ATHEROCLEROSIS, THROMBANGIITIS OBLITERANS (BÜRGER’S DISEASE), RAYNAUD’S PHENOMENON AND RAYNAUD’S DISEASE

ATHEROCLEROSIS

Definitions

- **Atherosclerosis** is a descriptive term used for thickened and hardened lipid-rich lesions of the medium and large muscular elastic arteries.
- **Arteriosclerosis** is a generic term used for thickened and stiffened arteries of all sizes.
- Other forms: Mönckeberg’s arteriosclerosis: focal, ring-like calcified arteriosclerosis.
- **Arteriolosclerosis**: a disease of small vessels.

The lesions of atherosclerosis

1. Early lesion - fatty streak
   - Is present at birth. Lesions are confined to the intima, containing two cell types: foam cells (Mϕ-s filled with lipids, principally cholesterol esters) and T lymphocytes (CD8+, some CD4+).
   - Foam cells are derived from blood-borne Mϕ-s. The fatty streak enlarges by continuing attachment and migration of monocytes into the intima with the consequent development into Mϕ-s.
   - Subsequently smooth muscle cells migrate from the media to the intima and also begin to accumulate lipid and take on the appearance of foam cells.
   - Fatty streaks may transform to advanced lesions, or remain at this stage throughout life, or may regress, even disappear.
   - Pathology: Yellow, flat lesions without clinical sequels.

2. Advanced lesion - fibrous plaque
   - Is also located in the intima causing eccentric thickening of the artery that often results in occlusion of the lumen.
   - Typically covered by a cap of dense connective tissue containing a special form of flattened, pancake-shaped smooth muscle cells that have formed the dense collagenous matrix in which it is embedded.
   - Beneath this cap, the lesion is highly cellular and contains large numbers of smooth muscle cells (some of which may be full of lipid droplets) and variable numbers of T lymphocytes.
   - These collections of cells usually overlie a deeper area of necrotic foam cells and debris. This necrotic area sometimes becomes calcified and often contains cholesterol crystals.

3. Complicated lesion
   - A fibrous plaque that has undergone extensive degeneration and often calcification.
   - May contain ulcerations, cracks, and fissures, which serve as sites for platelet adherence, aggregation and thrombosis, and subsequent organization.
• When this occurs, thrombosis may result in sudden occlusion of the artery.
• Pathology of fibrous plaques and complicated lesions: Are pearly gray and raised, but may be discolored with erythrocytes and thrombi.

The response-to-injury theory of atherosclerosis
• A primary injury that affects the endothelial lining, evoking a complex metabolic and immune response
• As a result of it, oxidized LDL and heat-shock protein (hsp) 60/65 are expressed on the surface of the cell.
• Both humoral and cellular immune responses are directed against them.

Atherogenous cytokines and their probable local effects

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Proatherogenic effect</th>
<th>Anti-atherogenic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>T, Mϕ, EC, SMC</td>
<td>EC and SMC adhesion molecule expr.↑ EC procoagulant effect SMC proliferation</td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T, NK</td>
<td>Mϕ activation EC and SMC adhesion molecule expr.↑ and MHC II expr.↑</td>
<td>Cell growth↓ Mϕ scavenger receptor expr.↓</td>
</tr>
<tr>
<td>M-CSF</td>
<td>T, Mϕ, EC</td>
<td>Mϕ activation, proliferation Scavenger receptor expr.↓</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>T</td>
<td>Monocyte chemotaxis</td>
<td></td>
</tr>
<tr>
<td>PDGF</td>
<td>T, THRC</td>
<td>SMC mitogen and chemoattractant</td>
<td></td>
</tr>
<tr>
<td>TNFα</td>
<td>T, Mϕ, SMC, EC</td>
<td>SMC growth EC and SMC adhesion molecule expr.↑, cytokine expr., etc.</td>
<td>Mϕ scavenger receptor expr.↓</td>
</tr>
<tr>
<td>IL-2</td>
<td>T</td>
<td>Monocyte activation</td>
<td></td>
</tr>
<tr>
<td>IL-3</td>
<td>T</td>
<td>EC adhesion molecule expr.↑</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>T, EC, SMC</td>
<td>Proatherogenic effect on EC-s</td>
<td>Extracell. matrix production↓ EC adhesion molecule expr.↓ Mϕ activation↓</td>
</tr>
<tr>
<td>TGFβ</td>
<td>T, Mϕ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Localization of the lesions
• Aorta (most commonly abdominal, thoracic)
• Femoral (most commonly superficial), popliteal, and tibial arteries
• Coronary arteries (most commonly the main stem and left anterior descendent)
• Internal and external carotid arteries (most commonly the bifurcation); the cerebral arteries.
• Pulmonary arteries are generally spared unless severe pulmonary hypertension develops.

