Atherosclerosis.
Stable and unstable plaque.
Complications of AS

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Arteriosclerosis

• arteriolosclerosis – small arteries and arterioles, downstream ischemic injury; two variants, hyaline and hyperplastic

• Mönckeberg medial sclerosis – calcific deposits in muscular arteries, persons older than 50, not clinically significant

• atherosclerosis – from Greek root words for „gruel“ and „hardening“, the most frequent and clinically important pattern
Atherosclerosis

- obstruction
- rupture ➔ thrombosis
- aneurysm formation

Figure: The basic structure of an atheromatous plaque.

FIBROUS CAP
(smooth muscle cells, macrophages, foam cells, lymphocytes, collagen, elastin, proteoglycans, neovascularization)

NECROTIC CENTER
(cell debris, cholesterol crystals, foam cells, calcium)

MEDIA
Epidemiology

- coronary artery disease (IHD)
- atherosclerosis: ~ 50% of all deaths
- myocardial infarction: ~ ¼ of all deaths
Environmental factors!!!
Etiology

Risk factors:

• Constitutional:
  o genetics
  o age
  o gender

• Modifiable:
  o hyperlipidemia
    (hypercholesterolemia / dyslipidemia)
  o hypertension
  o cigarette smoking
  o diabetes mellitus

• Additional:
  o inflammation
  o CRP levels
  o hyperhomocysteinemia
  o metabolic syndrome
  o other factors (lack of exercise, “type A personality”)
Hyperlipidemia (hypercholesterolemia / dyslipidemia)

• = ↑ total circulating cholesterol, ↑ LDL, ↓ HDL

• → dietary and pharmacologic interventions that lower total serum cholesterol or LDL, and raise serum HDL:
  • high dietary intake of cholesterol and saturated fats (in egg yolks, animal fats, butter) ↑ plasma cholesterol levels
  • omega-3 fatty acids (in fish oils) are beneficial, whereas trans-unsaturated fats in baked goods and margarine adversely affect cholesterol profiles
  • exercise and moderate consumption of ethanol raise HDL levels, whereas obesity and smoking lower them
  • statins
Etiology

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Pathogenesis

- response-to-injury hypothesis ↔ monoclonal hypothesis

- chronic inflammatory response of the arterial wall to endothelial injury
- interaction of lipoproteins, macrophages, T lymphocytes, cellular constituents of the arterial wall
Pathogenesis

Response-to-injury hypothesis
1. endothelial injury
   • hemodynamic disturbances (hypertension)
   • chronic dyslipidemia

2. smooth muscle cell proliferation
   • adhesion, aggregation, degranulation of platelets
   • infiltration with inflammatory cells
   • smooth muscle cell proliferation, ECM synthesis

3. role of monocytes
   • LDL → into intima
   • scavenger receptors – oxidized LDL → foam cells

4. role of dyslipidemia

5. thrombosis
Pathogenesis

Monoclonal hypothesis

• primary process – *monoklonal proliferation* of smooth muscle cell

• mutation
  o exogenous factors
  o endogenous metabolites
  o infections
Morphology

Fatty Streaks

• yellow, flat macules, lipid-filled foamy macrophages, minimally raised, without any significant flow disturbance
• in the aortas of infants younger than 1 year of age, in all children > 10 years
• the relationship of fatty streaks to atherosclerotic plaques - uncertain
Atherosclerotic plaque
- white to yellow raised lesions, thrombus superimposed on ulcerated plaques
- flow disturbances (turbulence at branch points)

- infrarenal abdominal aorta, the coronary arteries, the popliteal arteries, the internal carotid arteries, the vessels of the circle of Willis

- superficial fibrous cap, necrotic core
- periphery - neovascularization
- media deep to the plaque – fibrosis, smooth muscle atrophy and loss

- plaques continue to change, enlarge through ECM remodeling and thrombus organization; calcification
Clinical consequences of atherosclerosis

Signs and symptoms of *ischemia* in the:

- heart: MI (heart attack)
- aorta: aneurysms
- brain: CI (stroke)
- lower extremities:
- kidneys: gangrene
Clinical consequences of atherosclerosis

The principal pathophysiologic outcomes:

• occlusion

• plaques rupture → vascular thrombosis or distal embolization

• destruction of the underlying vessel wall → aneurysm formation → secondary rupture and / or thrombosis
Atherosclerotic thrombosis

Critical stenosis
• demand > supply

• coronary artery circulation
  ➢ rest → adequate cardiac perfusion
  ➢ exertion → chest pain = stable angina

• chronic arterial hypoperfusion: bowel ischemia, sudden cardiac death, chronic IHD, ischemic encephalopathy, intermittent claudication
Acute plaque change

1. rupture / fissuring
2. erosion / ulceration
3. hemorrhage into the atheroma

• rupture / erosion \rightarrow \text{thrombosis} \rightarrow \text{obstruction} \rightarrow \text{infarction}

• hemorrhage into the atheroma \rightarrow \text{obstruction}
Vulnerable (unstable) and stable plaques

