Cardiovascular diseases

Semmelweis University
II. Dpt. Of Pathology

Main topics of the practice

- **Arteriosclerosis** (sclerosis = „hardening”)
  - atherosclerosis
  - arteriolosclerosis
  - mediasclerosis (Mönckeberg)

- **Myocardial infarction** (acute / chronic)
- **Infective endocarditis**

Main categories of vascular changes

- Stenosis / occlusion
  - arteriosclerosis
  - thrombosis
  - embolism
- Structural weakening
  - dilation (varicosity / aneurysm)
  - dissection
  - rupture
- Inflammations

Etiology of atherosclerosis

Most accepted theory today:

„response to injury”
(„unitive theory”)

„Response to injury”

Atherosclerosis is a general reaction of the vessel!

Causes (for example) :

- Physical impacts
  (shear stress - hypertension, traumatic, iatrogenic)
- Inflammation
- Irradiation
- Toxic agents (oxidative stress !)

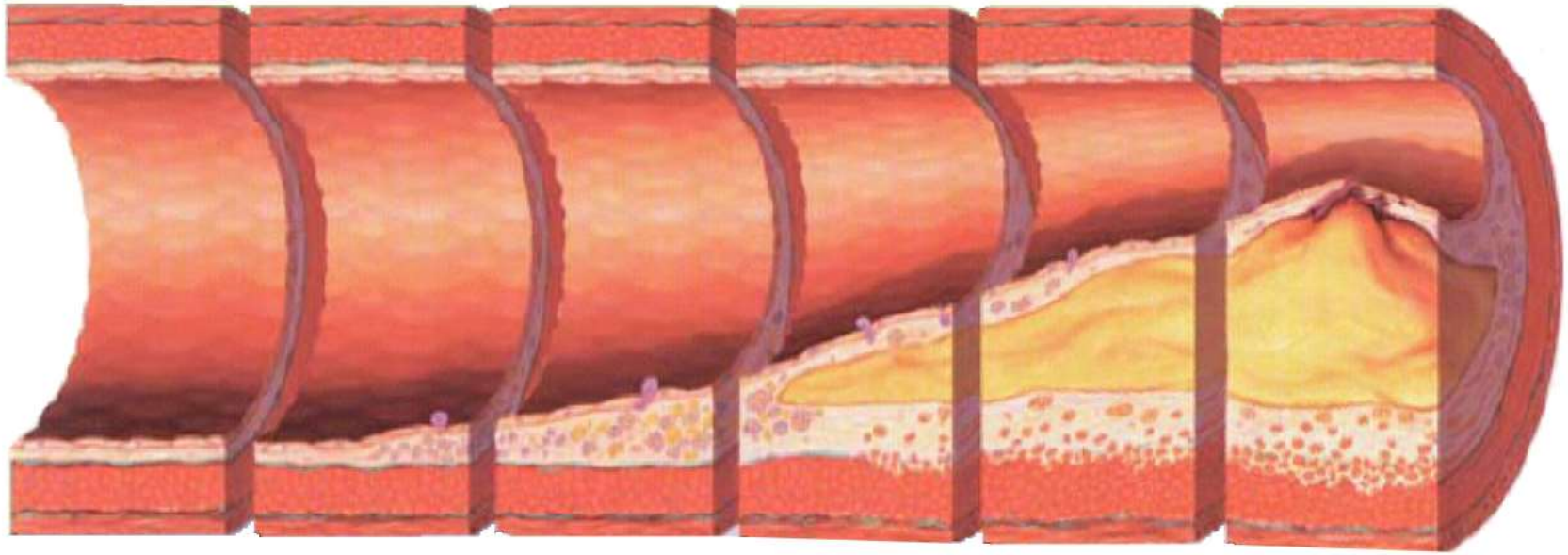
Sclerosis is more severe in bifurcations!
(turbulent flow)

Pathogenesis of atherosclerosis

(response to injury)

- Endothelial cell stimulation
- Inflammatory response-> permeability increases
- Lipid accumulation (oxi-LDL, scavenger receptors)
- Macrophages -> foamy cells
- Cytokine, growth factor secretion
- Smooth muscle cell migration to the intima
- Smooth muscle cell proliferation
- Extracellular matrix (ECM) formation
- ECM remodelling, calcification

Stages of atherosclerosis



Normal vessel wall

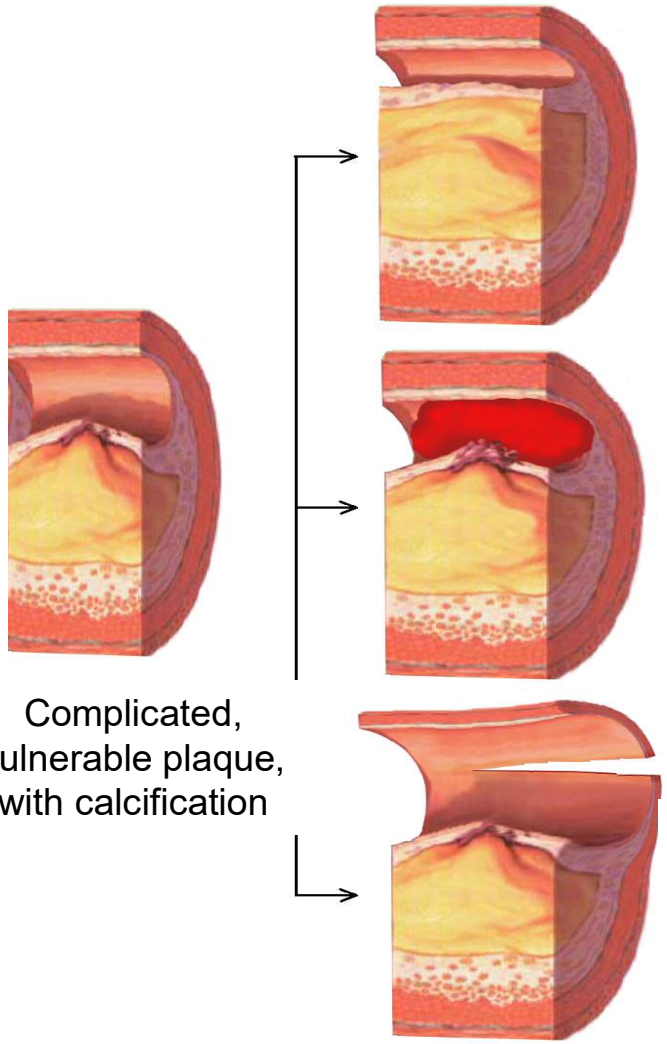
Fatty streak

Smooth muscle cell migration, ECM remodelling

Atheromatous lipid core and fibrous cap

Complicated, vulnerable plaque, with calcification

Complicated plaque…



Complicated, vulnerable plaque, with calcification

Severe / critical stenosis
-> ischaemia…. -> infarction

Rupture of fibrous cap
-> haemorrhage + thrombosis
-> sudden occlusion

Vascular aneurysm
Vessel wall rupture (or dissection)

Interesting fact

There is no sclerosis in intramyocardial coronary segments, and those parts that are covered by a thin myocardial layer are less affected!

*Scher, A. M. (2000). "Absence of atherosclerosis in human intramyocardial coronary arteries: a neglected phenomenon." Atherosclerosis **149**(1): 1-3.*

