Pathophysiology of Cardiovascular Diseases

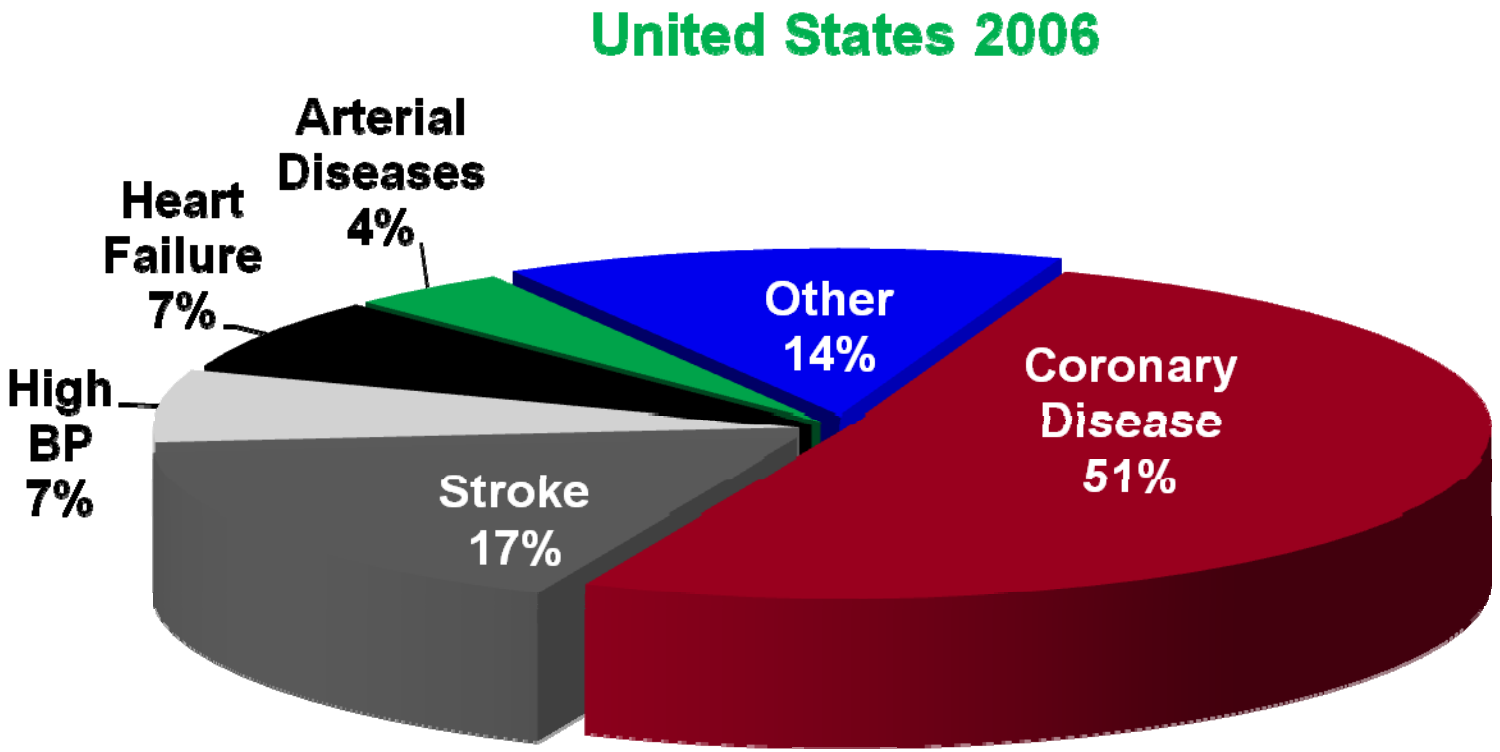
Cardiovascular Disease - all diseases of the heart and blood vessels.

- **Produces over 831,000 fatalities / year**
  - **2,500 / day**
  - **1 every 33 seconds**
- Responsible for approximately **51% of deaths from all causes**

Cardiovascular Diseases

- **CAD: coronary heart disease**
  - Ischemic heart disease – atherosclerotic heart disease
- **Non-ischemic heart disease**
  - Valve diseases, congenital & rheumatic diseases…….
  - Cardiomyopathy and congestive heart failure
- **Hypertension**
- **Stroke**
- **Peripheral vascular disease**
- **Deep vein thrombosis**

Heart Disease Statistics for 2006



Source: National Center for Heath Statistics

Pathophysiology of Cardiovascular Diseases

Coronary artery disease - narrowing and hardening of coronary arteries

- responsible for 51% of Cardiovascular disease deaths **(> 17.5 million / yr in US)**

Myocardial Infarction (MI) - death and subsequent necrosis (scarring) of myocardium

831,000 / year in US - **250,000 die before they can make it the hospital (31%)**

- Most MI's caused by: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/acute-myocardial-infarction/
  - Lodging of a clot (thrombus) in a coronary artery which has been narrowed by atherosclerosis (most common cause: 90% of the time)
    - Thrombus formation usually caused by plaque rupture or erosion
  - Coronary artery spasm (10% of the time)

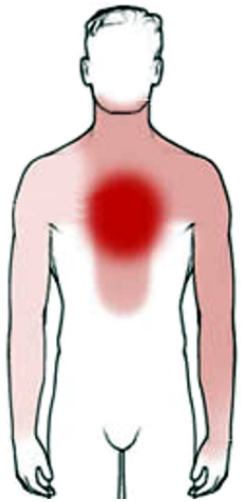
Initial Symptoms of Coronary Artery Disease:

- **Fatal MI (50% - 60% of the time)**
  - Actual cause of death in MI:
    - Arrhythmias (most often)
    - Pulmonary edema
  - note: the average MI victim waits over 2 hours before seeking help
- **Survivable MI** (25% of time) **Once hospitalized, survival rate is 90% - 95%**
- **Angina Pectoris** (15% of time)
- **Other** (10% of the time)

Pathophysiology of Cardiovascular Diseases

Symptoms of an MI: 80% experience chest pain, 15%-30% do not

- Pain in the center of chest lasting for more than a few minutes unrelieved by rest
  - Pain described as "fullness" "pressure" "squeezing“ “choking” “indigestion”
  - Pain is usually severe and radiates to shoulders, neck, and 1 or more arms
  - Can occur in back, neck, jaw, or stomach
- Shortness of breath
- A strong feeling of anxiety
- Pallor (gray color)
- Weak fast pulse
- Lightheadedness & fainting
- Chest palpitations
- Nausea & vomiting
- A mild MI may not have prominent symptoms (tiredness or fatigue)
  - This is called a Silent Infarction (occurs more often in diabetics)

