ATHEROSCLEROSIS

ARTERIOSCLEROSIS

APPROVED

arteriosclerosis- hardening of the arteries. arterio- artery sclerosis-fibrosis

ATHEROSCLEROSIS

athero- implies that there is a fatty component along with the thickening and fibrotic component

MONCKEBERG’S MEDIAL CALCIFIC SCLEROSIS

where someone may calcify the media of their arteries. usually not pathologic because it doesn’t impinge on the lumen.

ARTERIOLOSCLEROSIS

in smaller vessels.
Objectives

• Discuss the etiology of atherosclerosis and plaque enlargement

• Enumerate the clinical presentations of atherosclerosis in the following organ systems:
  - Heart
  - Central Nervous System
  - Peripheral vasculature/Extremities
  - Kidneys
  - Intestines

Define and discuss the concepts of “Critical Stenosis” and “Plaque Rupture and Thrombosis” in relation to the above.

• Compare and contrast thoracic and abdominal aortic aneurysms including dissections on the basis of:
  - Etiologic factors
  - Incidence
  - Complications
Comparison of heart disease vs. other causes of death.

CVD and other major causes of death: both sexes. (United States: 2006). Source: NCHS and NHLBI.
Cardiovascular Disease Deaths vs. Cancer Deaths by Age
United States: 2006

Source: NCHS

under 45 there are still thousands of deaths. both cancer and cvd increase with age.
A CVD (I00-I99; Q20-Q28) D Chronic Lower Respiratory Diseases
B Cancer E Diabetes Mellitus
C Accidents F Alzheimer’s Disease

CVD and other major causes of death for all males and females (United States: 2006). Source: NCHS and NHLBI.
Percentage Breakdown of Deaths From Cardiovascular Diseases
United States: 2003*

Source: CDC/NCHS and NHLBI. *Preliminary

CVD is mostly coronary heart disease.
Estimated Direct and Indirect Costs of Major Cardiovascular Diseases and Stroke
United States: 2006

- Coronary Heart Disease: 142.5
- Stroke: 57.9
- Hypertensive Disease: 63.5
- Heart Failure: 29.6

Huge costs related to CAD. If you add what we put into prevention...

Source: Heart Disease and Stroke Statistics – 2006 Update.
Atherosclerosis

imaging let's us see plaques.

anywhere you have an artery you are prone to have atherosclerosis. It can also happen in veins. can see plaque here.
Atherosclerotic Lesions

• **Progression**
  
  – **Fatty Streaks**
  
  ▶ Lipid filled myointimal cells
  
  ▶ Starts in second decade – Intimal Process

  – **Fibrous Plaques**
  
  ▶ Subendothelial fibrous cap over extracellular lipid pool

  – **Complicated Plaques**
  
  ▶ Fibrous plaque with erosion, intramural hemorrhage, thrombus, calcification

  atho- fatty, sclerosis- fibrosis.

  atherosclerosis starts as somewhat benign lesion called fatty streak. This is when you first get injury in your blood vessels. Usually in your second decade of life, end up getting into a vicious cycle in which you collect the plaque and response to injury adds fibrosis. Once you get to fibrous stage you have it for life.

  if you bleed into the plaque it will grow more rapidly and will calcify. Complicated just means that something happened and now it grows more quickly not necessarily a clinical complication.
Relatively Normal Muscular Artery

- rabbit artery.
- adventitia
- tunica media (contains muscle and elastin)
- intima thicker than humans (usually 1-3 cell layers thick)

gray is because it was perfused with gelatin solution
Artery with Fatty Streak

rabbit on human diet.
Fatty Streak

macrophages and modified smooth muscle cells. 1st stage.
Fibrous Plaque

This stain turns fibrous tissue blue. As plaques grow they compress on the media and can focally extend into it. As plaque grows it impinges on the media.