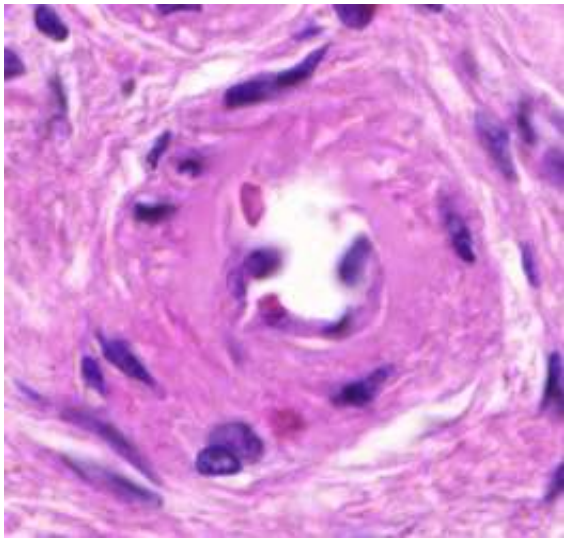
Arteriolosclerosis

Small arteries, arterioles

- Hyaline arteriolosclerosis

  homogenous thickening

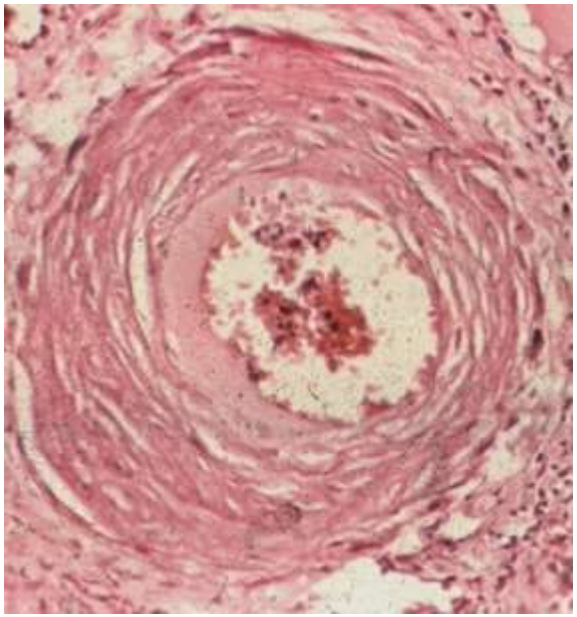
  increased extracellular matrix
  production of smooth mucle cells



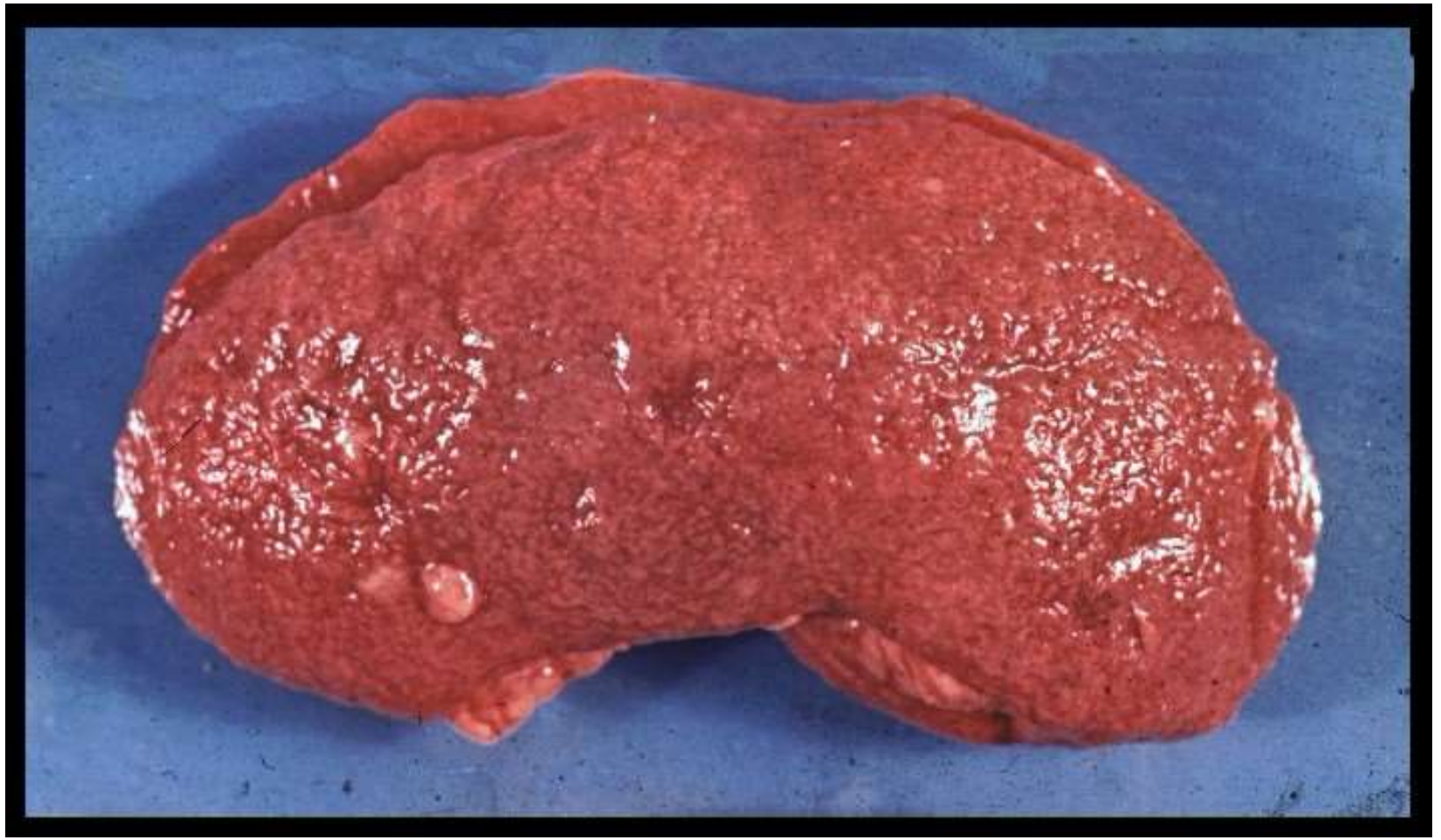
- Hyperplastic arteriolosclerosis

  „onion-skin-like thickening”

  associated with severe hypertension



Arteriolosclerotic nephrosclerosis



Ischaemic heart disease (IHD)

- All the alterations, that are caused by imbalance between oxygen supply and demand

Forms of IHD:

- Angina pectoris
  - stable / typical
  - Prinzmetal (vasospastic)
  - Unstable (crescendo)
- Acute myocardial infarction
- Chronic IHD
- Sudden cardiac death

Plaque rupture!

Acute myocardial infarction (AMI)

coagulation necrosis of the myocardium

Modifiable risk factors:

- hyperlipidaemia
- hypertension (> 140/90 Hgmm)
- diabetes
  (glycosilated proteins, increased fatty acid mobilization)
- smoking (oxidative endothelial damage)
- obesity / lack of physical activity

Coronary collateral growth is
induced by physical exercise!

Acute myocardial infarction

Non-modifiable risk factors:

- genetical predisposition
- age
- male sex

Novel risk factors:

- elevated serum fibrinogen level
- hyperhomocystinaemia
- elevated resting heart rate
- decreased estrogen levels
- oral anticoncipients
- psychic stress

Causes of coronary stenosis / occlusion

- Atherosclerosis and complications (90%)
  -severe stenosis, plaque hemorrhage, rupture, thrombosis
- Embolism
- Coronary spasm (Prinzmetal-angina)
- Inflammations, autoimmune diseases
- Iatrogenic: cardiac catheterisation

Acute myocardial infarction

Significant coronary stenosis: over 70%

(except the left main coronary branch: over 50%)

Causes:

- Coronary stenosis
  and increased demand for oxygen (collateral coronary branches!!)
  -> crescendo angina, NSTEMI -> **subendocardial AMI**
  (on ECG: no ST-segment elevation)

- Sudden and complete occlusion of a coronary branch:
  plaque rupture + thrombosis/embolism / coronary dissection -> STEMI (ECG: with ST-segm. elevation)
  = **transmural AMI**

Localisation of MI and affected coronary branch

- 40-50%: left anterior descending (LAD)
  - left ventricle's anterior wall
  - frontal 2/3 of the septum
  - right ventricle's areas that are near the septum
  - apex

„widowmaker artery"
(proximal LAD laesion)

- 30-40%: right coronary art. (RCA)
  - right ventricle, and:

Posterior: post.interventr.branch:
depends on coronary dominance!
-90% from RCA

-10% from CX

- 15-20%: circumflex art. (Cx)
  - left ventricle, lateral part, and:

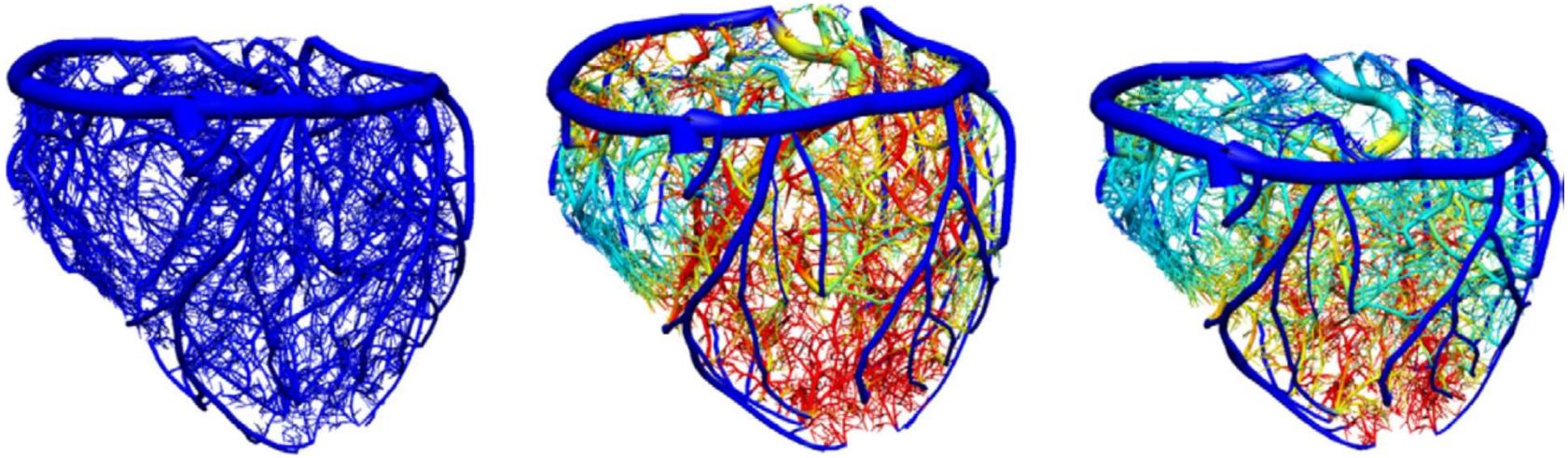
Isolated right ventricular infarction is a rare entity! 1-3 %

First, the subendocardium is damaged in an acute infarction!

Most pressure-affected region, higher oxygen demand!

Farthest from the epicardial vessels!

(proper blood flow in coronaries: only in diastole)



End-diastole

Isovolumetric contraction

End of ejection

Color: Low pressure

High pressure

Source: Nordsletten, D. A., S. A. Niederer, M. P. Nash, P. J. Hunter and N. P. Smith (2011). "Coupling multi-physics models to cardiac mechanics." Prog Biophys Mol Biol **104**(1-3): 77-88.

Acute myocardial infarction

Rare causes:

- Coronary developmental disorder
- „Myocardial bridge” over a coronary segment
- Coronary steal syndrome
- Extremely altered haemorheologic parameters, e.g.:
  - Disseminated intravascular coagulopathy
  - Polycythaemias
  - Thrombocytosis

AMI morphology: depends on the elapsed time

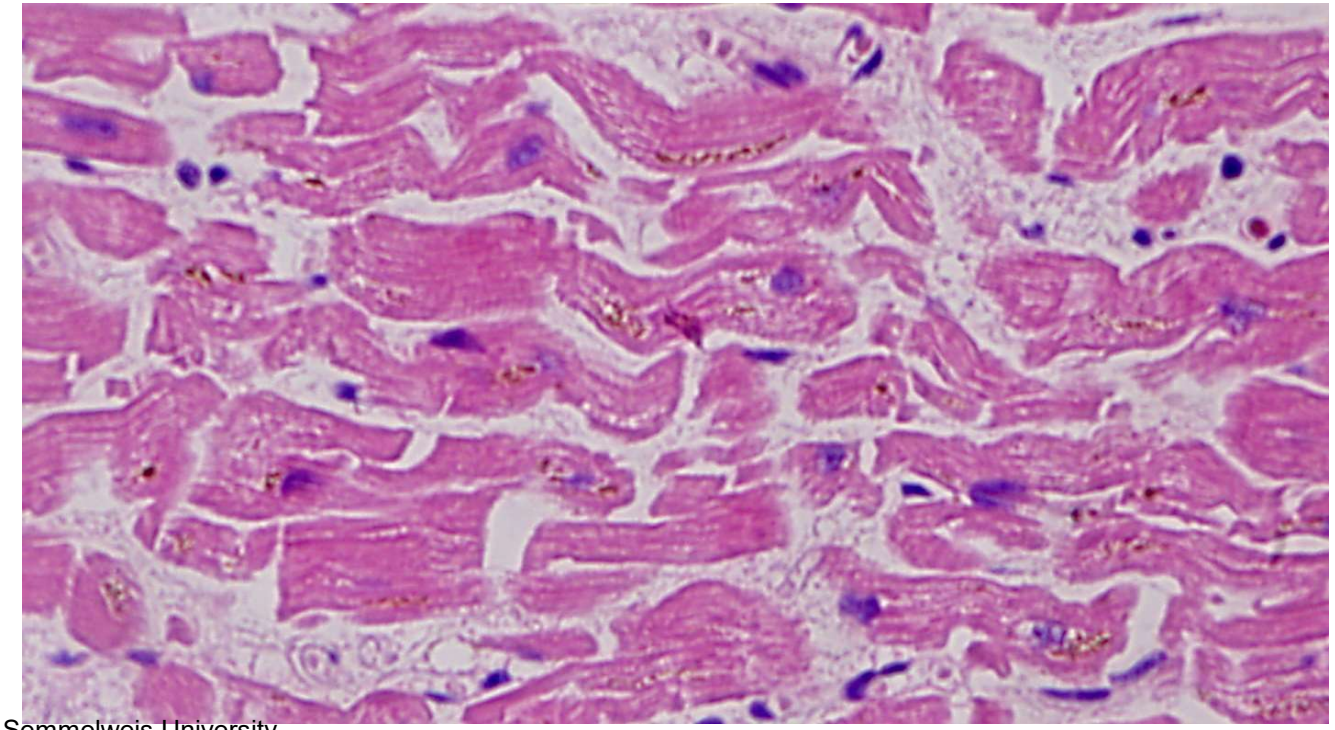
0-30 min: can be seen only with electron microscopy
glycogene depletion, mitochondrial swelling,
relaxed myofibrillar structures

Not visible with the naked eye,
nor by light microscopy!

Acute myocardial infarction

between 30 min - 4h

Can be seen with light microscopy
Relaxed muscle strings
Wavy strings in the infarction border
Glycogene depletion, cellular swelling…



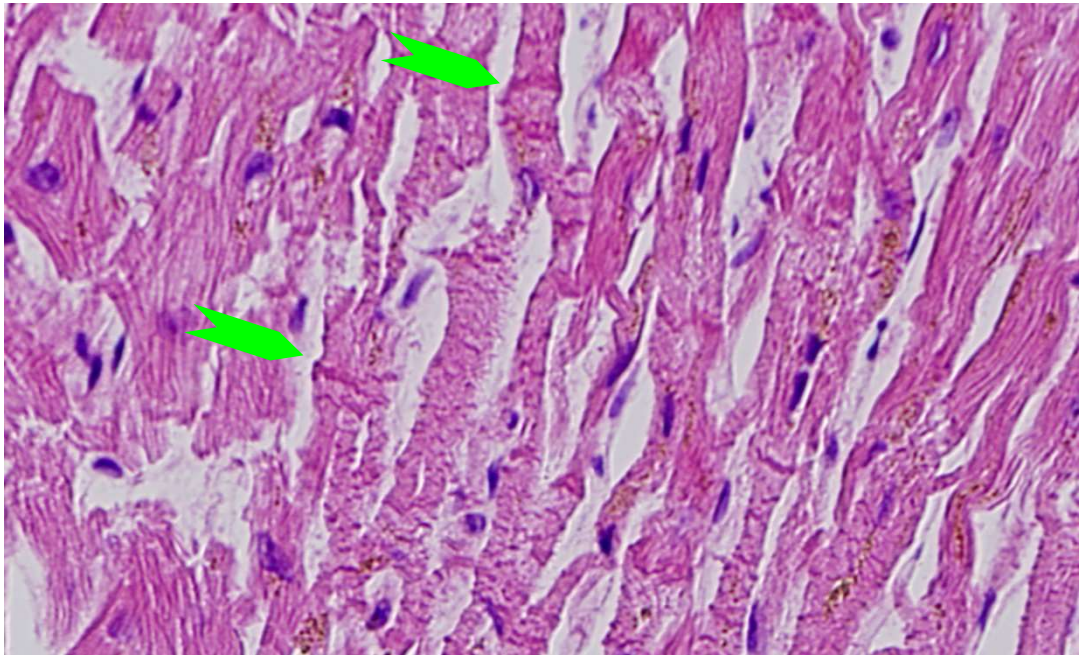
AMI Irreversible phase

between 4-12h

Beginning coagulation necrosis, hemorrhage

12-24h

Pycnotic cell nuclei, hypereosinophilia, contraction band necrosis (arrows)