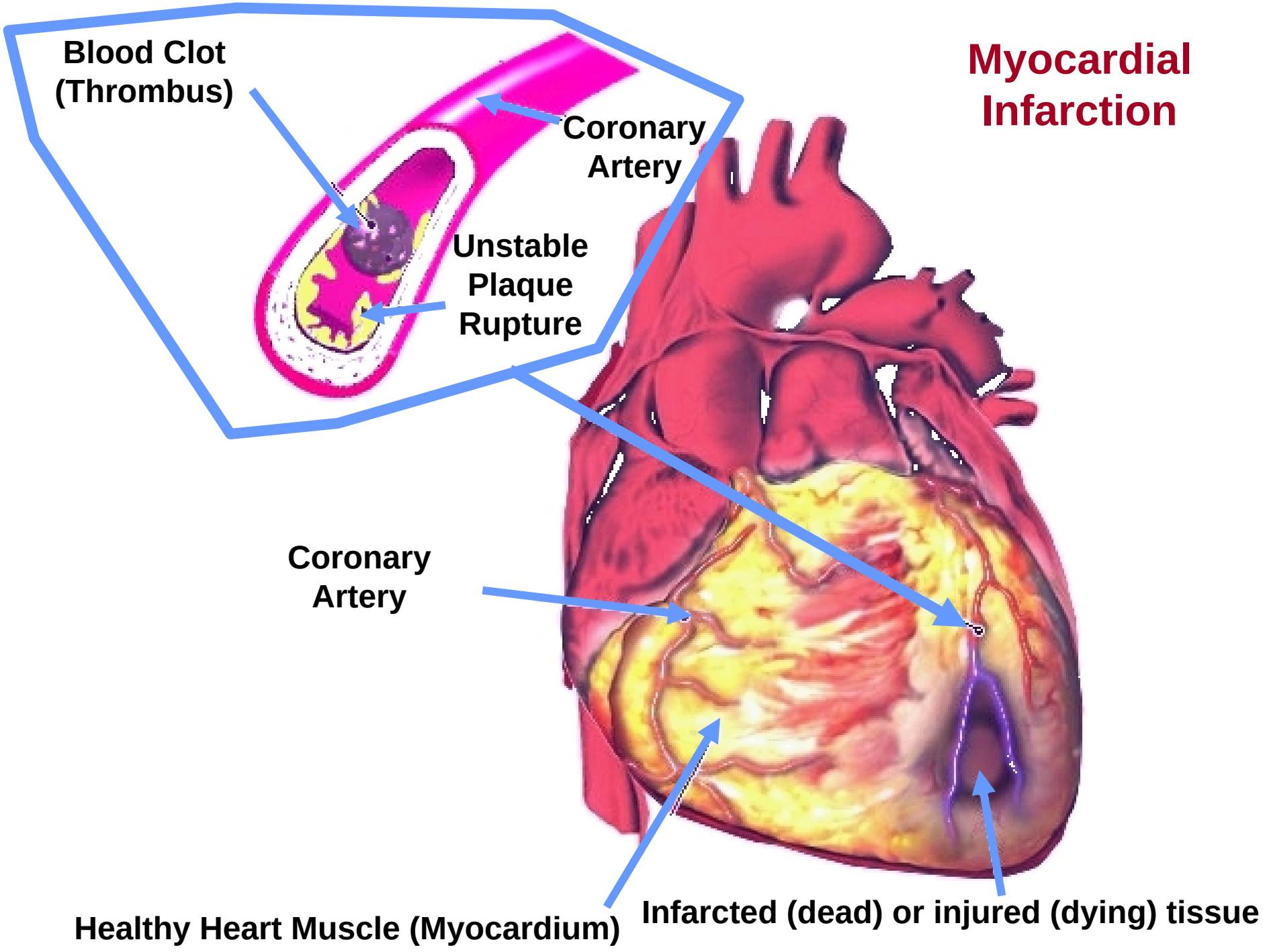


Women’s symptoms may be similar but can also differ to a large extent:

- Unusual fatigue & weakness
- Sleep disturbances

Notes:
- Only about 30% of women have chest pain
- About 75% report symptoms 1 month prior to their MI
- Prognosis worse for women because disease is discovered when more advanced
  - “Bikini Medicine” – women stay to long with OBGYN’s - treated differently than men
  - 40% of women die within 1 year of MI compared to 24% of men

Myocardial Infarction



Pathophysiology of Cardiovascular Diseases

Atherosclerosis - an abbreviated summary of the recurrent injury hypothesis

Injury to coronary artery endothelium (artery lining) caused by:

- Flow turbulence (shear stress), CO toxicity (smoking), Inflammation, Hypertension, Hyperinsulinemia, LDL-C accumulation in artery wall, Oxidative stress (↑ free radicals) → oxidized LDL-C accumulation

Endothelial dysfunction → collagen & smooth muscle exposed to blood

- Platelets adhere to injury & release growth factors + inflammatory mediators
- Macrophages engulf oxidized LDL-C → **Foam cells**, cytokine release
  - This is an inflammatory response

Accumulation & Proliferation of Smooth Muscle and Fibrous Tissue

- ↑ Proliferation of smooth muscle + ↑ amount of fibrous connective tissue

Lipid Accumulation & Mature Plaque Formation

- Macrophages continue to injest lipids → ↑ foam cell # → ↑ plaque size
  - Dead macrophages (foam cells) compose "necrotic core" of the plaque
- Cholesterol crystals from foam cells + Ca^{++} salts → hardening of artery
- Plaque (atheroma) becomes covered with smooth muscle cap, then calcifies
  - **Foam cells secrete chemicals that dissolve plaque & rupture cap**
    - **Matrix metalloproteinase is a common causative enzyme**
    - Blood comes in contact with collagen → **clot → MI**
  - Unstable plaque: plaque with thin calcification cover → ↑ chance of MI

Pathophysiology of Cardiovascular Diseases

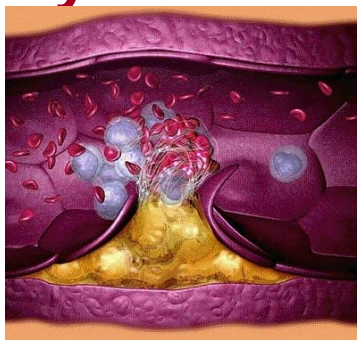
http://www.nytimes.com/packages/khtml/2007/04/06/health/20070408_HEART_FEATURE.html

Notes on atherosclerosis:

- Plaque formation is a ongoing dynamic process that begins in infancy
  - 45% of infants up to 8 months old and 65% of teenagers
- A plaque is hemodynamically significant (may cause symptoms) if it covers 60% - 70% of the diameter of the coronary artery lumen
- Reversal of the atherosclerotic process has be found in patients whose Total-C level is < 150 mg/dl & HDL-C is > high (> 55 mg/dl).

Determing Severity (& Prognosis) of Coronary Artery Disease

Factors Determining Severity:

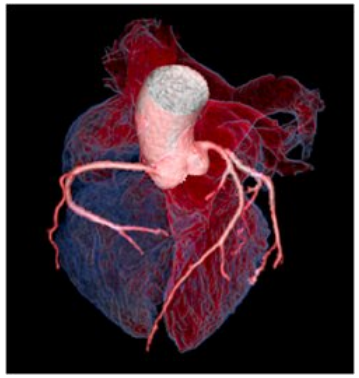


- **The size of the plaque (controversial)**

Patient type	Adjusted hazard ratio	p
Normal vessel	1	Reference
Nonobstructive CAD (<50%)	1.60	0.0023
Obstructive CAD (>50%)	2.60	<0.0001

It should be noted that, in contrast, some research shows smaller plaques are just as dangerous and that most MI's are associated with plaques that have obstructions < 30% (Falk et al. 1995 Circulation 92(3)).

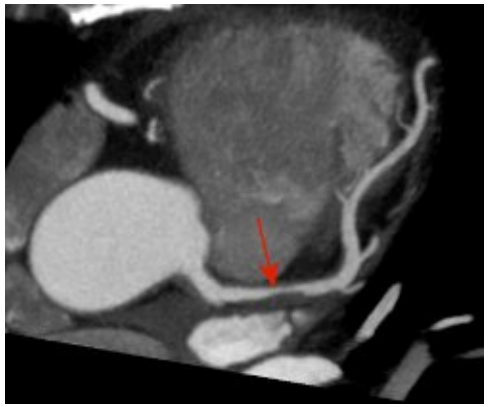
- **The number of plaques in the coronary tree**



Risk-adjusted hazards ratio for all-cause mortality per vessel

Type	Adjusted hazard ratio	p
Normal	1	Reference
Nonobstructive CAD	1.62	0.0018
One-vessel obstructive CAD	2.00	<0.0001
Two-vessel obstructive CAD	2.92	<0.0001
Three-vessel or left-main obstructive CAD	3.70	<0.0001

- **The location of the plaque**



  - A highly stenosed (narrowed) plaque in the LAD artery is called a "widowmaker"

- **Plaque calcification status**

  - Plaque regression is less likely to occur if plaque is calcified but highly calcified plaques are less likely to rupture ➞ MI.

A Summary of How Inflammation May be Involved in an MI

- Excess LDL-cholesterol sticks into the endothelial lining of the vessel
- Macrophages attack and ingest the LDL-cholesterol → foam cells
- Macrophages release cytokines (chemotaxis occurs) → ↑ inflammation
- ↑ inflammatory activity makes the plaque unstable → ↑ MI and stroke risk
- C-reactive protein (CRP), independent of other risk markers, has clearly been shown by **some** researchers to add prognostic value to scenarios involving the presence of atherosclerosis, MI, & stroke.

Risk Factors for CAD According to the ACSM & AHA

Age

- Men > 45 Women > 55 (or premature menopause & no E2 replacement) **??**
  - AHA: men & women > 40 are at some risk unless they have a negative GXT

Family History

- MI - sudden death < 55 for 1st-deg. male relative, < 65 for 1st deg. female relative

Smoking current or quit within past 6 months

Hypertension

- Blood Pressure ≥ 140 / 90 or currently medicated **new guidelines: ≥ 120 / 80??**

Hypercholesterolemia (high cholesterol)

- TC > 200 mg / dL or LDL-C > 130 mg / dL (preferred) or currently medicated
- HDL- C < 35 mg / dL (HDL-C level > 60 mg / dL is a "negative" risk factor)

Diabetes

- fasting glucose > 110 mg / dL confirmed on 2 separate occasions

Physical Inactivity

- not meeting surgeon general guidelines (30 min. or more most days of the week)

Obesity

- BMI ≥ 30 kg / m^2 or waist circumference > 100 cm (39.4 inches)

Which Risk Factors for CAD Cause More Risk ??

