Common Congenital Heart Lesions
(pg 349-370 from readings on Thursday 16th and Monday 20th)
Chapter 16: Congenital Heart Disease

Embryology:
- Two angioblastic cords form from the embryonic disc, cords canalize and fuse to form the endocardial heart tube (continuous with aortic arch)
- Heart tube has five sections:

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- Atrioventricular canal: separates the primitive ventricle and primitive atria, forms the mitral and tricuspid valves.
- Septation of the atria:
  - septum primum grows down from roof of common atrium
  - septum fuses with endocardial cushion at the sides, forming ostium primum
  - center of septum primum degenerates, forming ostium seconundum
  - ostium primum eliminated
  - septum secundum forms to right of septum primum and grows down
  - septum secundum overlaps ostium secundum
  - septum secundum fuses with EC cushion and forms foramen ovale
  - foramen ovale allows blood to pass from RA to LA in fetus
- Septation of AV canal: EC cushions swell and fuse to form the AV valves
- Septation of the ventricles and outflow tracts:
  - 4th week: common ventricle grows leaving a medial muscular ridge which forms the muscular part of the IV septum; does NOT fuse with EC cushions
  - 5th week: bulbus cordis and truncus arteriosus form bulbar ridges, which fuse and spiral 180°→ aorticopulmonary septum
  - 7th week: EC cushions fuse with right and left bulbar ridges, forming membranous part of IV septum
- Development of valves: proliferation of mesenchymal tissue, blood flow and cell death shapes valves, AV valves leave behind fine muscular strands connecting valve to wall of ventricle→ chordae tendineae
• Fetal Circulation:

Umbilical Vein → ductus venosus → IVC
OR
Umbilical Vein → portal vein → liver → hepatic veins → IVC

From IVC (high O₂) → RA → foramen ovale → LA → LV
   From LV: 1. carotid and subclavian to brain (60%)
             2. descending aorta (30%)
             3. coronary arteries (10%)

OR

From IVC (high O₂) → RA → RV* → PA → ductus arteriosus** → descending aorta
   OR → PA → lungs

*During fetal life, RV accounts of 2/3 of CO
**Most blood goes through the shunt because of increased pulmonary vascular resistance (because lungs filled with fluid)

• At birth
  o Ductus venosus constricts when umbilical cord clamped
  o Foramen ovale closes due to increased LA pressure and decreased RA pressure
  o Ductus arteriosus constricts after birth because of decreased prostaglandin E₁ levels

Congenital Heart Lesions: well tolerated before birth due to shunting

1. Cyanotic:
   a. right to left shunting in the heart
   b. ASD, VSD, PDA, AS, PS, Coarctation
   c. ASD, VSD, and PDA cause VOLUME overload
   d. AS, PS, and Coarctation cause PRESSURE overload

2. Acyanotic: left to right shunt, associated with Eisenmenger syndrome
   a. Eisenmenger syndrome: large left to right shunt → increased volume and pressure in LA → hypertrophy of pulmonary arterioles → increased pulmonary vascular resistance → increased pressure on right side of heart → SHUNT REVERSAL (RIGHT→LEFT) → hypoxemia and cyanosis
   b. Tetralogy of Fallot, TGA, Eisenmenger's
**Acyanotic**

1. **Atrial Septal Defect**

   **Clinical Presentation:** Usually asymptomatic and detected by murmur, may have dyspnea on exertion, fatigue, or recurrent lower resp. tract infections; also decreased stamina and palpitations (from atrial arrhythmias 2° to RA enlargement)

   **Physical Findings:**
   1. prominent systolic impulse along left sternal border (RV heave) (dilated RV)
   2. wide, fixed splitting of S2 (decreased ejection time)
   3. systolic murmur over pulmonary valve (increased volume over Pulm valve)
   4. mid-diastolic murmur over left lower sternal border/ tricuspid valve (increased flow over tricuspid valve)

   **Blood going through ASD does NOT cause a murmur**

   **Diagnostic Imaging and Testing:**
   A. Chest radiograph: dilated RA and RV, prominent PA, increased pulm markings
   B. ECG: RVH, RA enlargement, RBBB, Left axis deviation for ostium primum type ASD
   C. Echo: RA and RV enlargement, ASD visualized or determined using Doppler
   D. Cardiac cath: only to determine pulm. vascular resistance, shows increased $O_2$ in RA