Vessel initially tries to compensate for loss of lumen by enlarging. In severe disease this is not the case.
complicated plaque-
multiple events where the plaque has probably ruptured. get growth in sudden spurts, not gradual.
another very ugly complicated plaque. the artery is basically occluded.

re-canalized thrombus. can see blood vessels.
Cholesterol Clefts in Atherosclerotic Plaque Atheromatous Core
Focal disruption of internal elastic lamina
Prevalence of Cardiovascular Diseases in Americans Age 20 and Older by Age and Sex  
NHANES 2003-2006

Source: CDC/NCHS and NHLBI. These data include coronary heart disease, heart failure, stroke and hypertension.
start in teens, progresses, see clinical phase in 30s - 40s.
Common Sites of Atherosclerotic Plaques

- Larger vessels, branch pt.s
- Abdominal aorta and iliacs
- Proximal Coronaries
- Thoracic Aorta, Distal LE’s
- Internal Carotid and Cerebral

Uncommon Sites:
- Subclavian arteries
- Axillary arteries
- Renal arteries
- Superior Mesenteric and Celiac

(Not incl. aortic origin)
Risks and Etiology

- **Major – Can Not Be Changed:**
  - Genetic
  - Male Gender
  - Age older than 55.

- **Major – Can Be Changed/Managed**
  - Tobacco use
  - Hypertension
  - Lipidemias
  - Diabetes Mellitus

- **Contributing Factors:**
  - Obesity, Sedentary Life, Stress

**Strongest risk factor. Tons of genes are involved in atherosclerosis. Ask for family history.**

**Obesity contributes but is not a MAJOR risk factor.**
Atherosclerosis: Genetics

very complicated b/c multiple genes are involved.
Tobacco Use: Smoking

Red bars are myocardial infarcts
White bars are strokes

more you smoke the higher your risk.
**Blood Pressure**

A man whose blood pressure at systole (the moment the heart contracts) is over 150 has more than *two* times the risk of heart attack and nearly *four* time the risk of stroke of a man with systolic blood pressure under 120.

higher blood pressure, higher risk.
Cholesterol and Atherosclerosis

In adults, total cholesterol $> 240 \text{ mg/dL}$ is high risk

LDL cholesterol $> 130 \text{ mg/dL}$ is associated with increased risk of coronary artery disease

HDL cholesterol $< 40 \text{ mg/dL}$ is associated with increased risk of coronary artery disease
Inflammation

• > 50% of deaths from CAD have normal cholesterol levels
• Is there an overall “hyper-inflammatory” state?
• C-Reactive Protein (CRP) – Acute phase reactant - indicates ongoing inflammation
  – hs-CRP - Easily measured by blood test, low cost
  – Correlates with risk of adverse coronary events
    ▶ Short and long term risk
  – Medications can reduce levels and risk
    ▶ Statins (HMG-CoA reductase inh) – dual role also reduces CRP levels.

• Other Markers being developed
  – PlacentalGF – less influenced by ongoing inflammation

more specific markers that are specific to arteries and vascular inflammation being developed.
Inflammation

The paper looked at stratified risk in patients with both high cholesterol and high CRP. If patients controlled their levels of cholesterol and had elevated CRP they were still at risk. Elevated CRP is a stronger predictor for CAD than lipids.

- Rifai and Ridker, Clinical Chemistry. 2003;49:666-669
Pathogenesis of Atherosclerosis

Intimal Injury and Repair
(The Response to Injury Hypothesis)

Mural Thrombosis and Organization
(The Thrombogenic or Encrustation Hypothesis)

ppl thought it was a thrombus.

Monoclonal Proliferation
(The Monoclonal Hypothesis)

mini tumor- this idea is gone.
Injury and Repair

• Injury Mechanisms:
  – Hyperlipidemia
  – Hypertension/Shear Stress
  – Tobacco Abuse
  – Inflammatory State
  – Microorganisms/ Viruses: CMV, Adenovirus

• Effects – Vicious Cycle
  – Lipid Accumulation/ Free Radicals
  – Cytokines/Chemotaxis
  – Necrosis/Apoptosis/Thrombosis
  – Fibrosis

• Players:
  – Smooth Muscle Cells (medial and circulating),
    Macrophages, Endothelial Cells, White Cells and Platelets

- smooth muscle cells are VERY important because they are pluripotent
  here- can become secretory cells, cells that take up the fatty component,
  and can also be in our circulation and settle down in areas of injury and
  join the "riot". these and all the above-mentioned are involved.
as plaque forms we get smooth muscle cells, platelet aggregation, more cell recruitment->->-> accumulation on blood vessels
chemokines are involved. Just remember it's a COMPLICATED process with a lot of players that interact with each other.