Diabetes 52: 1210-1214, 2003

Risk Factor	Odds Ratio (normal risk = 1)
• High blood sugar	1.0
• High triglycerides	1.1
• Waist circumference	1.1
• Diabetes	1.6
• Low HDL-Cholesterol	1.7
• Hypertension	1.9

Odds Ratios Rounded to Nearest 10th

Which Risk Factors for CAD Cause More Risk ??

European Heart Journal 23: 620-626, 2002

Risk Factor	Odds Ratio (normal risk = 1)	
• High triglycerides	1.1	(1.3 in women)
• Obesity / High Cholesterol	1.2	
• Physical Inactivity	1.3	(1.4 in women)
• Smoking	1.4	(2.0 in women)
• Hypertension	1.5	
• Diabetes	1.7	(2.7 in women)

Odds Ratios Rounded to Nearest 10th

Other Recently Identified Potential Risk Factors for CAD

Inflammation Markers

- **C-reactive Protein levels (test is controversial)**
  - Protein produced by liver in cases of inflammation anywhere in the body
  - **Some** studies show high correlation with ongoing atherosclerosis
    - Libby et al. 2002
- **Lipoprotein Phospholipase A2 (Lp- PLA2)**
  - An enzyme that attaches to LDL-C and may contribute to CA inflammation
  - Studies have found that Lp-PLA2 to be independently linked to CAD
    - Ballantyne, et al., 2003; Packard, et al., 2000.

- **Gene Abnormalities**
  - DNA sequence on chromosome 9 may account for 20% of MI risk

The Metabolic Syndrome – Syndrome X
(NCEP Adult Treatment Panel III definition - 2001)

An atherogenic state in which a person has at least 3 of the following:

- **Disproportionate amounts of abdominal fat**
  - waist girth > 40 in. for men, 35 in. for women
- **Hypertension** (SBP > 130, DBP > 85)
- **Insulin resistance** (blood sugar > 110 mg/dL)
- **Prothrombic state** (↑ levels of coagulation factors)
- **Proinflammatory state**
  - ↑ levels of C-reactive protein (produced by the liver in inflammatory states)
  - ↑ levels of cytokines (a macrophage activator and inflammatory mediator)
- **Dyslipidemia**
  - Triglycerides > 150 mg/dL, HDL-C < 40 mg/dL in men - < 50 mg/dL in women

- **Affects 47 million American adults (1 in 5) drastically ↑ chance of MI, stroke, and diabetes**

- **<u>Controversial</u>……many argue that grouping risk factors together has no intrinsic value or implications for treatment**

The Metabolic Syndrome – Syndrome X (World Health Organization - 2001)

An atherogenic state in which a person has the following:

- **Fasting glucose > 110 mg/dL**
  or hyperinsulinemia (insulin levels in upper quartile of non-diabetics)
  or a 2 hour post-prandial glucose > 240 mg/dL.
- **Plus any at 2 of the following 3 disorders:**
  - **Obesity**
    - waist girth > 37 inches
    - waist / hip ratio **>** .9 in men, .85 in women
    - body mass index $\geq$ 30 kg/m^2
  - **Hypertension** (SBP $\geq$ 140, DBP $\geq$ 90) or currently taking BP medication
  - **Dyslipidemia**
    - triglyc. $\geq$ 150 mg/dL, HDL-C **<** 35 mg/dL (men) **<** 39 mg/dL (women)

Signs & Symptoms Suggestive of Cardiopulmonary Disease

- **Pain or discomfort in the chest, neck, jaw, or arms**

  "Constricting", "Squeezing", "Burning", "Heaviness" or "Heavy Feeling"

- **Shortness of breath (dyspnea) at rest or with mild exertion**

  "Abnormally uncomfortable awareness of breathing"

- **Orthopnea or Paroxsysmal Nocturnal Dyspnea (PND)**

  Orthopnea – dyspnea at rest in the recumbent position

  PND – dyspnea occurring 2 – 5 hours after onset of sleep

- **Dizziness or syncope**

  Brain is under-perfused, perhaps due to cardiac dysfunction or arrhythmia

- **Ankle edema – most evident at night**

  Bilateral edema is a characteristic sign of heart failure or venous insufficiency

  (inadequate venous draining from a body part – usually in lower body)

  Unilateral edema: usually from DVT (deep vein thrombosis) or lymphatic blockage

  Generalized massive edema (anasarca) - from kidney disease, CHF, liver cirrhosis

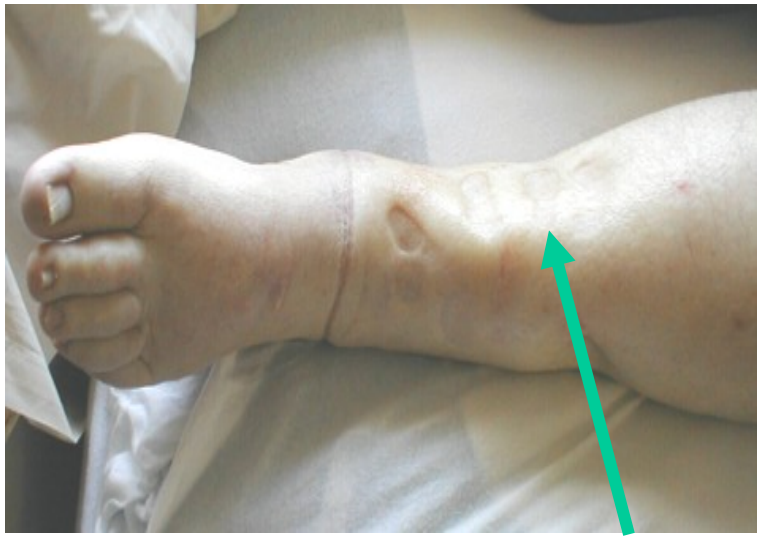
- **Chest palpitations from an accelerated heart beat**

  Usually from arrhythmia causing uncomfortable frightening awareness of heart beat

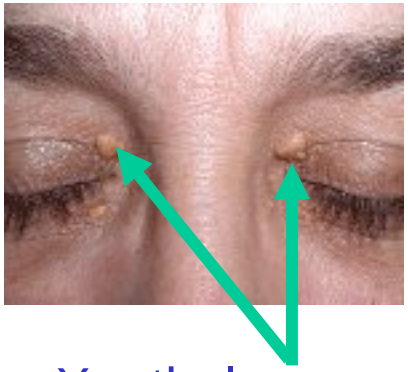
- **Known heart murmur - indicative of valvular or other heart disease**

- **Claudication – activity induced ischemic pain in the leg**

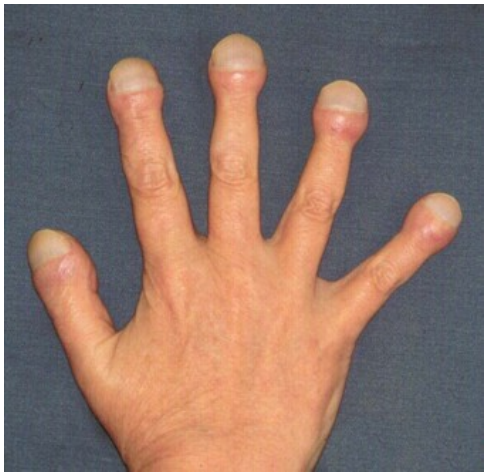
Major Physical Signs Suggestive of Cardiopulmonary Disease