   **Treatment:** surgical repair only if large volume through shunt

   **Etiology:** persistent opening in atrial septum allowing direct communication between left and right atria. Three types (most to least common):
   1. Ostium Secundum ASD: lesion near foramen ovale, caused by increased reabsorption of septum primum or inadequate formation in septum secundum
   2. Ostium Primum ASD: lesion near bottom of atrial septum, caused by failure of septum primum to fuse with endocardial cushions, assoc. w/ abnormal development of AV valves
   3. Sinus Venosus ASD: lesion at top of atrial septum, caused by incomplete absorption of sinus venosus into RA, assoc. w/ drainage of pulm veins into RA
   4. Patent foramen ovale: NOT ASD, 20% of the population has it, and it’s no big deal unless have 1.) increased pulmonary pressure resulting in right to left shunt 2.) paradoxical embolism

   **Pathology:** gross specimen has a hole in the atrial septum; enlarged RA and RV

   **Pathophysiology:** Flow through defect depends on its size and the compliance of the ventricles. If uncomplicated, blood goes from LA to RA, causing volume overload and enlargement of RA and RV. Can lead to Eisenmenger syndrome.

   **Epidemiology:** common (1/1500 live births)
2. Ventricular Septal Defect

**Clinical Presentation:** small VSD = no symptoms, large VSD = presents in infants as CHF (tachypnea, poor feeding, failure to thrive, frequent lower respiratory tract infections). Presents with dyspnea and cyanosis if accompanied by increased pulm vascular resistance. Bacterial endocarditis

**Physical Findings:**
1. Harsh holosystolic murmur, best heard at left sternal border. Smaller defects have LOUDER murmurs. **Unlike ASD, murmur results from blood going through defect.**
2. Systolic thrill over murmur
3. Mid-diastolic rumble at the apex (increased flow over mitral valve)
4. With increased pulm vascular resistance: holosystolic murmur diminishes, RV heave, loud P2 closure, cyanosis

**Diagnostic Imaging and Testing:**
A. Chest radiograph: small VSD = normal cardiac silhouette, large VSD = cardiomegaly and prominent vascular markings. If Pulm Vascular Resistance, than enlarged pulmonary arteries with peripheral tapering
B. ECG: If large shunt, LA enlargement and LVH are present. If Pulm vascular disease develops, then add RVH
C. Echo+ Doppler: location of VSD, direction and magnitude of shunt, estimate RV pressure
D. Cardiac Cath: increased O₂ in RV

**Treatment:** spontaneous closure in 50% of patients with small and medium VSD’s, surgical closure recommended within first few months of life if patient has CHF or pulmonary vascular disease. If patient has moderate-sized VSD but no Pulm Vascular Disease, then surgical closure can wait until later in childhood. Give prophylactic treatment for endocarditis for all VSD patients.

**Etiology:** abnormal opening in interventricular septum, 70% in membranous, 20% muscular, 10% below aortic valve or near AV valves

**Pathology:** hole in interventricular septum, dilation of RV, PA, LA, LV

**Pathophysiology:** depends on size of defect and relative resistances of pulmonary and systemic vasculature. Left to right shunt. If shunt is large, volume overload occurs in RV, pulm circulation, LA and LV, resulting in increased stroke volume. Over time, volume overload causes chamber dilatation, systolic dysfunction, and heart failure. Increase in pulm vascular resistance causes Eisenmenger syndrome

**Epidemiology:** common (2-4/1000)
3. Patent Ductus Arteriosus

**Clinical Presentation:** small PDA= asymptomatic, large PDA= CHF (tachycardia, poor feeding, slow growth, recurrent lower resp. tract infections). Moderate PDA: presents as teenager or adult with fatigue, dyspnea, palpitations or Afib., watch out for infection

**Physical Findings:**
1. *CONTINUOUS, machine-like murmur* at left subclavicular region
2. If pulm. vascular disease, then murmur shortens due to decreased pressure gradient between systole and diastole
3. Cyanosis and clubbing if Eisenmenger syndrome is present