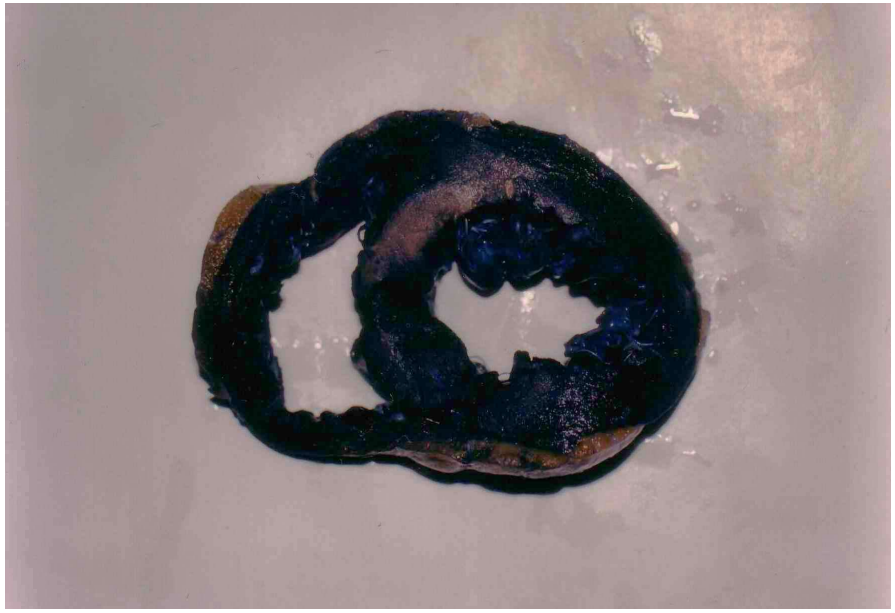
Following this: incipient neutrophil granulocye infiltration…
(can be recognised after 9hrs, with low cell count)

Macroscopy

First signs: dark-red patches, hemorrhage…

Ongoing neutrophil gr. infiltration, „yellow-tan” mottling

But until then…?



Nitro-blue tetrazolium-cloride reaction! -> loss of staining in damaged areas!
Detects a 3-4hrs infarction! Based on: intracellular oxidative reactions in the living cells.
(violet: viable myocardium, gray: zones of infarction)

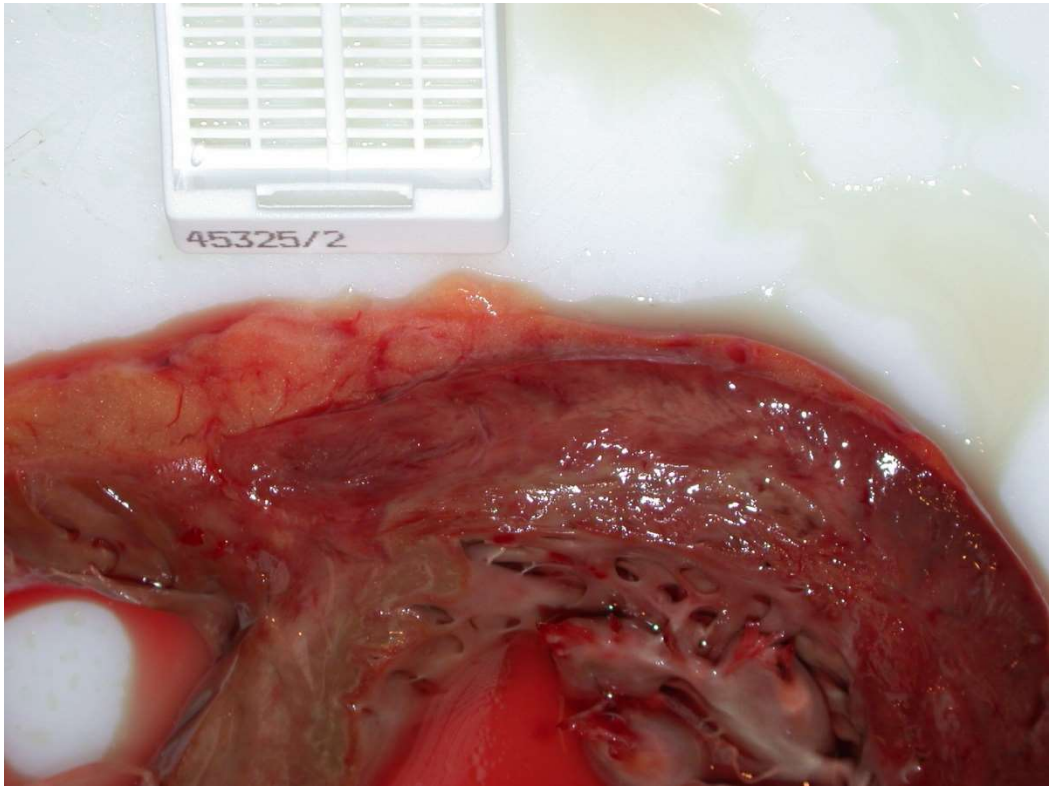
AMI morphology

- **1-3 days:**

- Progression of coagulation necrosis

- Intensive neutrophil granulocyte infiltration

- Loss of nuclei
  Loss of myocyte striations



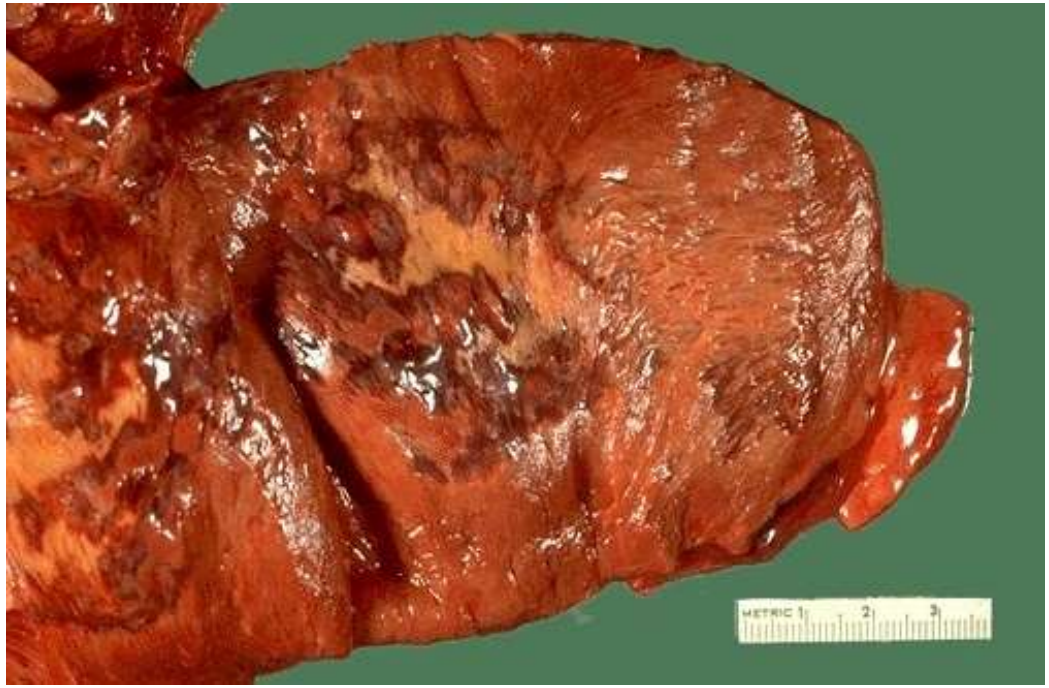
Mottling with yellow-tan infarct center

3.-7….10. days: „map-like heart”