Risk factors in atherosclerosis
• **Hyperlipidemia**
• Familial or secondary (diabetes, renal disease, alcoholism, chronic pancreatitis, hypothyroidism, dysglobulinemia, treatment with corticosteroids or estrogens
  - VLDL: by itself is not a risk factor
  - LDL-cholesterol: true risk factor
  - HDL: protective factor
• Cigarette smoking*
• Hypertension*
• Diabetes mellitus
• Sex: male
• Age
• Obesity, decreased physical activity
• Stress, personality type A
• Genetic factors
• Elevated C-reactive protein (CRP) level
• Hyperuricemia

* independent risk factors

The SCORE

The metabolic syndrome
1. Central obesity: abdominal circumference >102 cm in men, and >88 cm in women (norm. >94 cm, >80 cm, respectively)
2. Serum triglyceride >1.7 mmol/l (or treatment for this)
3. Serum HDL-cholesterol <1.0 mmol/l in men, <1.3 mmol/l in women (or treatment for this)
4. Blood pressure: RR syst. >130 Hgmm, RR diast. >85 mmHg (or treatment for this)
5. Fasting blood sugar >5,6 mmol/l (or treatment for this)

Diagnosis: 1 and two out of 2-5.

Treatment and prevention of atherosclerosis
• Treatment of hyperlipoproteinemia (diet, antilipemic drugs: statins, fibrates)
• Treatment of hypertension
• Cessation of smoking
• Change of diets, habits and lifestyles
• Physical exercise
• Anti-platelet drugs
• Follow-up of patients with no or mild symptoms but with a family history positive for myocardial infarction, stroke, etc.

Regression of atherosclerosis
• There is a complete regression of fatty streak in experimental animal models. In humans, fatty streaks can regress as a result of strict fat-free diet and aggressive lipid-lowering treatment.
• Fibrous plaques or complicated lesions in humans may also be partially reversible, if LDL can be lowered by 50%
THROMBANGIITIS OBLITERANS (BÜRGER’S DISEASE)

**Definition**
- Thrombangiitis obliterans is an obstructive arterial disease caused by segmental inflammatory and proliferative lesions of the medium and small arteries and veins of the limbs.

**Etiology**
- **Cause:** unknown. Almost all patients are heavy smokers, particularly cigarettes. Many patients have cutaneous hypersensitivity to intradermally injected tobacco products.
- High prevalence of HLA-A9 and HLA-B5 antigens.
- **Autoimmune mechanism:** lymphocytes from 77% of patients exhibit cellular sensitivity to human type I and type III collagen; 50% have anti-collagen antibodies. (Normal controls and patients with atherosclerosis obliterans had considerably lower percentages).

**Incidence**
- Occurs mostly in young males
- Starts between 20-40 years of age
- M/F = 9:1-75:1
- High prevalence in Israel, the Orient and India (genetic predisposition)

**Pathology**
Small and medium-size arteries and veins are affected in segmental fashion.
- **Acute lesions:** proliferation of the intima and thrombosis. Inflammatory infiltration with PMN-s, lymphocytes, and giant cells of all coats of the artery or veins, extending into the thrombus. The media remains intact. Distinguishing features from atherosclerosis: more cellular thrombus, preservation of the media, inflammatory infiltration of all coats of the vessel.
- **Older lesions** are less cellular, with eventual scarring. Lesions of different age can be found simultaneously.

