PATHOPHYSIOLOGY OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

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I. Structure of a Normal Artery

- **Endothelium**: monolayer of endothelial cells lining the luminal surface of all blood vessels. It is not just a simple semipermeable membrane, but a highly metabolically active organ with endocrine and paracrine functions;
- **Intima**: amorphous collagens, proteoglycans & elastic fibers;
- **Media**: layer of smooth muscle cells whose contraction controls the diameter of the vessels & influences the blood pressure;
- **Adventitia**: layer of connective tissue & cells that form the interface between the vessel and the tissue.

II. Definitions of Atherosclerosis

Atherosclerosis is a type of arteriosclerosis, meaning the **hardening of the arteries**. The term atherosclerosis, which comes from the Greek words atheros (meaning “gruel” or “paste”) and sclerosis (meaning “hardness”), denotes the **formation of fibrofatty lesions in the intima of the large and medium-size arteries** such as the aorta and its branches, the coronary arteries, and the large vessels that supply the brain.

1. **Arteriosclerosis** (in Greek, “arterio” = artery and "sclerosis“= hardening)
   - Chronic disease of the arterial system
   - Thickening, loss of elasticity & hardening of the vessel walls
   - Greatest morbidity and mortality of all human diseases **via:**
Narrowing of the vascular lumen  
- Insufficient tissue perfusion  
- Weakening/ouptouching of arterial walls

2. Three Patterns of Arteriosclerosis:  
- **Atherosclerosis (ATS)**  
  - Dominant form of arteriosclerosis which primarily affects:  
    - elastic arteries (aorta, carotid, iliac)  
    - large to medium muscular arteries (coronary & popliteal arteries)  
- **Arteriolosclerosis**  
  - Primarily affects the small arteries and arterioles (!!! in hypertension and diabetes mellitus)  
- **Monckeberg medial calcification & sclerosis.**

**ATS = Disease of the intima characterized by:**  
- Intimal thickening  
- Intra- and extracellular lipid accumulation  
- Chronic Inflammation

**Basic Lesion:**  
- Is termed atheroma, fibro-fatty plaque or atheromatous plaque  
- Is formed over several years, secondary to endothelial injury.

III. Risk Factors of Atherosclerosis  
The cause or causes of atherosclerosis have not been clearly determined. However, epidemiologic studies have identified **predisposing risk factors.** Some risk factors can be affected by a change in health behavior and others cannot. Risk factors that cannot be changed include age, male gender, and family history of premature coronary heart disease.

**Not modifiable risk factors:**  
- Age (> 45 in men & > 55 in women)  
- Sex (males/complications)  
- Familial history  
- Genetic (hypercholesterolemia due to mutations of genes encoding the LDL receptors)

**Modifiable risk factors:**  
*Classic factors:*  
- Hyperlipidemia / dyslipidemia  
- Hypertension  
- Diabetes mellitus  
- Obesity  
- Cigarette smoking  
- Sedentary life-style  
- Stress
− Heavy alcohol consumption

**Novel Factors:**
− Increased serum markers of inflammation & thrombosis (hsCRP, von Willebrand factor, ESR, fibrinogen, IL-1, IL-6, TNF-α)
− Elevated plasma homocysteine
− Infections (Chlamydia pneumoniae, H. pylori)

**IV. Pathogenesis of Atherosclerosis**

1. **Four Major Components of Plaque:**
   − Cells: smooth muscle cells, macrophages and other WBC (lymphocytes, polymorphs)
   − Extracellular matrix: collagen, elastin, and proteogycans
   − Lipids: cholesterol
   − Calcium (often calcification of plaque)

2. **Two Major Processes Occurring in Plaque:**
   − Intimal thickening via:
     o Smooth muscle cells proliferation
     o Extracellular matrix synthesis
   − Lipid accumulation:
     o Intracellular (in macrophages and smooth muscle cells)
     o Extracellular (free)

3. **Four Major Steps in ATS Progression**
   Although the risk factors associated with atherosclerosis have been identified through epidemiologic studies, many questions regarding the mechanisms by which these risk factors contribute to the development of atherosclerosis are still unanswered. There is an increasing evidence that atherosclerosis is at least partially the result of: (1) endothelial injury (! Endothelial dysfunction) with leukocyte (lymphocytes and monocytes) adhesion and platelet adherence, (2) smooth muscle cell migration and proliferation, (3) lipid swallowed up by activated macrophages (fatty streaks), and (4) subsequent development of an atherosclerotic plaque with lipid core (Fibrous plaques).