-Hyperemic border,
yellow-tan center

- Beginning disintegration of dead myofibers, with dying neutrophils

-Phagocytosis of dead cells



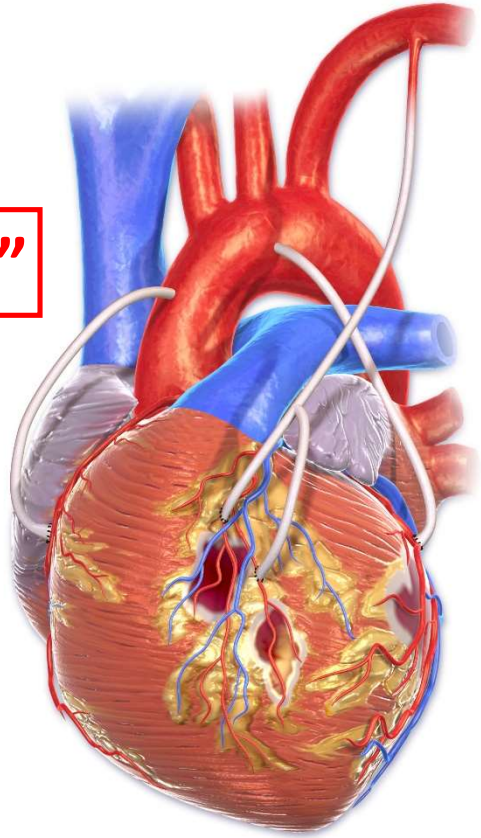
Mechanical complications (myocardial rupture) occurs most commonly within 3 to 7 days after infarction!!!

AMI early complications

- Decreased contractility -> left ventricular failure
- Arrythmia…bradycardia, conductance disorders, ventricular fibrillation or flutter -> sudden cardiac death
- Rupture
  - free wall-> tamponade
  - ventricular septum -> shunt
  - papillary muscle -> acute valvular insufficiency
- Mural thrombus
- Fibrinous pericarditis

AMI expansion is affected by:

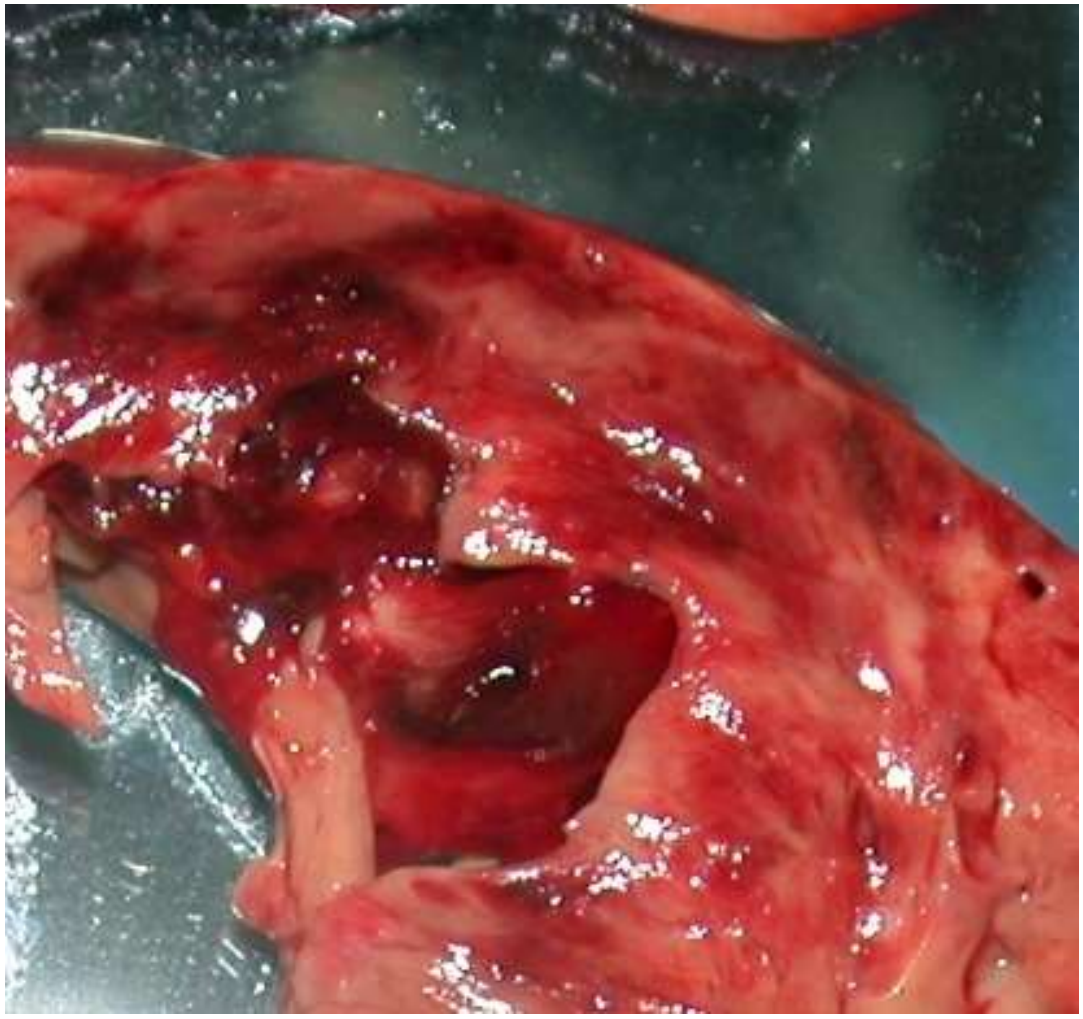
- Coronary reserve = resting / max. flow volume
- Localisation of coronary lesions
- Collaterals
- Reperfusion…(0-6h) **„time is muscle”**
  - own fibrinolytic system
  - thrombolysis
  - PCI (percutan coronary intervention)
  - CABG (coronary artery bypass grafting)



Coronary Artery Bypass Graft (CABG)
Quadruple Bypass

Kép forrása: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014".
WikiJournal of Medicine **1** (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436

Reperfused infarction area with hemorrhage



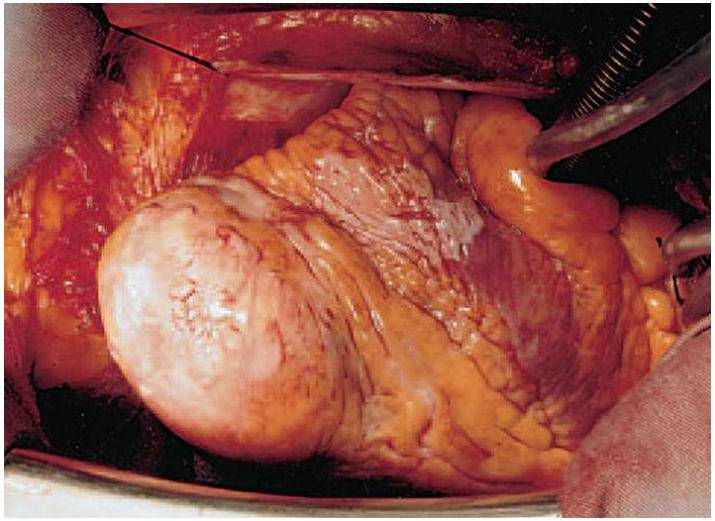
Morphology of a MI later on

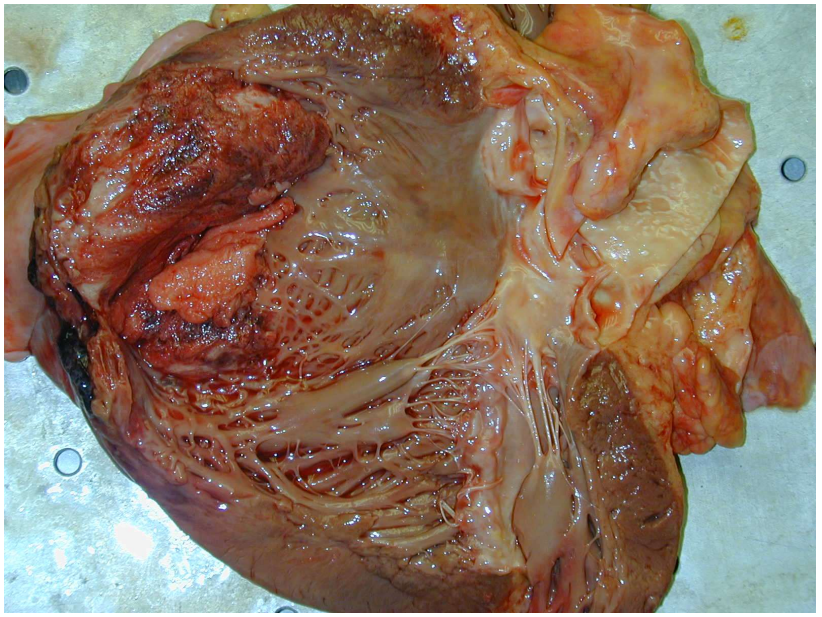
- 10-14. days:
  - red-gray infarct, depressed borders
  - granulation tissue is well formed
- 2-8 weeks:
  - gray-white scar
  - from border toward core
  - increased collagen deposition
  - decreased cellularity
- 2 months+:

  -dense collagenous scar

Late complications after MI

- Ventricular remodelling
- Persisting arrythmia
- Dressler syndrome (postinfarct. pericarditis)
- Ventricular aneurysm
  - mural thrombosis
    -> embolism
  - calcification
- Chronic heart failure





Aneurysms of the left ventricle

- Extended akinetic or dyskinetic (paradoxically pulsating) area in the ventricular wall, that decreases ejection fraction.
- Localisation:
  - anterior + apical = 88%
  - few inferior, posterior is the rarest

- They do evolve in the PCI-era, in 10% of the infarcts!
- Aneurysm expansion -> remodelling

Endocarditis

- Localisation: parietal / valvular
- Infective (acute or sub-acute)
- Non-infective:
  - Rheumatic endocarditis (as a part of rheumatic fever)
  - Non-bacterial thrombotic:
    hypercoagulable state and malignant tumors!

    „endocarditis marantica”

    -> sterile, non-destructive vegetations, but more fragile -> embolia!
  - Libman-Sacks endocarditis (sterile)
    -> Immuncomplex depositions in systemic lupus erythematosus (on the ventricular side of the valves)

Rheumatic fever

- Can cause: valvular, and myocardial disease (pancarditis)
- Antibodies directed against group A streptococcal molecules that cross-react with host myocardial antigens
  - 2-3 weeks after the infection

- Decreased incidence in developed regions
  - better social circumstances
  - quick diagnostic of the disease (mostly pharyngitis)
  - proper treatment of the infection with antibiotics

Rheumatic fever – acute

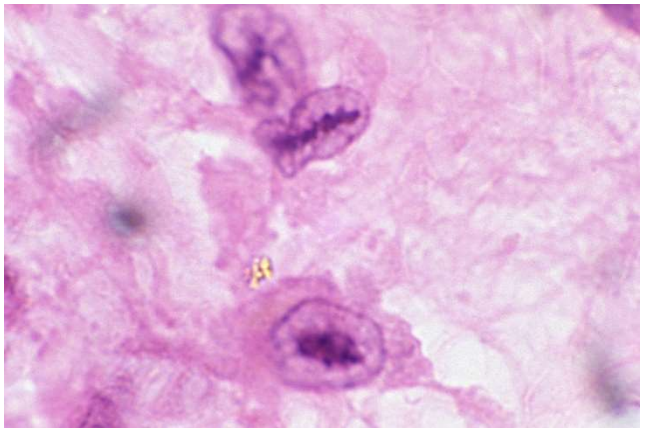
Inflammatory foci in a variety of tissues

-> Jones-criteria: (2 is needed for the diagnosis)

carditis
migrating polyarthritis
migrating erythema
subcutaneous nodules
chorea („St. Vitus dance")
(+nephritis)

Histology:

- Anichkov giant cells (1)
- Aschoff-nodules (2),
- Fibrinous exudate in the pericardium
- Myocarditis
- Valves: fibrinoid necrosis and fibrin deposition



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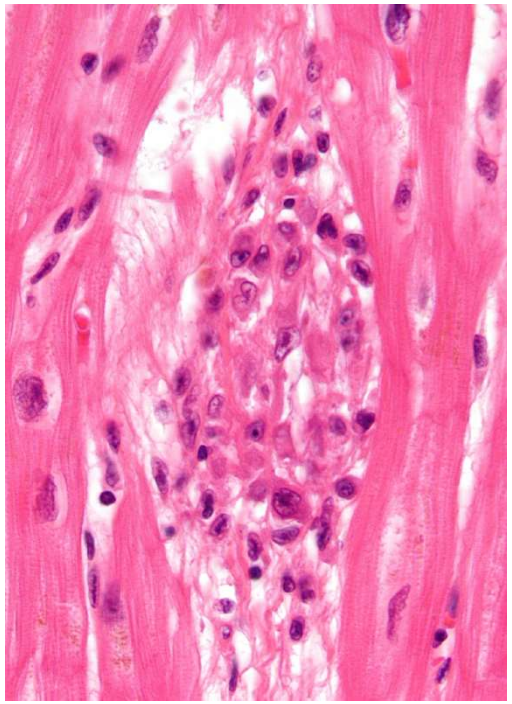

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1. By Ed Uthman, MD - http://www.flickr.com/photos/euthman/1858191477/, CC BY-SA 2.0, https://commons.wikimedia.org/w/index.php?curid=3062799
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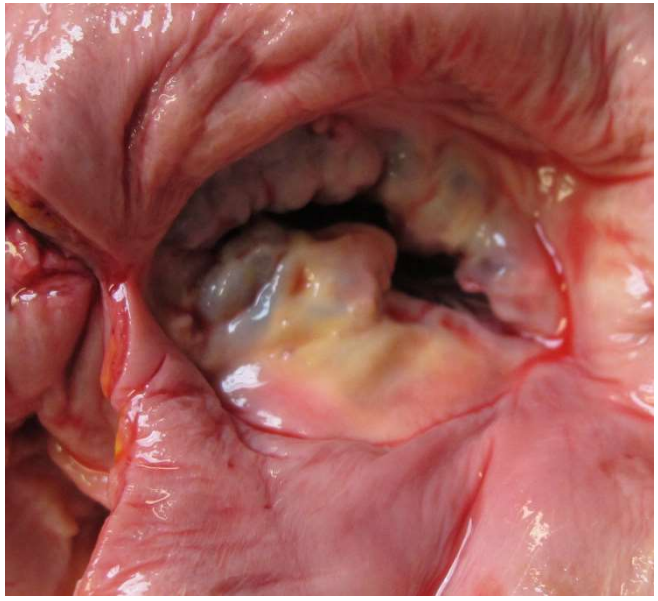
Rheumatic fever- chronic

- Organization of acute inflammation, scarring
- Most prominent on valves!
  - thickening
  - leaflet and chordae fusion and shortening
- Microscopically:
  -fibrosis
  -neovascularisation



Mitral valve, „fishmouth stenosis”

- Affectes: mitral- (70%) and aortic valve (25%)
- Consequence: stenosis and/or insufficiency (mostly combined)

Infective endocarditis (IE)

- Acute and sub-acute categories
- Difference: tempo and severity of the clinical course

Determined by:

- type and virulence of the pathogenic agent
- underlying heart disease

Most important for the clinical diagnosis:

-echocardiographic findings
-blood culture tests

IE – Acute symptoms and complications

Pathogens with high virulence! Pyogenic bacteria!

- Fever
- Destruction of valves -> acute insufficiency!
- Spreading:

  -septic infarcts, inflammation, abscesses, sepsis!
- Spreading to other heart valves
- Myocardial abscesses
- Intracardial fistula (e.g.: aorta – right atrium)
- Pericarditis, pleuritis

Sub-acute symptoms

- Fever („FUO”), exhaustibleness, splenomegaly…
- Inflammation in joints
- Nail bed (splinter) hemorrhages
- Painful fingertip nodules (Osler nodes)
- Painless palm or sole erythematous lesions (Janeway lesions)
- Retinal hemorrhages (Roth spots)
- Mycotic aneurysm (vasa vasorum embolisation)

! Schottmüller triad: cardiac murmur, splenomegaly (septic infarctions), hematuria

IE – predisposing factors

A highly virulent germ can cause IE on a normal valve!!!