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Macrophage activation

PDGF

IL-1
TNFα
TGFβ

Endothelial Cell

PDGF-AA

Smooth Muscle Cell

PDGF
Inflammation: Toll-Like Receptors

- **Immune functions**
  - React to pathogens
  - Endogenous ligand stimulation

- **Responses**
  - Affects lipid transport and macrophage uptake and release (cholesterol)
  - Interact with oxidized lipoproteins
  - Cytokine upregulation

- **Cycle**
  - Injury can further activate TLR’s

- **Remodeling**
  - May also stimulate arterial remodeling to accommodate progressing atherosclerosis

TLRs are present in your intima. React to pathogens and thus can trigger advanced atherosclerosis.

ongoing topic: it's a CYCLE.

initially they might try to help the artery.
Thrombotic Theory

Mural Thrombus

Occlusive Thrombus

doesn’t speak to how plaque begins to form but once plaque forms a thrombus can form on it and as your body organizes and turns thrombus into fibrous tissue it occludes the blood vessel.
Atherosclerotic plaque with organized mural thrombus

thrombus doubles size of plaque
Concentric atherosclerotic plaque, central organized thrombus, small central lumen
Clinical Atherosclerosis: Luminal Narrowing

Critical Stenosis: Supply < Demand

Symptoms related to flow restriction

• **Episodic Ischemia**
  - Heart: Angina Pectoris
  - Brain: Transient Ischemic Attacks (± emboli)
  - Extremities: Intermittent Claudication
  - Kidneys: Renovascular Hypertension
  - Intestines: Mesenteric Ischemia

2 "ends of the spectrum" - 1. critical stenosis.

when you require higher blood flow (exercise) you feel symptoms.

further discussed in road show.

Not as common.

patients cramp when they walk.
Clinical Atherosclerosis: Plaque Rupture and Thrombosis

Acute Arterial Occlusion - leads to sudden significant or total obstruction of lumen

Most Common Cause: Thrombus superimposed over plaque rupture/erosion site
Clinical Atherosclerosis: Plaque Rupture and Thrombosis

Vulnerable Plaque

Vulnerability to Plaque Rupture
- Large Atheromatous Core
- Thin Fibrous Cap/Increased Cap Tension
- Inflammation or Foam Cells in Fibrous Cap
- Matrix Metalloproteases
- Cap Fatigue

plaques more likely to rupture.
cap- cells degrading can loosen the cap, so do inflammation and foam cells.
Vulnerable Plaque

- Large lipid-core
- Thin fibrous cap
- Cap and adventitial inflammation
- Increased neovascularity
- Positive remodeling

**Inflammation**

- Other proteases
- MMP/TIMP imbalance

**Increased matrix degradation**

**Inflammation**

- Cytotoxic agents (oxidized LDL and others?)
  - Increased smooth muscle cell death
  - Reduced matrix synthesis
  - Reduced smooth muscle cell function

**Fibrous Cap**

- Matrix Depletion and Cap Thinning

**Spontaneous**

- Systemic Thrombotic/Fibrinolytic Balance
  - Activated Circulating Leucocytes
  - Circulating Tissue Factor

**Triggers**

- Inflammatory cells
  - Plaque Tissue Factor
  - Local stenosis severity and shear rate

**Fibrous Cap Rupture**

**Thrombosis**

**Clinical Events**
Acute Manifestations of Coronary Artery Disease

Angina Pectoris
Prevalence - 13,000,000

Myocardial Infarction
Deaths/Year - 600,000

Sudden Cardiac Death

50% of Deaths are Sudden Cardiac Death (SCD)
50-60% of SCD are First Clinical Manifestation of CAD
10% of Patients with CAD First Present as SCD