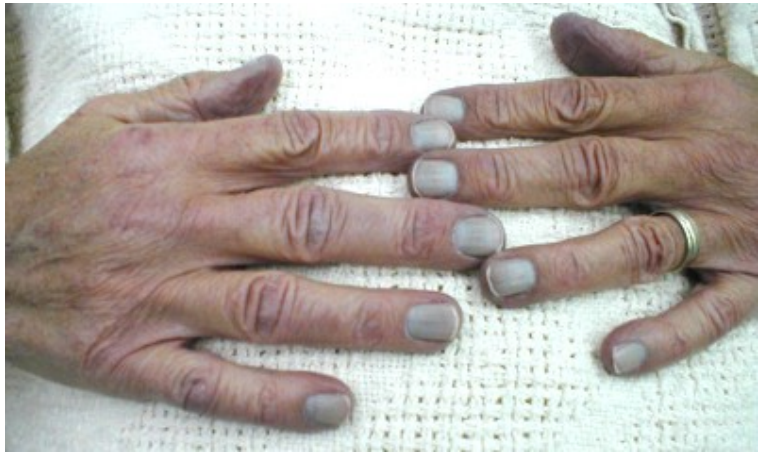
Pitting Edema (note handprint)

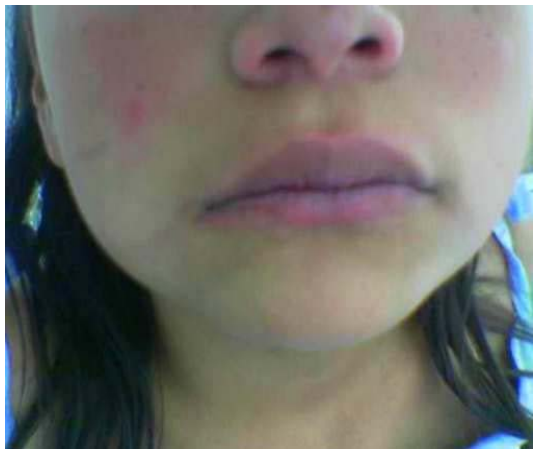


Xanthelasma

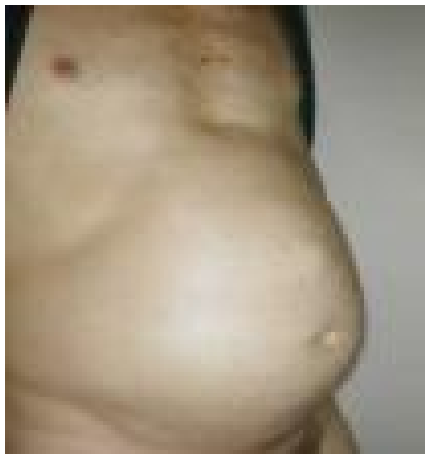


Clubbing of the fingers



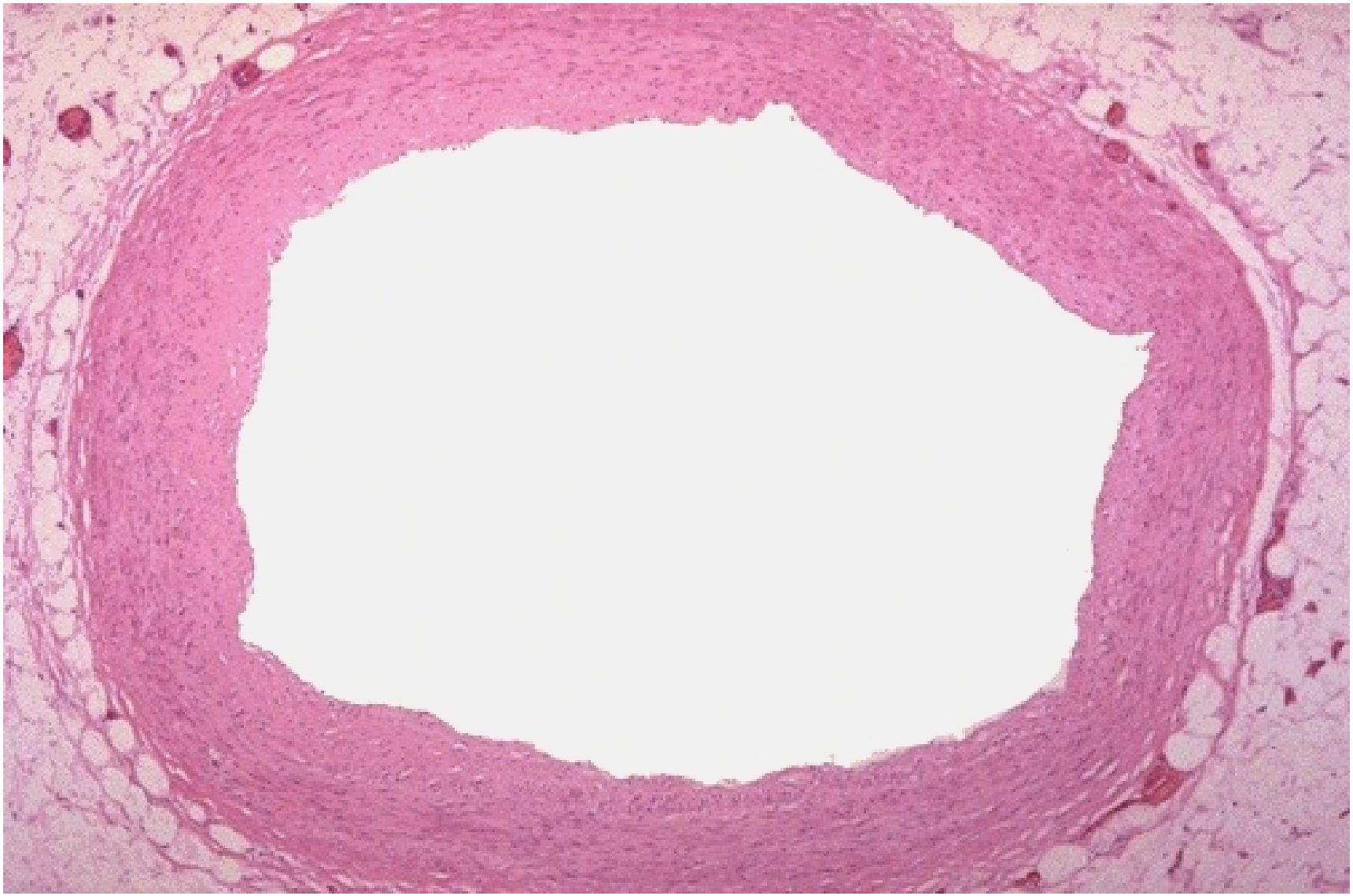


Cyanosis
(blue fingernails &lips)

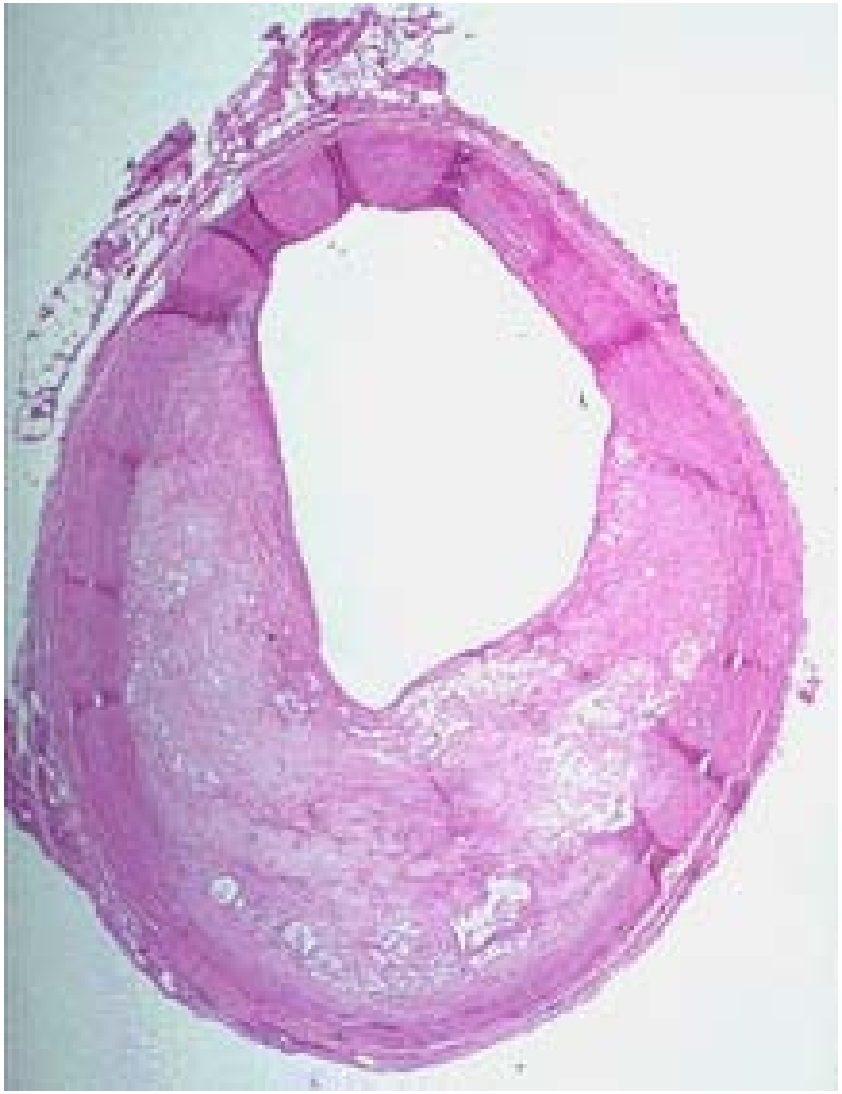


Ascites
(fluid in the peritoneum)