**Clinical manifestations**
- Young heavy smoker male with a history or evidence of superficial thrombophlebitis.
- Presenting complaints: Raynaud’s phenomenon with digital ulceration, pain from ischemia.
- Trophic lesions: changes in color or temperature. Ischemic neuropathy (paroxysmal, shock-like pain), paresthesia.
- Typical intermittent claudication of the forearm or hand.
- Migratory thrombophlebitis (inflamed, red, tender segments of the superficial veins).

**Physical examination**
- Impaired arterial pulsations. The more proximal arteries are normal.
- Cyanosis, or pallor, or persistent redness in the digits, associated with changes in temperature.
- Edema of the foot is common.
- Occasionally stenosis or occlusion of mesenteric, coronary, cerebral, or renal arteries.

**Diagnosis**
- Age, sex, involvement of the upper extremities are helpful.
• **Arteriography:** segmental multiple occlusions of the medium-sized and small arteries associated with collateral vessel visualization. The larger arteries are generally spared.

• Final confirmation by biopsy of an early lesion, characteristic inflammatory and proliferative changes.

**Therapy**

• Cessation of smoking, protection from cold, local care of ulceration or gangrene, eventually amputation.

• Sympathectomy, vasodilative drug therapy.

**Prognosis**

• Usually not life-threatening, but is generally more rapidly progressive than arteriosclerosis obliterans. Continuation of smoking results in rapid progression.

---

**RAYNAUD’S PHENOMENON AND RAYNAUD’S DISEASE**

**Definition**

• Attack of pallor and cyanosis of the digits to cold or emotion. As the attack abates the color changes are replaced by redness.

• **Primary, Raynaud’s disease:** 60%

• **Secondary, Raynaud’s phenomenon:** 40%.

**Etiology and incidence**

• **Raynaud’s disease** can start at any age, commonly between 20-40 years. Is much more common in females than in males. Cause is unknown. Theories:
  1. Increased sympathetic nerve activity.
  2. Hypersensibility of vessels to cold due to a fault in the arterial wall, including destruction of the sympathetic activity.
  3. Increased release of serotonin and TXA due to accelerated destruction of platelets.

• 25% of patients with variant angina pectoris were found to have migraine and 24% were found to have **Raynaud’s phenomenon** → a generalized defect predisposing to arterial vasospasm. The association with idiopathic pulmonary fibrosis may also reflect a high level of peripheral vascular tone secondary to the severe reduction in cardiac output.

**Causes of secondary Raynaud’s phenomenon**

1. **Oclusive arterial disease**
   a) Arteriosclerosis obliterans
   b) Bürger’s disease
   c) Arterial embolism
   d) Vasculitis
   e) Arterial thrombosis

2. **Connective tissue disorders**
   a) Scleroderma, CREST syndrome
   b) Mixed connective tissue disease
   c) Rheumatoid arthritis
   d) Systemic lupus erythematosus
3. Vascular injury
   a) Repetitive minor occupational trauma, e.g. pneumatic hammer operators, pianists, typists, or users of hand-held vibrating tools
   b) Frostbite

4. Neurogenic causes
   a) Thoracic outlet compression by cervical rib, by scalenus anticus muscle, or in hyperabduction syndrome
   b) Carpal tunnel syndrome
   c) Sympathetic causalgia
   d) Spinal cord diseases

5. Drugs or exposure to chemicals
   a) Ergotamine, ergotism, methysergide, polyvinyl chloride, $\beta$-receptor blockers, antimetabolite drugs (cisplatin, vinblastine, bleomycin)

6. Intravascular coagulation or aggregation
   a) Cryoglobulinemia
   b) Cold agglutinins

Pathophysiology
- **Initially**: intense vasoconstriction or spasm of digital arteries $\rightarrow$ pallor.
- **Later**: capillaries and veins are partially filled with blood containing markedly deoxygenated hemoglobin $\rightarrow$ cyanosis. Upon rewarming: reactive hyperemia $\rightarrow$ intense red color.
- Blood flow is reduced between the attacks $\rightarrow$ trophic changes may occur.