<table>
<thead>
<tr>
<th>Vulnerable plaque</th>
<th>Stable plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>thin fibrous cap</td>
<td>densely collagenized and thickened fibrous cap</td>
</tr>
<tr>
<td>large lipid core</td>
<td>negligible atheromatous core</td>
</tr>
<tr>
<td>increased inflammation</td>
<td>minimal inflammation</td>
</tr>
</tbody>
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Morphology of atheromatous plaques

- **Rupture or ulceration** → **thrombus formation** - if the patient survives → thrombi become *organized and incorporated* into the growing plaque

- **Hemorrhage into a plaque** → rapid plaque expansion or plaque rupture

- **Atheroembolism** = discharge of debris → microemboli

- **Aneurysm formation** – atrophy of the media, loss of elastic tissue → structural weakening → aneurysmal dilation and rupture
Summary

- **atherosclerosis**: intima-based lesion, fibrous cap and atheromatous core

- **atherogenesis**: driven by an interplay of vessel wall injury and inflammation

- **multiple risk factors** cause endothelial dysfunction + influence smooth muscle cell recruitment and stimulation

- Plaques develop and grow slowly over decades
  - **stable plaques** = symptoms related to chronic ischemia
  - **unstable plaques** = dramatic and potentially fatal ischemic complications (related to rupture, thrombosis, or embolization)

- **stable plaques**: dense fibrous cap, minimal lipid accumulation, little inflammation,
- “**vulnerable**” unstable plaques: thin caps, large lipid cores, dense inflammatory infiltrates
Figure 9–17  Aneurysms. A, Normal vessel. B, True aneurysm, saccular type. The wall bulges outward and may be attenuated but is otherwise intact. C, True aneurysm, fusiform type. There is circumferential dilation of the vessel. D, False aneurysm. The wall is ruptured, creating a collection of blood (hematoma) bounded externally by adherent extravascular tissues. E, Dissection. Blood has entered the wall of the vessel and separated (dissected) the layers.
Pathogenesis

• inadequate or abnormal connective tissue synthesis
  ❑ Marfan syndrome – fibrillin
  ❑ Ehlers-Danlos syndrome type IV – type III collagen

• excessive connective tissue degradation
  ❑ ↑ MMP

• loss of smooth muscle cells or change in the smooth muscle cell synthetic phenotype
  ❑ cystic medial degeneration
Pathogenesis - causes

• two most important causes of aortic aneurysms
  ❑ atherosclerosis
  ❑ hypertension

• other conditions
  • trauma, vasculitis, infections = so called mycotic aneurysms
Abdominal aortic aneurysm (AAA)

• men, smokers, >50 years
• atherosclerosis

• typically between the renal arteries and the aortic bifurcation

• clinical consequences:
  - vessel obstruction → distal ischemia
  - embolism
  - impingement on adjacent structures
  - an abdominal mass (palpably pulsating)
  - rupture into the peritoneal cavity / retroperitoneal tissues → fatal hemorrhage
Thoracic aortic aneurysm

• hypertension
• Marfan syndrome

• encroachment on mediastinal structures

respiratory / feeding difficulties, persistent cough, pain, cardiac disease, aortic rupture
Aortic dissection

• mainly in 2 age groups:
  - men aged 40 to 60 with HT
  - younger patients with connective tissue abnormalities (Marfan syndrome)

• iatrogenic
• pregnant women
Pathogenesis

- **hypertension**
  - medial hypertrophy of the vasa vasorum
  - degenerative changes in ECM
  - loss of medial smooth muscle cells

- **hereditable / acquired connective tissue disorders**
  - Marfan syndrome, Ehlers-Danlos syndrome type IV, defects in copper metabolism
Morphology

• **external rupture** → massive hemorrhage / cardiac tamponade

• **double-barreled aorta** – dissecting hematoma reenters the lumen of the aorta through a second distal intimal tear = second vascular channel

• **cystic medial degeneration**
Clinical consequences

• depends on the affected portion of the aorta
• most serious – proximal aorta and arch

• Stanford classification:
  • type A: affects ascending aorta and arch (with or without involvement of the descending aorta)
  • type B: begins beyond brachiocephalic vessels

• DeBakey classification
  • type I
  • type II
  • type III

Figure 9-21 Classification of dissections. Type A (proximal) involves the ascending aorta, either as part of a more extensive dissection (DeBakey type I), or in isolation (DeBakey type II). Type B (distal, or DeBakey type III) dissections arise after the takeoff of the great vessels.
Clinical consequences

• sudden onset of excruciating tearing or stabbing pain, beginning in the anterior chest, radiating to the back

• cause of death
  ❖ rupture into the pericardial, pleural, or peritoneal cavity
  ❖ retrograde dissection into the aortic root → fatal disruption of aortic valvular apparatus / compression of the coronary arteries

• clinical presentations with cardiac involvement
  ❖ tamponade, aortic insufficiency, myocardial infarction
Type A: antihypertensive therapy + surgical plication

Type B: conservative management
Summary

• **aneurysms** - congenital or acquired; involve the entire wall thickness; complications - rupture, thrombosis, and embolization

• **dissections** - blood enters the wall of a vessel and separates the various layers; complications - a result of rupture / obstruction of vessels branching off the aorta

• **aneurysms and dissections** - result from structural weakness of the vessel wall - consequence of ischemia, genetic defects, or defective matrix remodeling