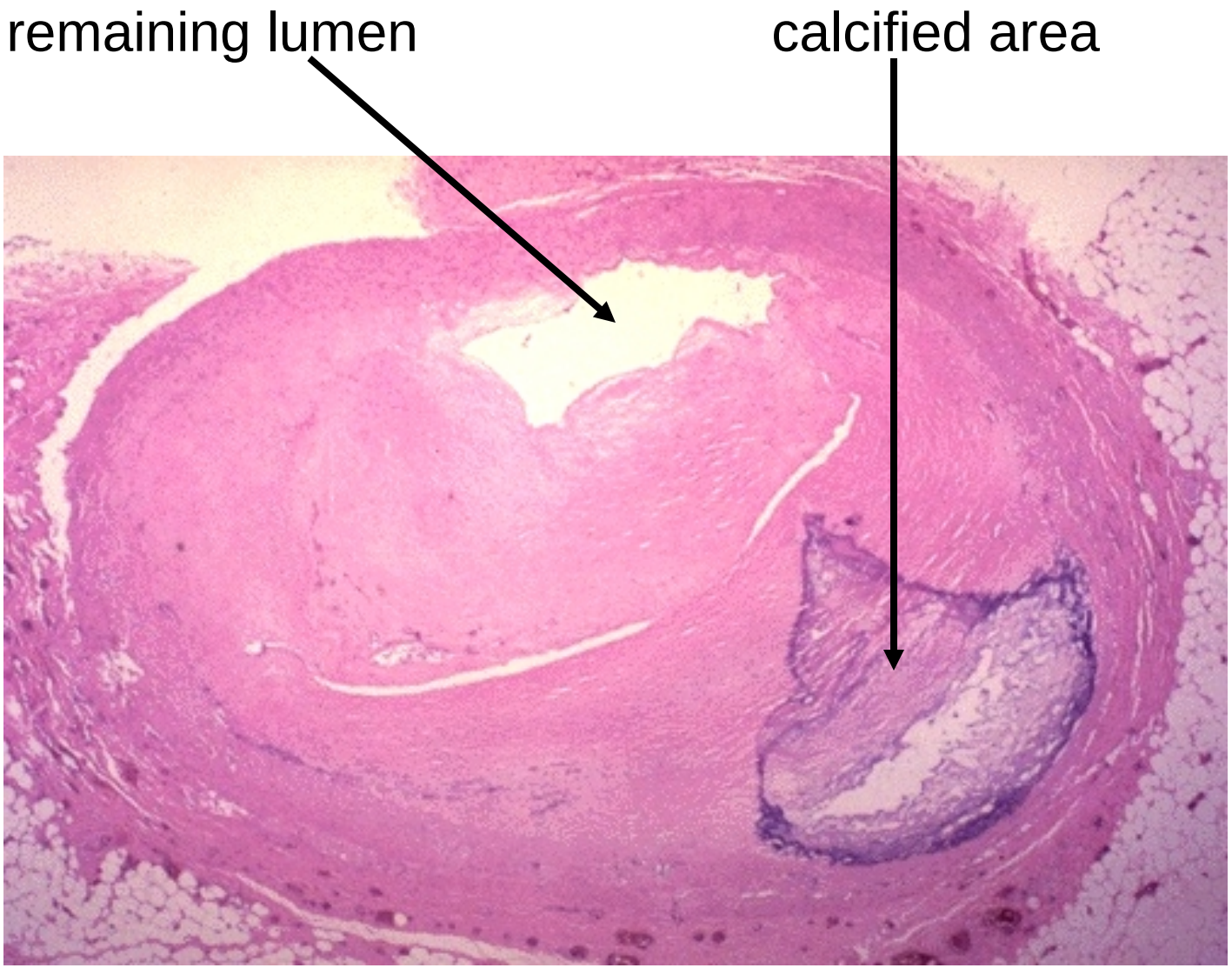
Normal Coronary Artery Cross Section



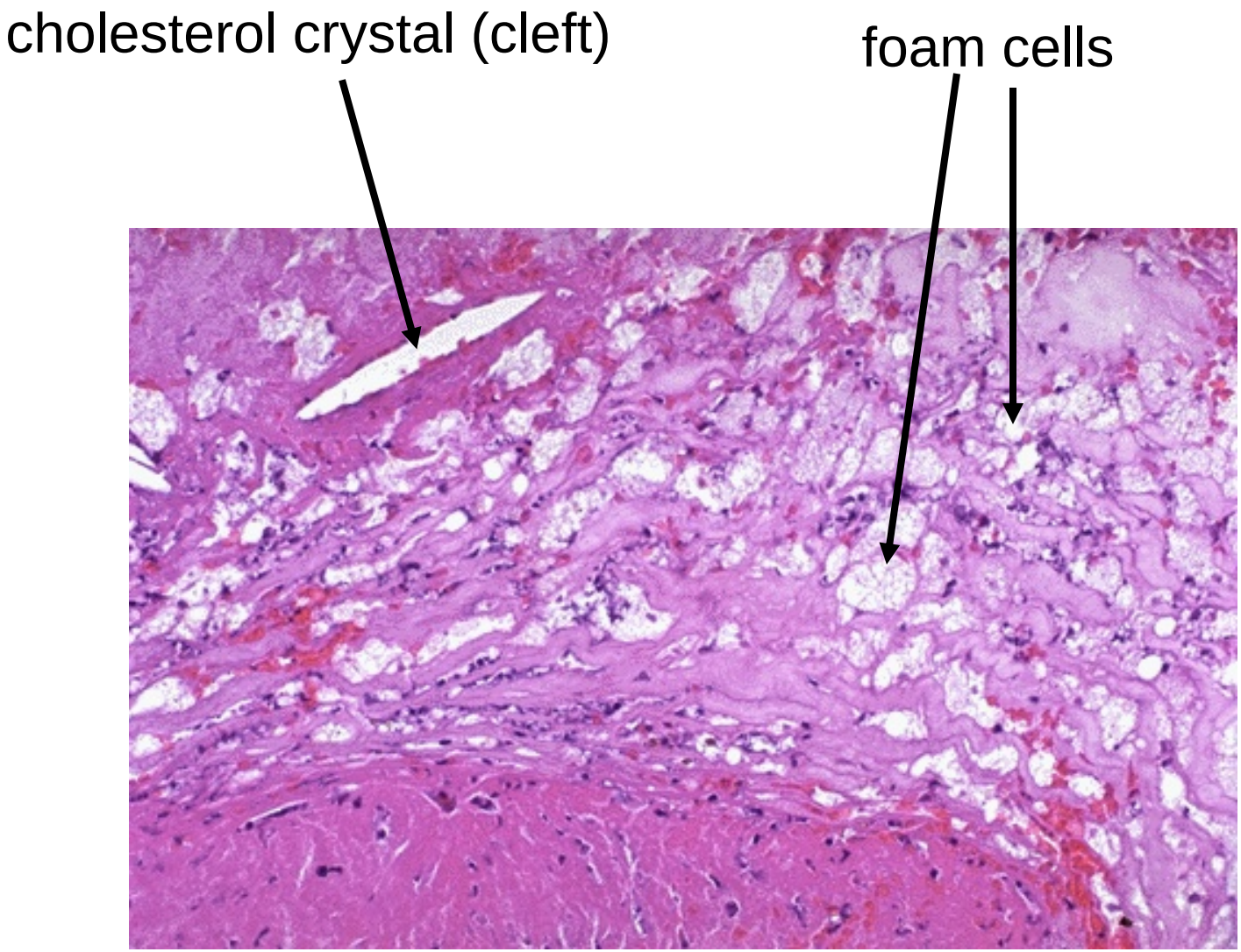
60% Narrowing of Coronary Artery



90% Blockage of Coronary Artery



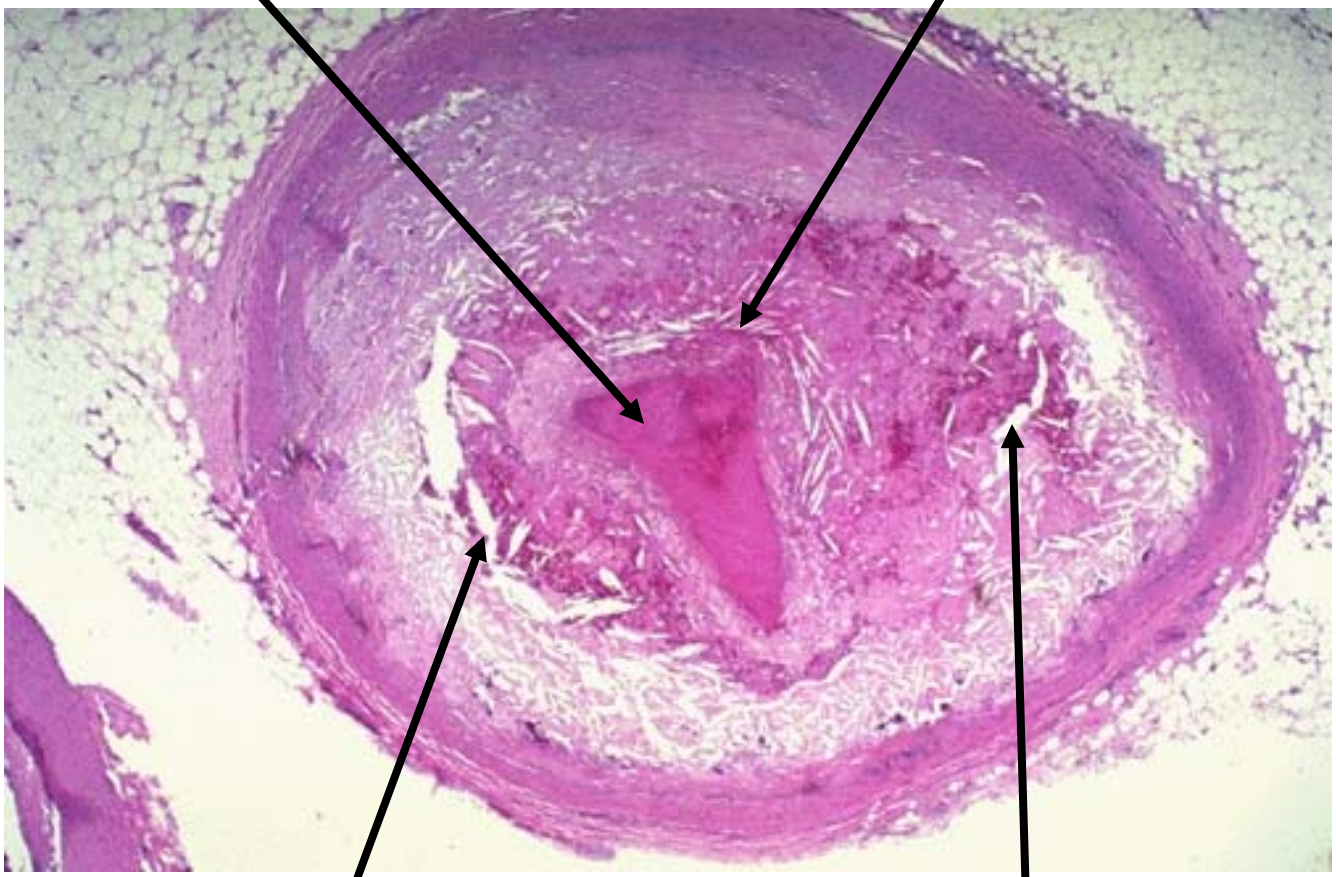
Atherosclerotic Plaque Histology



Thrombus Causing MI

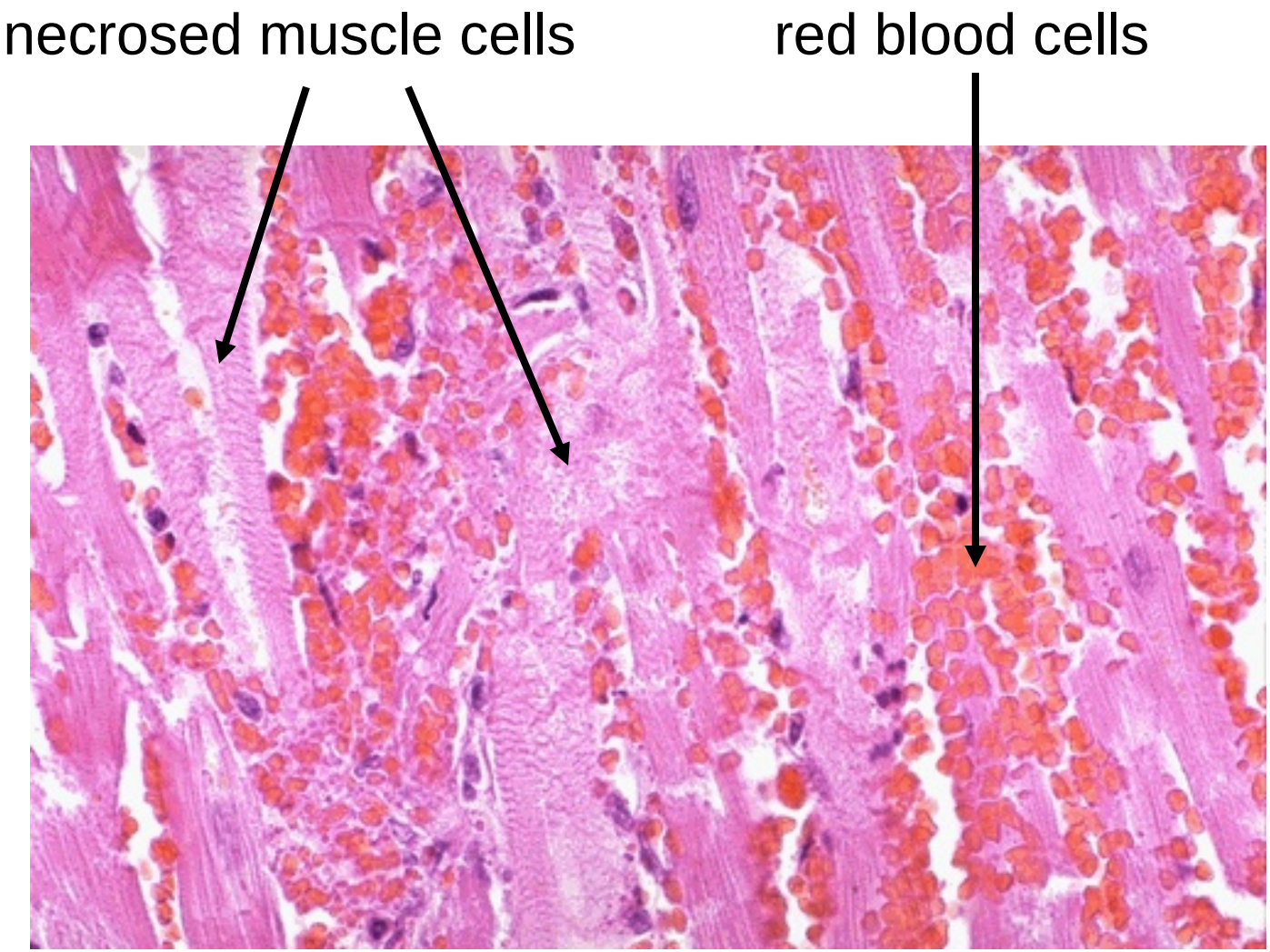
Thrombus ocluding artery

Likely site of plaque rupture



“Needle-Like” white spots are cholesterol crystals

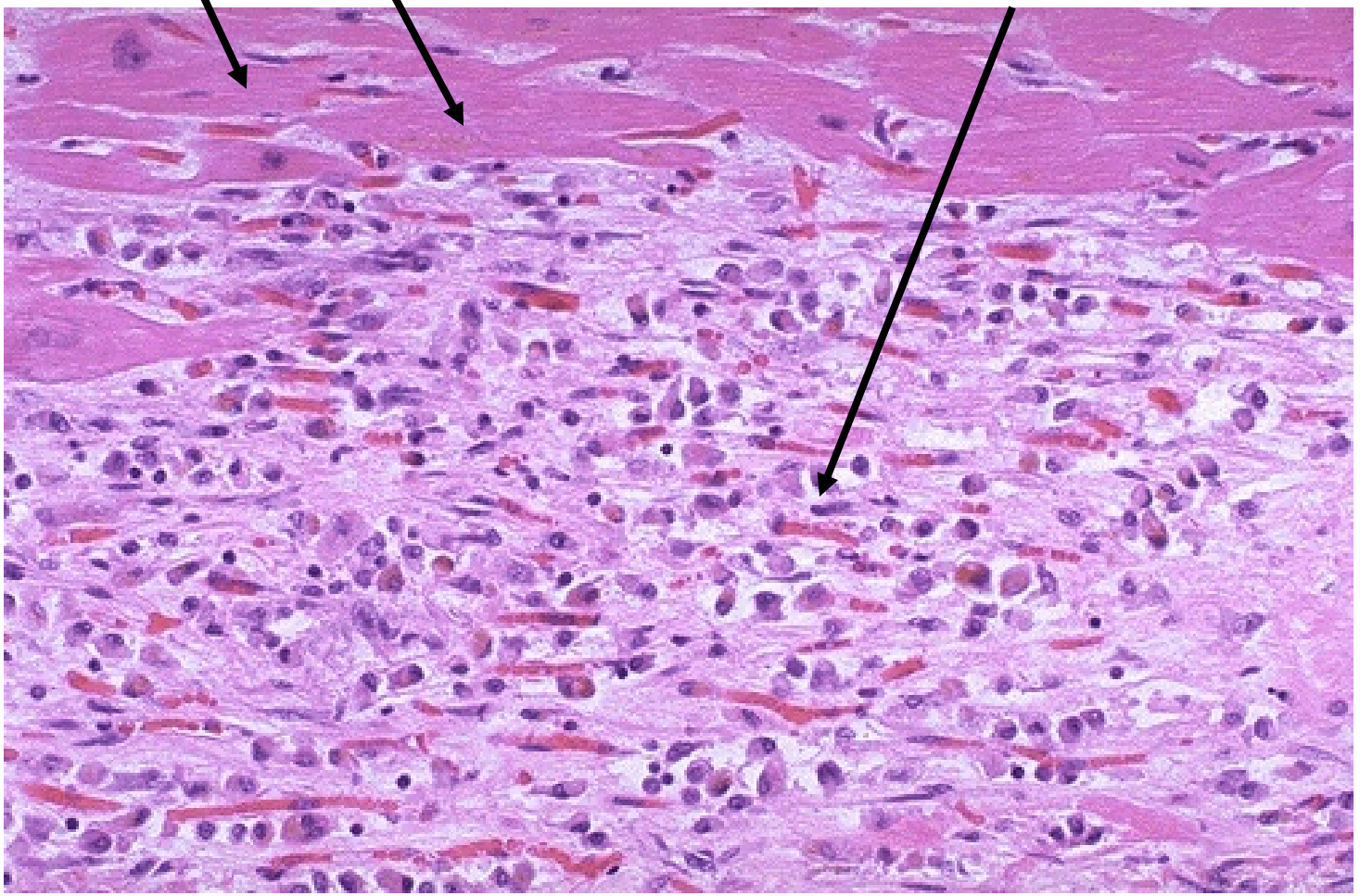
Myocardial Infarction Histology



Myocardial Infarction Histology

normal muscle cells remaining

macrophages and the beginnings of scar tissue



Pathophysiology of Congestive Heart Failure

Heart Failure - inadequate $\dot{Q}$ and consequent pressure ↓ that may result in:

- Fluid accumulation in lungs (left ventricular failure)
  - Shortness of breath (the major symptom)
  - Rales – crackling sounds in the lungs heard upon auscultation
- Fluid accumulation in extremities (right heart failure)
- Most people with CHF have signs of both right and left side failure
- 12.2% of all hospice patients in 2004 were heart failure patients

Heart failure (↓ $\dot{Q}$) is caused by a ↓ in the force of LV contraction due to:

- Chronic LV overload (↑ afterload) → hypertension → CHF
- Cardiomyopathies - cardiac muscle disease & structural malformation
  - Results in chronic heart failure
  - Body tries to maintain blood pressure → water retention → edema
- Heart Attack – infarcted heart muscle may cause **acute heart failure**

Introduction to Stroke

http://www.nhs.uk/Conditions/Stroke/Pages/Introduction.aspx

Stroke: Types

Stroke - death or damage of brain tissue

- **Ischemic Stroke – accounts for 87% of strokes**