4. **Endothelial Dysfunction**
   a) Causes
   There are 2 current hypotheses:
   • The “Response to Injury” Hypothesis
   • The “Oxidative Modification” Hypothesis

   Endothelial dysfunction is responsible for:
   • Up-regulation of endothelial and leukocyte adhesion molecules
   • Entry of monocytes and T lymphocytes across endothelium
   • LDL transcytosis
• LDL oxidation into proinflammatory lipids
• Foam cells generation
• Recruitment and proliferation of smooth muscle cells
• Synthesis of connective tissue proteins

• Imbalance of factors controlling the arterial tone & platelet aggregation:
  
  \[ \downarrow \text{Nitric oxide (NO)} \quad \uparrow \text{Endothelin (ET)} \]
  
  \[ \downarrow \text{Prostacyclin (PG I2)} \quad \uparrow \text{Thromboxan (TxA2)} \]

### IV. Coronary Artery Disease

#### 1. Definition:

**a) Etiological definition:** a multifactorial, chronological progressing inflammatory disease that:

- begins in childhood
- progresses through adulthood
- culminates in old age with overt disease manifestation
- elicits consequences leading to severe disability & death

**b) Pathophysiological definition:** an imbalance between:

- coronary oxygen supply
- myocardial oxygen demand

**Supply vs. Demand:**

**Reduced blood supply:**

- ATS (99% of cases) + coronarian spasm
- Hemodynamic factors (hypotension ± hypovolemia)
- Hematologic factors (↓ O2 content/availability)

**Increased myocardial demand:**

- ↑ Afterload (hypertension)
- ↑ HR (exercise, stress, hyperkinetic diseases)
- ↑ Contractility
- ↑ Preload (maladaptive Frank - Starling)
- ↑ Myocardial thickness (maladaptive hypertrophy)

#### 2. Effects of Myocardial Ischemia

**a) Mechanical Abnormalities**

- Failure of normal relaxation and contraction
- Subendocardial layer – undergoes more intense ischemia!
- Involvement of papillary muscles – mitral regurgitation
- Large portion of LV – transient LV failure
b) Metabolic Abnormalities
- Impairment of FA oxidation
- Anaerobic Glycolysis:
  - lactic acidosis
  - decreased myocardial stores of high energy phosphates (ATP, CP)
  - abnormal function of ATP-ases:
    - SERCA ⇒ diastolic dysfunction
    - Na-K pump ⇒ systolic dysfunction & arrhythmias

c) Bioelectrical Abnormalities
- Repolarization abnormalities: ST & T changes
  - Subendocardial ischemia:
    - ST depression
  - Transmural ischemia:
    - ST elevation (transient!)
  - Isolated T changes – non-specific
- Electrical instability
  - Malignant tachyarrhythmias

d) Effects Of Ischemia - Summary
- Metabolic abnormalities due to anaerobic glycolysis
  - Lactic acidosis
  - Decreased ATP
  - Impaired cell membrane function
- Bioelectrical abnormalities
  - angina pectoris: abnormal repolarization (ST-T)
    - ST depression = subendocardial ischemia
    - ST elevation = transmural ischemia
  - myocardial infarction - abnormal depolarization (QRS) + abnormal repolarization (ST-T)

- Mechanical abnormalities
  - diskinesia
  - transient LV failure
  - mitral regurgitation

3. Asymptomatic Coronary Artery Disease (Silent angina“)
   Silent myocardial ischemia occurs in the absence of anginal pain. The factors that cause silent myocardial ischemia appear to be the same as those responsible for angina: impaired blood flow from the effects of coronary atherosclerosis or vasospasm.
   - Proposed mechanism: abnormality in left ventricular afferent innervation
Causes:
- diabetes mellitus
- following surgical denervation during:
  - coronary artery bypass grafting
  - cardiac transplantation
- following ischemic local nerve injury by myocardial infarction.

4. Symptomatic Ischemic Heart Disease
Characterized by chest discomfort due to:
- Angina pectoris
- Myocardial infarction.

V. Angina Pectoris

1. Definition:
Acute pain, usually in the chest, resulting from an increased demand for oxygen and a decreased ability to provide it.

2. Major causes:
- Partial occlusion of a coronary artery
- Vasospasm

3. Typical Presentation
- Squeezing, Crushing, Heavy, Tight
- Pain/Discomfort may radiate to shoulders, arms, neck, back, jaw or epigastrium
- Usually lasts 3-5 min and rarely exceeds 15 min ≠ myocardial infarction where > 20 min
- Not changed by swallowing, coughing, deep breathing or positional changes.