**Diagnostic Imaging and Testing:**
- A. Chest x-ray: enlarged cardiac silhouette with large PDA (LA and LV enlargement), calcification of ductus can be seen in adults
- B. ECG: LA enlargement, LVH
- C. Echo+ Doppler: visualize PDA, look at flow and right heart pressure
- D. Cardiac Cath: Nope. However, it will show higher blood O₂ in PA than in RV
- E. Angiography: abnormal flow through PDA

**Treatment:** Prostaglandin synthesis inhibitors to close PDA in most patients, PDAs rarely close spontaneously. Can be corrected surgically

**Etiology:** Ductus arteriosus connects left pulmonary artery to ascending aorta, PDA occurs when ductus fails to close.

**Pathology:** LA and LV dilation

**Pathophysiology:** magnitude of flow through PDA depends on cross-sectional area and length of ductus and resistance of systemic and pulmonary vasculatures. During fetal life, blood goes from pulmonary artery to aorta. After birth, blood flow reverses direction, resulting in a left to right shunt. Volume overload in Pulm circulation, LA, and LV, causing dilatation and left-sided heart failure. Right heart is only involved if patient has pulm vas. disease. Eisenmenger's results in cyanosis in feet with sparing of upper extremities

**Epidemiology:** 1/2500-5000 live births. Risk factors: 1st trimester maternal rubella infection, prematurity, birth at high altitude
4. Congenital Aortic Stenosis

Clinical Presentation: usually asymptomatic. 10% of infants have symptoms of heart failure (won’t eat, breathin’ too fast, heart beatin’ too fast, and failure to thrive). In adults, symptoms include fatigue, exertional dyspnea, angina pectoris, and syncope.

Physical Findings:
1. Harsh crescendo-descrendo systolic murmur heard loudest at base of heart and radiating to the neck
2. Murmur preceded by Systolic Ejection Click
3. Murmur is present from birth and is not dependent on decline in pulm vascular resistance (unlike ASD, VSD, and PDA)
4. Increased ejection time, peak of murmur occurs late in systole
5. Reverse splitting of S2 in severe cases (A2 closes after P2)

Diagnostic Imaging and Testing:
A. Chest x-ray: enlarged LV, dilated ascending aorta
B. ECG: LVH
C. Echo: identify structure of aortic valve and degree of LVH, Doppler is used to estimate the pressure gradient across the aortic valve and the size of the opening
D. Cardiac Cath: used to confirm pressure gradient across the valve

Treatment: Endocarditis prophylaxis for all cases, mild forms do not require treatment, severe obstruction is repaired by balloon angioplasty or surgery

Etiology: abnormal development of aortic valve resulting in BICUSPID leaflets and an eccentric, stenotic opening

Pathology: LVH and dilated aorta

Pathophysiology: Increase in left ventricular systolic pressure in order to pump blood across the narrowed valve opening. Increase in pressure causes LVH. Also, blood travels over valve and hits the aorta with increased speed, causing trauma to the aorta and resulting in dilation of the aortic wall.

Epidemiology: 4x more common in males than females, 20% have other abnormalities, usually coarctation of aorta, occurs in 2% of population, but only rarely causes congenital AS
5. Congential Pulmonic Stenosis

**Clinical Presentation:** Mild or moderate PS: asymptomatic, diagnosis made based on murmur on routine physical exam. Compensated severe PS: exertional dyspnea, exercise intolerance. Uncompensated severe PS: symptoms of right-sided heart failure (abdominal fullness and pedal edema)

**Physical Findings:** For severe pulmonic stenosis:
1. RVH and RV heave over left sternum
2. prominent jugular venous "a" wave
3. Loud, late-peaking, crescendo-decrescendo systolic ejection murmur heard over left sternal border, associated with palpable trill
4. Widened splitting of S2 with soft P2 (delated closure of pulmonic valve)

For moderate PS:
1. Pulmonic ejection click following S1 and preceding systolic murmur resulting from opening of stenotic pulmonic valve. Click diminishes with inspiration.
2. Loud, late-peaking, crescendo-decrescendo systolic ejection murmur heard over left sternal border

