• release of substances from activated platelets, macrophages and leukocytes → migration of SMCs from media to intima
• SMCs proliferation and synthesis of collagen in the intima
Atherosclerosis - pathogenesis

role of particular factors:

- **endothelial damage** (oxidised LDL, homocysteine, viruses?, chronic mechanical stretch,...)
- **lipids** (hyperlipidemia/hypercholesterolemia → oxidative stress, → inactivation of NO = relaxation ↓, activation of EC → adhesion molecules (Mo, leukocytes)
- **monocytes/Mf** - oxidized LDL chemotactic; Mf → IL1, TNF → chemotaxis of leukocytes
- **SMCs proliferation** – together with hypercholesterolemia → atheromatous plaque
- **SMC clones** - proliferate; **infection** - víruses, chlamydia...
Hypertension disease - physiology

> **140/90** torr

**Complications:** coronary heart disease, cerebrovascular events, heart failure, vascular changes.

**BP regulation:**
- \( \uparrow \) Na+, angiotensin II, catecholamines, thromboxan, leukotrienes, endothelin
- \( \downarrow \) kinins, prostaglandins, NO (local H+, hypoxia, lactic acid)

**Kidneys:** key in BP regulation
- renin/angiotensin/aldosterone system
- prostaglandine production, activation of callicrein-kinine syst., platelet activating factor, NO
- regulation of Na+/volume: \( \downarrow \) GF - \( \uparrow \) reabsorption Na+, H₂O;
- atrial natriuretic hormone
Hypertension disease - pathogenesis

Genetic faktors:
- combination of genetic and environmental effects – on heart ejection and peripheral resistance.

Essencial hypertension - multigenic and heterogenic defects with mutations/polymorphism in multiple locuses with influence on BP (angiotensin II R, angiotensinogen R …)

- environmental effects: - contribute to expression of genetic determinants for high BP (stress, obesity, smoking, salt consumption)

- mechanisms - Na+ retention - increased volume leads to increased heart ejection - results in regulatory peripheral vasoconstriction.
- direct dependency of BP increase on age and salt consumption
- diuretics with salt loss are effective antihypertensives
Hypertension disease - vascular changes

Increased resistance = one of hypertension mechanisms
- functional vasoconstriction
- thickening/remodeling of vessel wall
- defect of Na+, Ca++ transport → intracellular Ca++, contraction
- some vasoconstrictors = growth factors (angiotensin II)
  - **remodeling** often precedes BP increase

Hypertension - accelerates AS
- leads to Ao dissection
- cerebrovascular hemorrhage
- arteriolarosclerosis
  - hyaline
  - hyperplastic
Hypertension disease - vascular changes

**Hyaline arteriolosclerosis**
- in hypertension patients of higher age
  (also DM) - plasmarrhagia and extracellular matrix synthetised by SMCs
- organ damage

**Hyperplastic arteriolosclerosis**
- result of serious hypertension (diastole <110)
  onion-like concentric thickening of the wall
  sometimes deposits of fibrinoid material and necrosis
  (necrotising arteriolitis)
VASCULITIDIES

Inflammation of the vascular wall
- in various diseases
- with different manifestation:
  fever, myalgia, arthralgia, weakness

Most frequent mechanisms:
- immune damage
- invasion of pathogens
- physical, chemical damage
Classification of vasculitis

Invasion of pathogens - bacteria (neisseria)
- rickettsia (Rocky mountain…)
- spirochetes (syphilis)
- fungi (aspergillus, mukor)
- viruses (herpes zoster)

Immunologic vasculitis - Immunocomplex
in infections (HepB, C), Schonlein-Henoch purp.
SLE, RA, medicine v., cryoglobulinemia, serum thickness.
- Antineutrophil Ab (ANCA)

Wegener granulomatosis, Churg-Strauss sy.
- Directly reacting Ab

Goodpasture sy. (anti-BM), Kawasaki dis. (anti-Ec)
- Cell mediated

Graft rejection (acute rejection)
- Paraneoplastic v.

Unknown cause - Giant cell temporal arteritis,
Takayasu arteritis, Polyarteritis nodosa (classic)
Immunologic (noninfectious) vasculitis

- **Immunocomplex**
  
  in serum/vascular wall - i. complexes, Ig, C
  [in infections (HepB, C) … polyart. nodosa;
  HepC…glomerulonefritis]
  Schonlein-Henoch purp., SLE, RA, medicine v.,
  cryoglobulinemia, serum thickness.