4. Triggering Factors
- Usually Provoked by:
  - Exercise
  - Eating/heavy meal
  - Emotion/stress
  - Exposure to cold
- Usually Relieved by:
  - Rest/Removal of provoking factor
  - Nitroglycerin (NTG)
- Associated with (especially angina due to acute MI !):
  - Anxiety
  - Diaphoresis or clammy skin
  - Nausea, vomiting
  - Shortness of breath
5. Types of angina pectoris:
   - Stable angina
   - Variant or Prinzmetal angina
   - Unstable angina

a) Stable Angina
   - Causes: ATS (luminal narrowing and hardening of arterial walls)
   - Reasonably predictable frequency, onset, duration
   - Relief predictable with rest, NTG
   - Treatment goals:
     - Reduce myocardial oxygen demand
     - Improve myocardial oxygen supply

b) Variant Angina (Prinzmetal Angina)
   - Causes:
     - Hyperactivity of sympathetic nervous system
     - Increased calcium influx in arterial smooth muscle
     - Impaired production or release of thromboxane
     ⇒ Vasospasm of an epicardial artery
   - Characteristics:
     - Recurrent, prolonged attacks of severe transmural ischemia
     - Occurs at rest or at night during rapid eye movement sleep
     - Episodes at regular times of day
     - May result in ST elevation that resolve with minimal treatment

c) Unstable Angina
   - Associated with advanced ischemic heart disease:
     - significant or progressing occlusion of a coronary artery or severe vasospasm
     - in postinfarction states ⇒ risk of reinfarction
   - Prolonged chest pain/ischemic symptoms or an atypical presentation of angina without ECG or laboratory evidence of AMI (“pre-infarction angina”)
   - Types:
     - New onset severe/frequent angina (≥3 episodes/day)
     - Angina at rest
     - Accelerating angina:
       - Increased frequency or duration of episodes
       - Onset with less exertion than normal
       - Increased severity of symptoms
       - Requires greater number of NTG tablets to relieve symptoms
VI. Myocardial Infarction (MI)

1. Definition: Necrosis of myocardial tissue caused by a lack of oxygenation and reduced blood flow resulting from total occluded coronary artery.

2. Precipitating Factors:
   - Coronary thrombosis (most common)
   - Coronary vasospasm
   - Microemboli
   - Severe Hypotension/Shock
   - Acute Hypoxia
   - Acute Volume Overload

3. Location, size and severity depend on site of vessel occlusion:
   - Majority involve the left ventricle
     - LCA occlusion:
       - anterior (antero-septal, antero-apical) & lateral MI
     - RCA occlusion:
       - inferior & right MI

Often defined further as:
   - subendocardial: involves only subendocardial muscle
   - transmural: full thickness of ventricular wall involved

4. Structural changes
   a) Myocardial stunning
      - Temporary loss of contractile function that persists for hours to days after the restoration of perfusion
   b) Hibernating myocardium
      - Myocardial adaptation of persistently ischemic myocardium aimed at prolonging myocyte survival until perfusion can be restored
   c) Myocardial remodeling
      - Myocyte fibrosis & hypertrophy, with impairment of contractile function in the areas distant from the site of infarction (major role for AII, catecholamines, reversed by ACEI & beta-blockers)

5. Functional changes
   a) Decreased LV compliance:
      - ↑ LVEDP (left ventricle end diastolic pressure)
   b) Decreased LV contractility:
      - ↓ Ejection fraction & Stroke volume
   c) Life-threatening arrhythmias
d) Heart failure

6. Positive Diagnosis:
   - Clinics – anginal pain
   - ECG
   - Laboratory

a) ECG changes:
   - Pronounced, persisting pathological Q waves
   - ST elevation
   - T wave inversion

Classification by timing - 3 stages:
   - Acute/evolving: 6 h - 7d (PMNs)
   - Recent/healing: 7-28 d (mono-, fibroblasts, no PMNs)
   - Chronic/healed: >29 d (scar, without cellular infiltration)

Corresponding direct ECG changes:
   - Acute: injury (ST), necrosis (Q), ischemia (T)
   - Recent: necrosis (Q) ± ischemia (T)
   - Chronic: necrosis (Q)

Classification by location:
   - Anterior
   - Lateral
   - Inferior
   - Posterior

Pathological classification by size:
   - Microscopic - focal necrosis
   - Small - < 10% of left ventricle
   - Medium - 10-30% of left ventricle
   - Large - > 30% of left ventricle

b) Laboratory
Serum cardiac markers are released into the circulation from the necrotic heart muscle:
   - CK (creatine phosphokinase) rises 4-8 hrs after onset of MI and normalize by 48-72 hrs
   - MB isoenzyme of CK is specific!
   - Cardiac specific troponin T (cTnT) and I (cTnI): more sensitive and specific for identification of myocardial necrosis!
   - Myoglobin: first serum marker to rise after MI, but lacks specificity.
   - Non-specific reaction to AMI:
     - WBC (up to 7 days) = 12,000 – 15,000 cells/mm3
     - Polymorphonuclear leucocytosis
     - ESR (erythrocyte sedimentation rate) (for 1 – 2 weeks)