Pathology
- Normal vascular morphology at early stages. In long-lasting cases: thickening of the intima, hypertrophy of the media.
- In severe progressive cases: complete obstruction from thrombosis, gangrene of the tips.

Clinical manifestations
- Onset is usually mild (mild and short-lasting attacks during winter). Becomes more severe and prolonged over the years. Attacks are provoked by cold, rarely by emotion. Rewarming terminates the attacks.
  - **1st phase**: all digits become pale, which is sharply demarcated at the level of the MCP joints.
  - **2nd phase**: cyanosis, coldness, numbness, occasionally pin.
  - **3rd phase (rewarming)**: intense redness, tingling or throbbing.
- Frequently the feet are also affected, rarely the nose, cheeks, ears, and chin.
- Atypical attacks: asymmetric involvement of the digits, only one or two digits are affected, or only the distal portions are affected.
- Severe progressive cases: trophic changes: loss of hair from the dorsal aspect of the digits, nails grow slowly, become brittle and deformed. The skin is atrophic, tight (sclerodactyly), painful ulceration at the fingertips or around the nail beds that heal slowly with pitted scars.

Diagnosis
- History of vasospastic attacks.
• Provocation tests: immersion of hands in water of 10-15 °C temperature. Whole body
  provocation is more successful.
• A negative result does not exclude Raynaud’s phenomenon.

Differential diagnosis
• **Acrocyanosis** (no pallor, the whole hand or foot is involved, palms are wet, clammy, and
  sweating, trophic changes and ulcerations are rare).
• **Obstruction of major arteries** (no pulses, but arteriographic alterations, no symmetricity).
  Secondary Raynaud’s phenomenon, however, may be superimposed (patent arteries and
  sharply peaked blood flow velocity patterns in the digits on Doppler, normal major arteries
  and diffuse spasm of the digital arteries on arteriography).
• **Raynaud’s disease vs. Raynaud’s phenomenon**: by exclusion of underlying disorders.

Treatment
• Reassurance and protective measures against exposure to cold.
• Since vasoconstriction is induced reflexively by exposure of other parts of the body,
  protection of the whole body is needed: limitation of exposure time, heavy clothing,
  warming of hands and feet by water, hair dryer or special devices.
• Attacks can be terminated by prompt rewarming.
• **Smoking must be stopped!**
• Biofeedback to teach patients to raise skin temperature voluntarily will limit the duration or
  frequency of attacks. In cases induced by vibration, the use of vibrating tools must be ceased
  (elimination is not as effective as in forms induced by cold).

Some drugs useful in the treatment of Raynaud’s phenomenon

1. Calcium antagonists
• Nifedipine 3-4x10-20 mg/d
• Diltiazem 3-4x60 mg/d

2. ACE-inhibitors
• Captopril 3x25-50 mg/d
• Enalapril 10-20 mg/d

3. Alpha-adrenergic blockers
• Phenoxybenzamie
• Tolazoline
• Prazosin

4. Drugs that interfere with sympathetic activity
• Reserpine 0.1-0.5 mg/d PO, intra-arterially 0.5 - 1 mg intra-arterially or in tourniquet-
  controlled IV injection (Bier’s block)
• Guanethidine
• Alpha-methyldopa

5. Vasodilators
• PGE1 6-10 ng/kg/min IV for a few hours up to 3 days.
• PGE2
• PGI2 prostacyclin 6-10 ng/kg/min IV for a few hours up to 3 days
• PGI2-analogue Iloprost 0.5-2 ng/kg IV for several hours
- Nitroglycerin ointment
- Misoprostol

Preganglionic sympathectomy: long term results are disappointing.

**Prognosis**
- Good in *Raynaud’s disease*. No mortality, low morbidity, associated with ulcerations.
- Improvement and disappearance occurs in 50% of cases. Amputation is needed in 1%. 15% will develop a connective tissue disease, particularly scleroderma.
- **Secondary Raynaud’s phenomenon**: prognosis depends on the primary disease; is bad in scleroderma.

**References**
- Current Diagnosis and Therapy (ed. Thierney)
- Harrison’s Principles of Internal Medicine