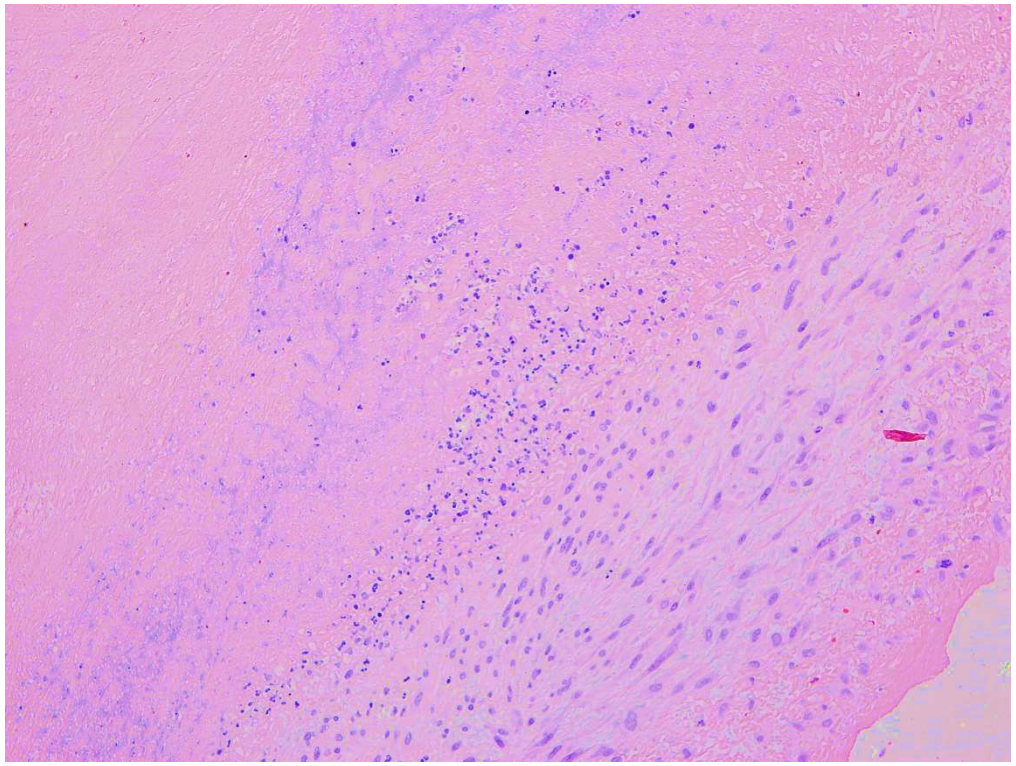
- Rheumatic valvular diseases
- Cardiac developmental disord.
- Hypertrophic cardiomyopathy
- Any valvular defect…
- Degenerative cardiac diseases
- Iv. drog users (right heart!)
- „entrance sites”
  (open wound, ulcer…)
- Artificial heart valve
- Pacemaker electrodes
- Immunodeficiency
- Previous endocarditis
- Diabetes mellitus
- Malignant tumors

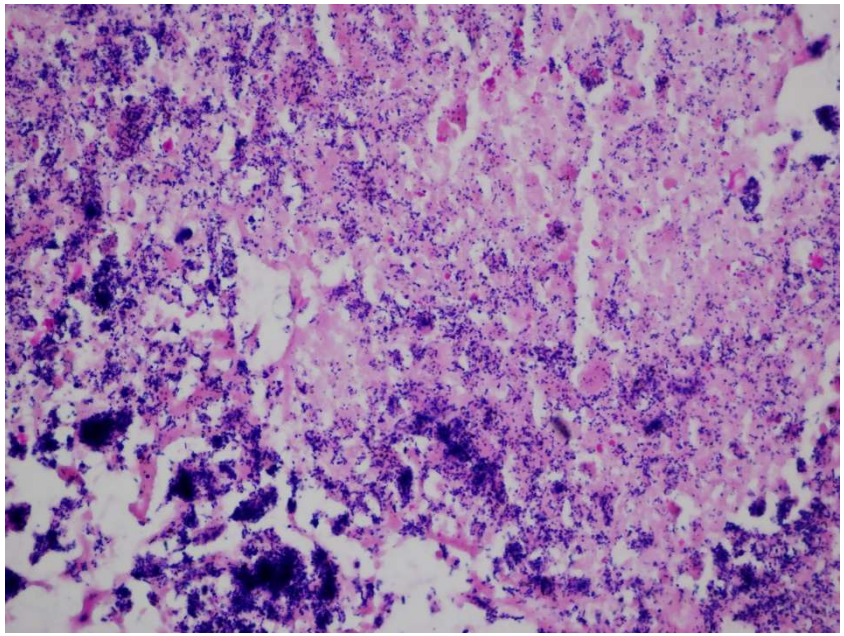
Tipical IE pathogens

- Staphylococcus (mostly aureus)
- Streptococci (alfa-hemolysing, oral flora)
- HACEK-group (Haemophilus, Actinobacilus, Cardiobacterium, Eikenella, Kingella)
- Gram-negative bacteria
- Enterococci (faecalis / faecium)
- Rarely: fungi, Rickettsia, Chlamydia
- !!! Bartonella, Coxiella, Legionella, Nocardia…

“culture-negative” infective endocarditis!!!