50% of Deaths are Sudden. Difficult because we are not able to treat for their CAD.

from 600,000 - 800,000 in the US
Plaque Rupture

- Rupture of fatty core
- Erosion
- Calcification erodes to the surface -> vulnerable plaque
Atherosclerotic Plaque with Acute Thrombus

(Plaque Rupture, with lipid debris on left, inducing thrombosis)
Ruptured atherosclerotic plaque (right), superimposed thrombus (left)
Severe atherosclerotic narrowing, superimposed thrombus more distally

likelihood of developing an acute event does not necessarily correlated with obstruction but rather the QUALITY of the plaque.
Anteroseptal Myocardial Infarct due to LAD Thrombus
Clinical Effects

- Plaque Rupture vs. Obstructive Stenosis
- Severity of stenosis does not necessarily equal vulnerability or acute event risk at that focus
Stress Test Raises Questions About Bank Capital

The Obama administration's announcement that it will begin a series of stress tests on Wednesday on the biggest financial institutions …

Obama Seeks to ‘Clean Out the System’ with Bank Stress Test

Stress tests: demonstrate symptoms of flow restriction when requirements increased

Designed to demonstrate ischemia due to Critical Stenosis through exercise or pharmacology

Predicts severity of stenosis, not plaque vulnerability

stress test looks at critical stenosis not quality- patient can do great on stress test and drop dead.
Interventional Frontier

- **Reduced** Lipid content
- **Reduced** Inflammation
- **Reduced** Neovascularity
- **Reduced** Matrix Metalloproteinase Activity
- **Reduced** tissue Factor Activity
- Smooth Muscle Cell Activity/death
- Increased collagen content/Strength

- **Identification Techniques:** MR, IVUS, OCT
**Figure 3** *In vivo* optical coherence tomography images of different coronary plaque types compared with intravascular ultrasonography of the corresponding sites.

OCT

Fibrous Plaque

Atheromatous Plaque

Although this plaque is only 40% lesion, it will probably be followed up by intervention.
Atherosclerosis:

Other Complications
Thrombosis in entire aorta. Kidneys are "unhappy looking". If disease goes on long enough you can get collateral flow to lower extremities so people walk around with this.
Aneurysms

In the vascular system, an aneurysm is an area of weakness in the wall of a blood vessel that typically results in bulging due to arterial blood pressure.
Etiology: **Medial Injury or Weakness**

**Congenital / Genetic**
- Ex: Polycystic Kidney Dz

**Atherosclerosis**

**Infectious**

**Autoimmune**

- Marfan's disease, too.
- when it goes through the media.
- can directly destroy the wall and lead to aneurysm.
- connective tissue disorders or lupus, arthritis.
Atherosclerotic aortic aneurysm (renal arteries on right, bifurcation on left), which has **ruptured** (see probe).
Syphilitic Aortitis
(Obliterative Endarteritis)

- Aortic Aneurysm
- Aortic Valve Insufficiency
- Coronary Stenosis

* Late Complications*

**Note:** Syphilis attacks small vessels that supply bigger ones (vaso vasorum). End up with a fibrous scar that over time stretches.
Aortic Dissection
“Dissecting Aneurysm”

dissection- get a tear in a wall and it propagates to the media and adventitia.

- Cystic Medial Necrosis (Degeneration)
  - Loss of elastin fibers and smooth muscle
  - Replacement with Ground Substance
- Isolated lesions
- Marfan’s Syndrome
  - Fibrillin-1 gene on chr 15

Hypertensive injury
- Essential, “pharmacologic”

when we are out jogging we probably create micro-dissections every day but our bodies can handle it.

these patients often have a connective tissue disorder. Cystic tissue necrosis. replace elastin fibers with ground substance.

cocaine. high systolic BP leads to tears.
tear lets blood in and dissects through.
blood in false lumen occludes real lumen.

can dissect up into branches and cut them off.
saw this in road show. abdominal aortic aneurysm was originally repaired and then developed a dissection that over time expanded and eventually got stopped by aortic repair and expanded out to pick off the celiac, and vertebral arteries. ultimately died of dead bowel.
Any Questions?