- **Antineutrophil Ab (ANCA):**
  
  proteinase 3 (c-ANCA),
  MPO (p-ANCA)
  Wegener granulomatosis, Churg-Strauss sy.,
  microscopic polyangiitis
  (binding to PMN … degranulation, endothelial damage)

- **Directly reacting Ab**
  
  Goodpasture sy. (anti-BM),
  Kawasaki ch., SLE (anti-Ec)
Immunologic (noninfectious) vasculitis

Large vessels

Giant cell (temporal) arteritis

-mostly: over 50, affecting also Ao and branches; ocular aa. …blindnes
granulomatous form (giant cells), or fragmentation LEI
without granulomas … lumen narowed, rough surface, pain.
?Reaction to elastin?
Immunologic (noninfectious) vasculitis

Large vessels
Takayasu arteritis
= pulseless disease ...upper extremities
  sight disorders
lymphocytes around vasa vasorum,
  may also necroses and giant
cells   ...fibrosis of media

affected aa. renales, coronary,
femoral, pulmonal...

?pathogenesis?
Immunologic (noninfectious) vasculitis

Medium size vessels
Polyarteritis nodosa
= systemic vasculitis …medium aa., not in lungs
  in acute phase - neutro and eosinophils, fibrinoid necrosis
  + thrombosis, aneurysm, fibrosis

Kawasaki syndrome
arteritis + mucocutaneous
  lymphadenopathy
(children, fewer, cervical lymph nodes)
autoAb anti- Ec … ?cause?
…frequently IM
  (aneurysm of coronary aa.,
   thrombosis, narrowing)
Immunologic (noninfectious) vasculitis

Small vessels
Microscopic polyangiitis
(leukoclastic vasculitis)
= like polyarteritis nodosa - affect arteriols, capillaries and venules
-especially skin; other organs…lung, kidney
-reaction to medicine (PNC), bacteria, proteins (tumors…)
-(fibrinoid necrosis) + especially PMN in the media, which is “splitted”
-pANCA
Immunologic (noninfectious) vasculitis

Small vessels
Microscopic polyangiitis
(leukoclastic vasculitis)
Immunologic (noninfectious) vasculitis
Small vessels
Wegener granulomatosis
Immunologic (noninfectious) vasculitis

Small vessels

Wegener granulomatosis
= necrotising vasculitis - triad:
1. Necrotising granuloma in upper respiratory pathes (nose, sínuses, pharynx) or/and lungs
2. Focal necrotising granulomatous vasculitis (arteriols, venules)
3. Kidney disease (focal necrotising glomerulonefritis with crescents)

?immunol. mechanisms? – cell-mediated immunity, cANCA

- mucosal granulomas, ulcerations, necroses with Ly, Pc, Mf, giant cells;
  granulomas around vessels, + PMN, fibrosis.
Immunologic (noninfectious) vasculitis

**Small vessel**

**Trombangiitis obliterans (Buerger disease)**
- segmental trombotising inflammation of small and medium-sized arteries
- inflammation affects neighbouring vein and nerve (painful in rest)
- connection to tabakism (direct toxicity to endothelium?)
- chronic inflammation in the wall, thrombosis in the lumen with “microabscess” formation with PMN and granulomatous inflammation around
- ulcerations or gangrene
Immunologic (noninfectious) vasculitis

Trombangiitis obliterans (Buerger disease)
Immunologic (noninfectious) vasculitis

Small and medium-sized vessels
Vasculitis as manifestation of other disease
= collagenoses, malignity, cryoglobulinemia,
  Schonlein-Henoch purpura
- rheumatoid arthritis, SLE
- lymphoproliferative diseases

Raynod disease
= paroxysmal pallor/cyanosis of acral parts
- extreme vasospasm (benign course, rarely skin atrophy)
  - reaction to stress, emotions…

Reynod phenomena
= manifestation of vascular insufficiency for various reasons
  (SLE, Buerger d., scleroderma, …)
Aneurysms and dissection of vascular wall

Aneurysm
= local dilatation of a vessel, heart chamber
- arteriosclerotic, syphilis, congenital, after MI, cystic medio-necrosis of Ao, polyarteritis nodosa, Kawasaki sy.
- *pseudoaneurysm* = extravascular hematoma communicating with lumen (pulsating hematoma)
- *mycotic aneurysm* = from septic embolus, penetration of suppurative process, circulating bacteria

Dissection
= blood penetrates the arterial wall and splits its layers
  (SLE, Buerger dis, scleroderma, …)
Aortic aneurysm