  - Stroke resulting from an **obstruction** within an atherosclerotic blood vessel (**usually a blood clot**) that causes reduced or lost blood flow to the brain.
  - Obstruction can be a cerebral thrombosis: a clot that forms at the site of the stroke
  - Obstruction can be a cerebral embolism: clot usually from large arteries of neck/chest

- **Hemorrhagic Stroke**
  - Stroke resulting from a weakened vessel or group of vessels that rupture and bleed into the brain. Blood → irritation of tissue + ↑ intracranial pressure → damage
  - Weakened vessels are usually classified as either an aneurysm or an arteriovenous malformation (AVM)
    - Aneurysms usually develop after age 40
    - 30%-40% of bleeds die, 20% have moderate /severe damage, 15%-30% minor / no damage
    - Multiple bleeds from the same aneurysm are possible → treat ruptures quickly

      Intracerebral hemorrhage - bleeding inside the brain

      Subarachnoid hemorrhage - bleeding outside the brain in the subarachnoid space

Transient Ischemic Attack (TIA) - 1/3 of TIA's victims stroke within a year

Temporary clot causing temporary symptoms ("mini strokes" or "warning strokes")
Usually last less than 5 minutes
Have same symptoms as stroke → As a precaution, TIA's should be treated as a stroke

Watershed Stroke - ↓ blood flow to brain → brain ischemia…..caused by:

- **Atherosclerosis of the carotid arteries**
- **Congestive heart failure**
- **Hemorrhagic shock**

Stroke: Symptoms

Specific neurologic, motor, and sensory deficits such as:

- Sudden numbness, weakness, or paralysis of the face, arm or leg,
  - Especially on one side of the body
- Sudden confusion, trouble speaking (aphasia) or understanding
- Sudden trouble seeing in one or both eyes or writing on paper
- Sudden trouble walking, dizziness, loss of balance or coordination