Infected valve

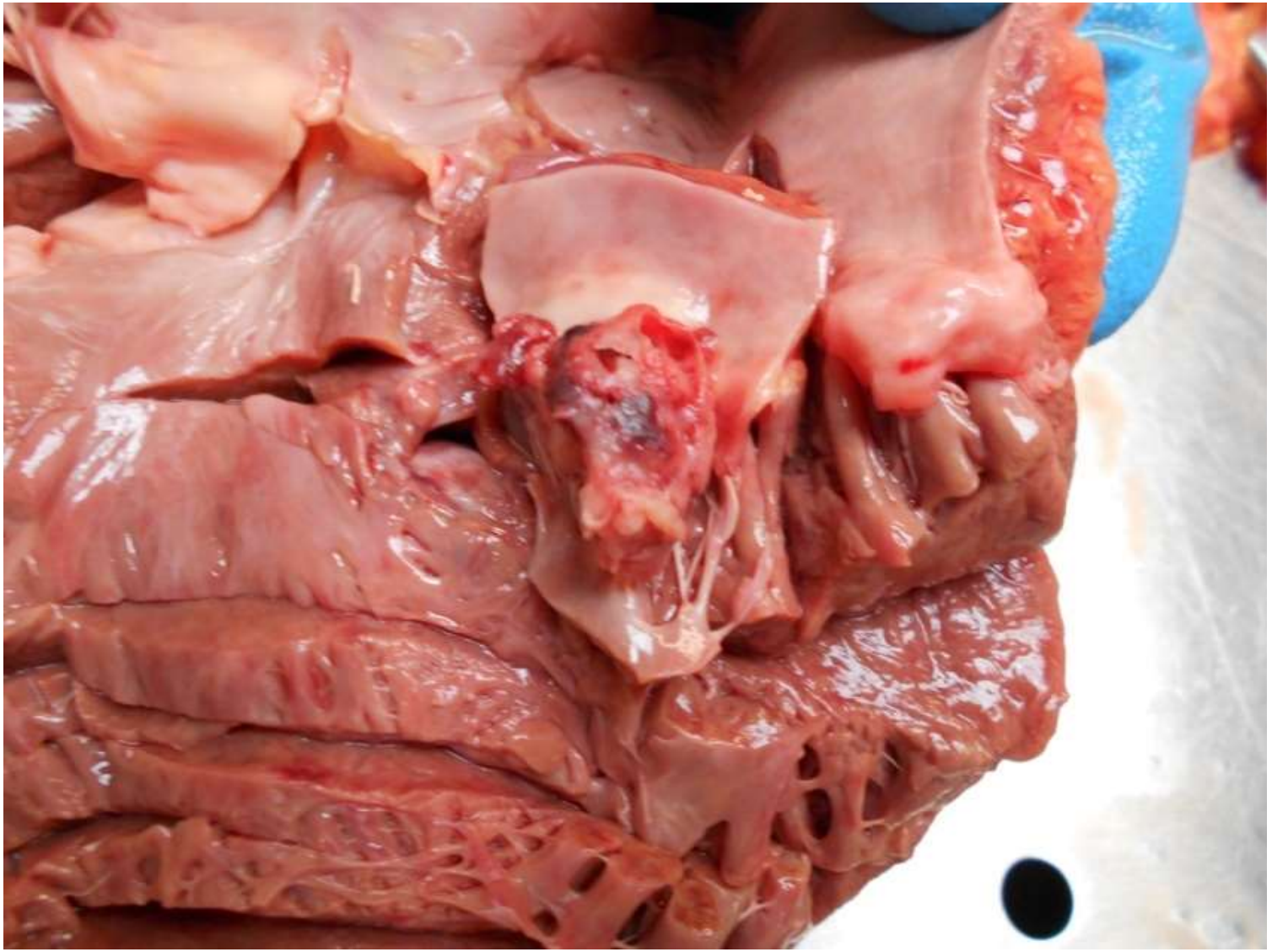




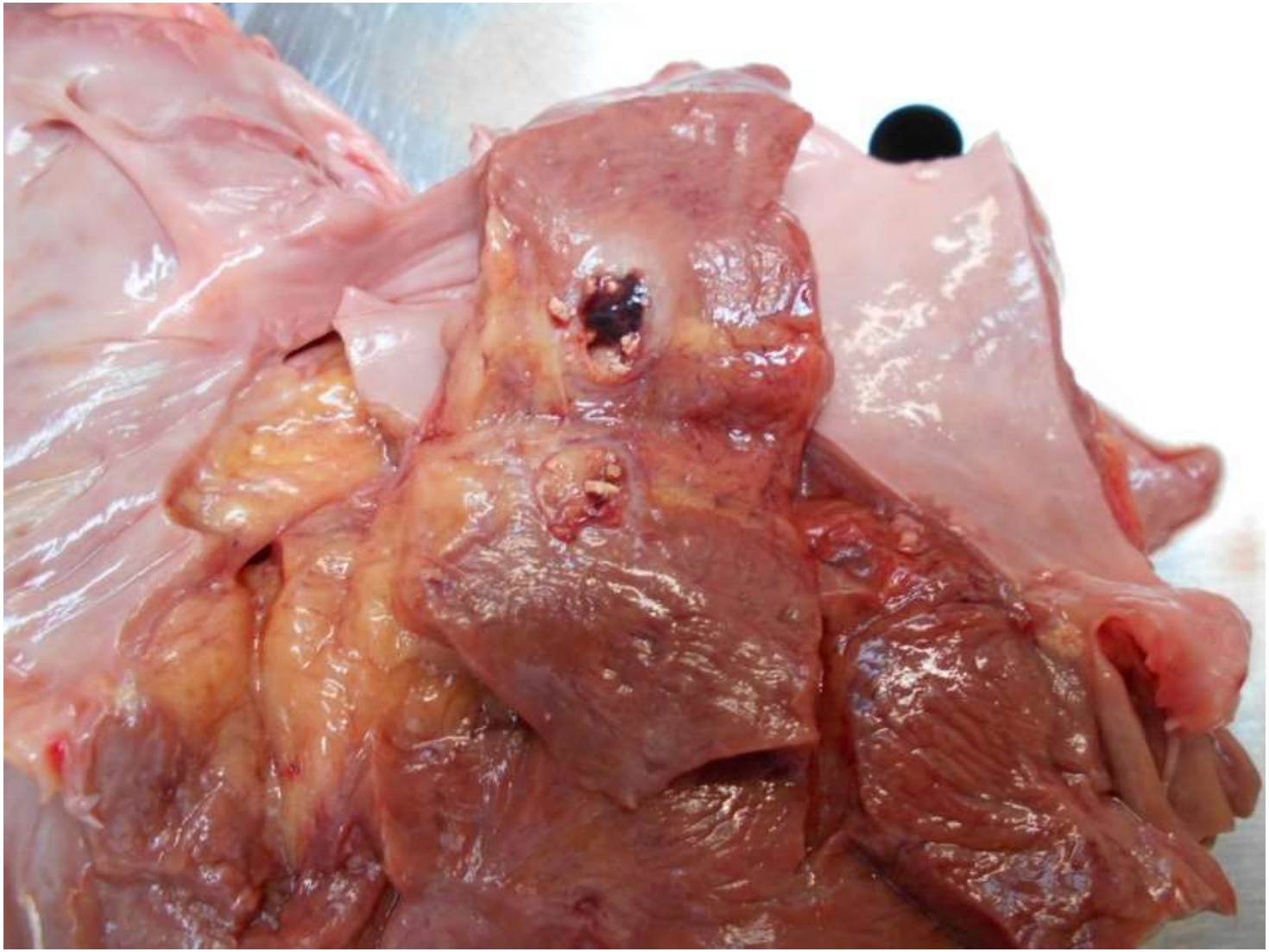
Mass of Gram-positive cocci
(same tissue)

Thickened valve, with fibrinous deposition.
In the tissue:
neutrophil granulocytes, cell debris, „clouds” of bacteria

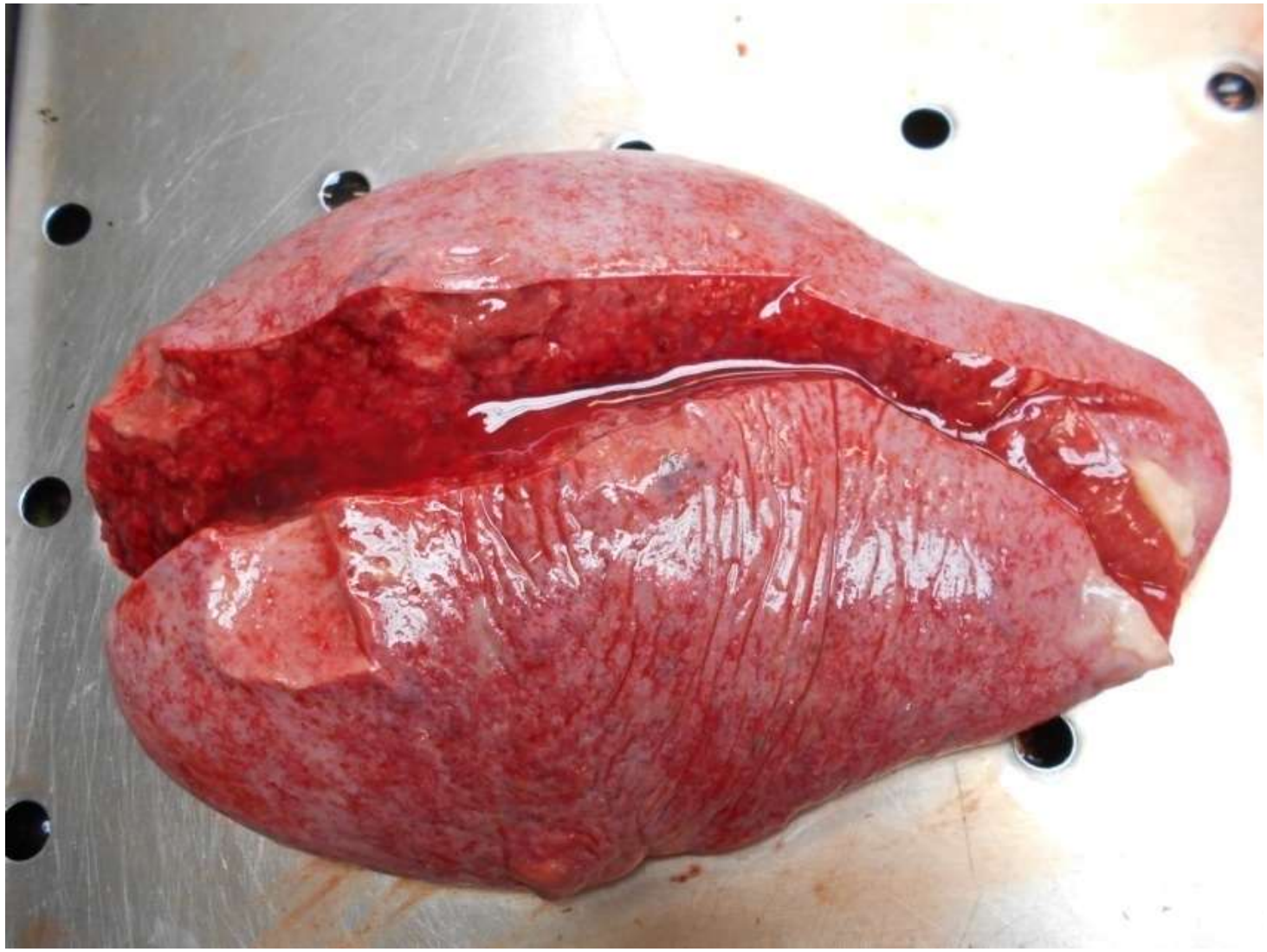
Vegetation on the mitral valve



…abscess beneath the vegetation!



IE spreading to the spleen



IE cerebral emollition caused by an embolizing vegetation