Aneurysm
Atherosclerosis = most frequent cause
- abdominal Ao
- less thoracic Ao, Ao arch
Syphilis
- oblitering endarteritis of vasa vasorum
  ischemic damage of media

Aortic dissection
- usually without significant dilatation
- Hypertenion (40-60 y.)
- Collagen abnormalities (Marfan sy. - 40 year.
  Cystic medionecrosis of Ao… “cystic degeneration of media“
  fragmentation of elastic fibres
Veins

Varicous veins
= abnormally dilated, tortuous – result of lasting increased pressure
- deformation of valves, thrombosis, fibrosis
- later affection of the deep venous system of LE
  edema, thrombosis, trophic changes, ulcus cruris
- hemoroids

Thromboflebitis and phlebothrombosis
- predisposing factor – coagulation disorders, heart failure, obesity, neoplasia, pregnancy, immobilisation
- frequently embolia a.pulmonalis = first manifestation
Veins

Obstruction of v. cava superior
= obstruction by a tumor (bronchogenic Ca, mediastinal Ly), aortic aneurysm

Obstruction of v. cava inferior
= tumors (hepatocellular Ca, renal Ca)
edema of LE

Lymphangitis
- most frequently streptococci

- Lymphedema
  various causes - inborn sporadic
  - familial lymphedema
Vascular tumors

Hemangioma
= accumulation of normal/abnormal vessels
- local appearance, sometimes large
- (mostly superficial)

Capillary hemangioma – capillary-like vessels
- skin, mucosas, internal organs
  mm - cm, red, bluish, may protrude.
Thin-walled capillaries + sometimes fibrosis, thrombosis, hemosiderin.

Pyogenic granuloma - fast growing lobular hemangioma
- lip, skin, oral mucosa - after trauma?
“Granuloma gravidarum” especially on gingiva, disappear after delivery
Vascular tumors

Hemangioma

**Cavernous hemangioma** - dilated vascular spaces
- less common, 1-2 cm, fibrous septae, thrombosis.
Brain, internal organs…compression, hemorrhage -
- (von Hippel Lindau disease)
Vascularr tumors

Lymphangioma
= masses of normal/abnormal lymphatic vessels.

Capillary lymphangioma - small lymphatic vessels
- dermis (head, neck, axilla), rarely internal organs
- differentiated from hemangiomas ... absence of blood.

Cavernous lymphangioma - dilated vascular spaces without blood, fibrous septae with lymphatic tissue
- 1-2 cm,
- in children retroperitoneal, in axilla - upto 15 cm.
Vascular tumors

Glomangioma (Glomus tumor)
= painful tumor from SMCs of glomus body
- typical location on finger tips, underneath nail
two components: branching vessels + nests of SMCs
Vascular tumors

Vascular ectasias (not true neoplasms)
= local dilation of existing vessels, often inborn anomalies (teleangiectases)

Nevus flammeus
- most frequently face and neck

Spider teleangiectases
- mostly: on face, neck and on trunk
  pregnancy, liver cirrhosis (estrogen effect?)

Hereditary hemorrhagic teleangiectases
- Osler-Weber-Rendu disease
  genetic malformation
  - dilated capillaries on mucosas and skin
    (hemorrhage into GIT, lungs, urinary system...)

Vascular tumors

Bacillary angiomatosis

= opportunistic infection by *Bartonella*
  - often in immunocompromised patients
- dark red papules to nodules in dermis
  - proliferation of ECs of epitheloid appearance
    in interstitium numerous PMN and long rod-shape bacilli
Vascular low-grade malignant tumors

Kaposi sarcoma
= vascular proliferation caused by HHV-8
Forms: - classic (chronic) – older male, distal LE
  - endemic (lymphadenopathic) - Bantu children in S Africa
  - transplant-associated (immunosuppressive therapy)
  - epidemic (AIDS-associated)
Typical course = 3 stages: patch / plaque / nodule
Vascular low-grade malignant tumors

Kaposi sarcoma

HHV-8
Vascular low-grade malignant tumors

Hemangioendothelioma
= vascular proliferation somewhere between hemangioma < and < angiosarcoma

Epitheloid hemangioendothelioma
= typical lesion - cuboidal epitheloid endothelial cells.

Hemangiopericytoma
rare
= capillary spaces surrounded by SMCs
- infiltrates locally, recurs, metastasizes
• Vascular high-grade malignant tumors
• Angiosarcoma
  • = often difficult to distinguish from epithelial tu. or melanoma
  • - location: skin, soft tissue, liver, breast
• Hepatal angiosarcoma – arsenic (pesticides), Thorotrast,