- Sudden severe headache with neck pain with no known cause
- Sudden drowsiness, inattentiveness, or loss of consciousness
- Sudden vertigo or gait imbalance

Unique to women:

- Sudden face & limb pain, hiccups, nausea, chest pain & palpitations
- Sudden generalized weakness and shortness of breath

Stroke: Simple Tests With the Acronym FAST

- **F - Face: ask the person to smile**
  - One side of the face drooping is a sign of a stroke
- **A - Arms: ask the person to raise both arms**
  - One arm drifting downward is a sign of a stroke
- **S - Speech: ask the person to repeat a simple phrase**
  - Is their speech slurred or strange (aphasic)…stroke sign
- **T - Time: if any of these signs are present call 911 IMMEDIATELY**
  - Time is brain tissue
  - 3 hour window to be a candidate for the latest treatments

Ischemic Stroke: Acute Treatment

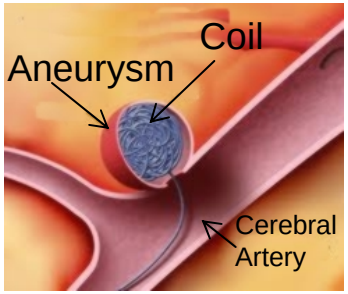
- CT used to determine cause: clot, bleed, aneurysm / AVM rupture
- Ischemic Strokes come in two types
  - **Thrombotic (cerebral thrombosis) most common type of ischemic stroke**
    - Thrombus forms inside brain artery damaged by atherosclerosis
    - Blood flow is blocked
  - **Embolic (cerebral embolism)**
    - Clot or small piece of plaque forms upstream and lodges in narrow artery
    - Common cause: atrial fibrillation - these folks need to be anticoagulated
- CT and MRI used to determine location & extent of brain damage
- Ischemic strokes treated with thrombolytic drugs (TPA) and sometimes antiplatelet drugs (aspirin & clopidogrel).
  - Is the patient a good candidate (prior hemorrhagic stroke, bleeding ulcers, etc.?)
  - Sometimes prophylactic anti seizure meds are given
- Clot retrieval systems may now also be used http://www.youtube.com/watch?v=1cVwqNePlew

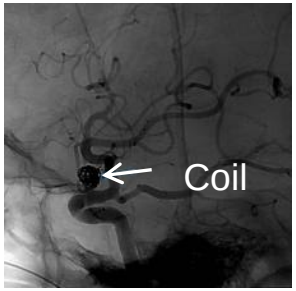
Hemorrhagic Stroke: Acute Treatment

- CT and MRI used to determine location & extent of brain damage
- Hemorrhagic strokes treatment based on underlying cause of bleed
  - Immediate ↓ BP via hyperosmotic agents (Mannitol, Glycerol, hypertonic saline)
  - Sometimes prophylactic anti seizure meds are given
  - Pain relievers and anxiolytics may be given for headache pain

- Aneurysms may be treated with surgical clipping
  - Helps prevent secondary leakage from affected artery

- Aneurysms may be treated with endovascular coils
  - Placement of platinum coils in the aneurysm to prevent blood from entering
- AVM's may be treated with Microsurgery to remove the malformation
- AVM's may be treated with radiation causing blood to clot & AVM disappear
- AVM' may be treated by endovascular deposition of a "glue block" to reduce blood flow through the AVM → ↓ AVM size for surgery
- In both aneurysms and AVM's, surgical hematoma removal may be needed





Stroke: Risk Factors

- Age: stroke risk doubles for each decade after age 55
- Heredity: Strokes run in families; blacks at greater risk than whites
- Gender: Strokes are more common in men but more women die of them
- Birth control, hormone replacement, & pregnancy
- Prior stroke or MI - TIA's ↑ person's stoke risk 10-fold
- Hypertension
- Diabetes
- Coronary / Carotid artery atherosclerosis, peripheral atherosclerosis
- Atrial fibrillation: quivering left atria leads the blood to pool then clot
- Hypercholesterolemia and bad lipoprotein B to A1 ratio
- Diet, Physical inactivity, stress, and depression
- Alcohol and Drug Use

Stroke: Rehabilitation Considerations

The severity of the stroke depends on which type of rehab program a patient is put into.

- Acute care and rehab hospitals (inpatient) include 24 hour medical care in a hospital or special rehab unit. This program is the most demanding and more intense.

- Long-term care facilities include nursing homes. These people have their medical problems under control but still need 24 hour Assistance

- Outpatient facilities include doctor's office and other out patient centers. These people have their medical problems under control and can travel to get their treatment

- Home-based programs allow the patient to live at home and receive rehab from visiting professionals. An important advantage to this program is that patients learn skills that they use most in their home.

Stroke: Rehabilitation Principals

- The earlier and more intense the therapy the better the outcome
    - Especially for gait training (Arch Phys Med Rehabil. 74(6) 1993)
- Aerobic, resistance & balance training are recommended (Circ. 2004)
- General Stroke Rehabilitation Exercises (later stage)

  http://www.youtube.com/watch?v=j5rEAPVelDs&playnext=1&list=PL83963F74299E2BF0&index=6
- Visual Retraining Exercises

  http://www.youtube.com/watch?v=bdodSqveggA
- Balancing Exercises

  http://www.youtube.com/watch?v=ILxjRhyK_ak
- Water Exercises progressing to support beams & walker

  http://www.youtube.com/user/HydroWorxPools?v=-X_SAK36G9s&feature=pyv&ad=5229453017&kw=therapy&gclid=CO7ug6OR56UCFTRa7AodVi-pzQ

Sensory & Pain Pathways to the Brain and Motor Pathways to Muscle: Stroke interruption

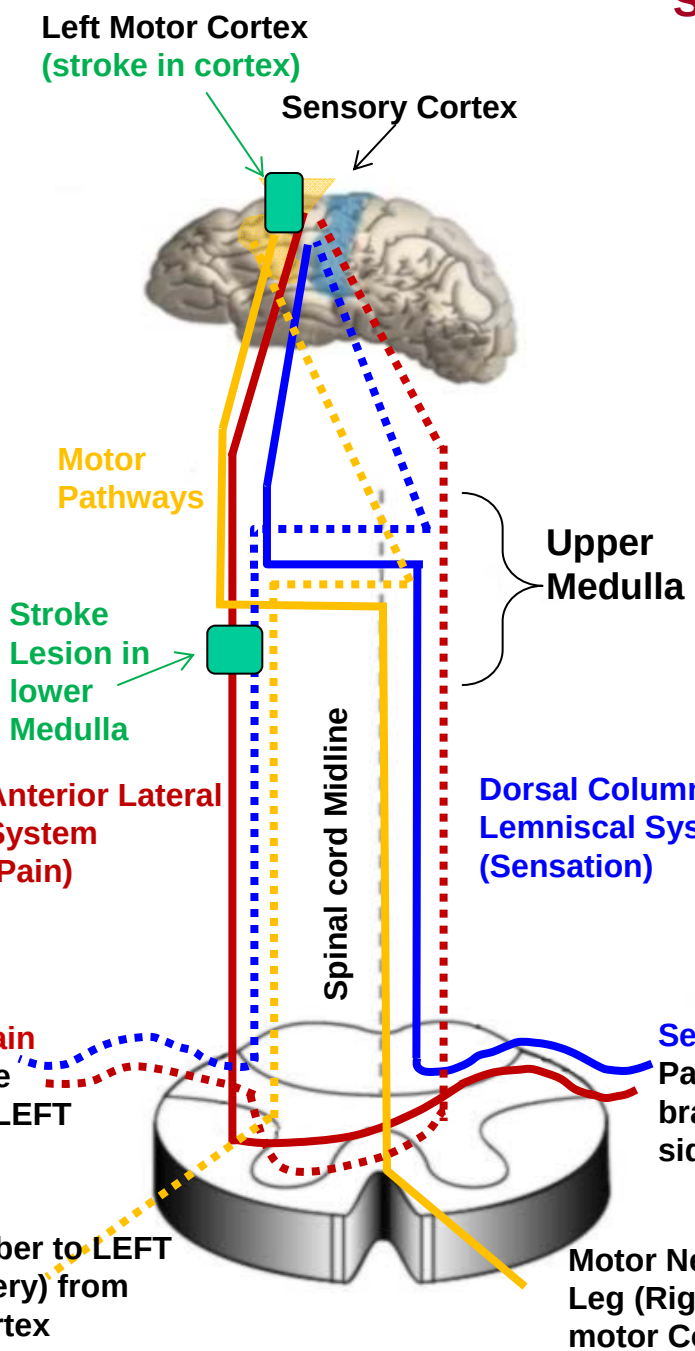
Patient presents with:

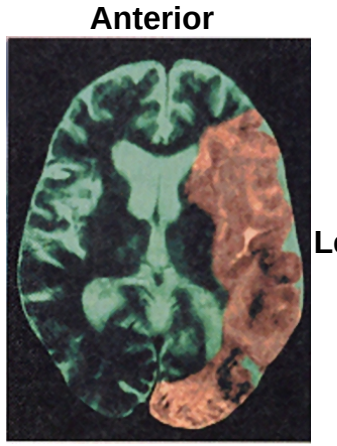
*1.Weakness in **right** limbs + loss of sensation on the **left** side of face*
*2.Loss of pain perception in the lower **right** limbs*
3.Ataxia (inability to walk well)
4.Drowsiness and inattentive

Pathophysiology:

1.Stroke on left side of cortex & and left brainstem

1. *Right Motor neurons originate in left motor cortex. Motor fibers cross over at medulla above stroke level ➞ motor symptoms on right side.*
2. *Pain fibers cross over at spinal cord level ➞ loss of pain in lower right leg implies left sided stroke lesion*
3. *Sensory fibers cross over at medulla (brainstem). Sensory loss on the left side of the face ➞ lesion occurred in a place before crossover occurred.*
4. *Ataxia ➞ stroke affected brainstem ands cerebellum*
5. *Drowsiness, disorientation are indicators of general neurologic damage (seizures and depression are common).*





MRI to be "viewed from below looking up into brain"

Efferent Motor Pathways and Afferent Sensory Pathways cross over at the mid brain Medulla Area

Afferent Pain Pathways crosses over before ascending to mid brain Medulla Area at the same level of the spinal cord at which they enter