**Diagnostic Imaging and Testing:**

A. Chest x-ray: enlarged RA and RV, post-stenotic PA dilation (from high velocity blood hitting vessel wall)
B. ECG: RVH and Right axis deviation
C. Echo+ Doppler: visualize valve, look for presence of RV, and assess magnitude of obstruction

**Treatment:** Mild shows no progression, therefore only moderate and severe require treatment: If pulmonic valve is the problem, then dilate valve with transcatheter balloon valvuloplasty, results are excellent, RVH regresses. Also, treat patients with antibiotic prophylaxis to prevent endocarditis.

**Etiology:** Narrowing or obstruction of pulmonary outflow tract. Arises from:
1. Pulmonic Valve problem (>90%): Congenital fusion of the pulmonic valve commisures
2. R Ventricle problem: abnormal configuration→ obstruction of outflow tract
3. Pulmonary Artery problem: narrowing of vessel or obstruction of lumen

**Pathology:** RVH, RA enlargement, dilation of PA post-stenosis

**Pathophysiology:** PS decreases RV systolic ejection, increases RV pressure, and increases RV chamber hypertrophy. Clinical course depends on severity of obstruction, which is measured by pressure difference on either side of the stenotic area during systole (AKA: peak systolic transvalvular pressure gradient).

Assuming normal CO: Mild: <50 mmHg  Moderate: 50-80 mmHg  Severe: >80 mmHg
6. Coarctation of the Aorta

Clinical Presentation: Preductal and severe postductal coarctation: presents shortly after birth with symptoms of heart failure. Preductal also causes differential cyanosis—the upper body is normal and the lower body is cyanotic. (The pressure after the constriction is low, causing deoxygenated blood to flow from the PA through the ductus arteriosus and into the aorta. R→L shunt)
Moderate coarctation: child presents with hypertension (usually postductal)

Physical Findings:
1. Elevated BP in upper body (Most common presentation)
2. Weak and delayed femoral pulses
3. If coarctation is distal to branching of left subclavian, then BP in arms > BP in legs (normal person has higher BP in legs). If coarctation is proximal to branching of the left subclavian, then BP in right arm > BP in left arm
4. Weak, systolic ejection murmur caused by flow through coarctation.
5. Continuous murmurs over chest from collateral circulation

Diagnostic Imaging and Testing:
A. Chest x-ray: notching of inferior surface of ribs, indented aorta at coarct.
B. ECG: LVH due to pressure load
C. Echo: visualize coarctation, determines pressure across coarctation
D. MRI: length and severity of coarctation

Treatment: Severe obstruction in neonates: prostaglandin infusion to keep ductus arteriosus open and maintain blood flow to descending aorta until surgery. Surgical repair for kids: excise coarctation and put in a synthetic patch. For older kids and adults (or people with recurrent coarctation), use a transcatheter balloon to dilate, may/ may not use stent. Antibiotic prophylaxis for endocarditis

Etiology: Discrete narrowing of aortic lumen, 2 types:
I. Preductal (2%): narrowing occurs proximal to the ductus arteriosus, results from intracardiac anomaly during fetal life, causing decreased blood flow through left side of heart and hypoplastic development of the aorta
II. Postductal (98%): narrowing occurs distal to the ductus arteriosus, caused by ductal tissue extending into the aorta. When the ductus constricts after birth, ductal tissue in aorta constricts too, obstructing the aorta

Pathology: LVH
Pathophysiology: coarctation causes increase in LV pressure, decreased blood flow to descending aorta and lower extremities (head and upper extremities rarely affected.) LV pressure load → LVH and dilation of collateral (intercostals) blood vessels (latter causes erosion of lower ribs = rib notching)
Epidemiology: 1/6000, associated with Turner’s syndrome (45, XO)
Cyanotic
1. Tetralogy of Fallot

Clinical Presentation: patients with TOF present in childhood with dyspnea on exertion or after feeding or crying (vasodilation of systemic vasculature increases right to left shunt). Other symptoms: irritability, cyanosis, hyperventilation, syncope, convulsions. Major symptom: child reflexively squats down during spells (“kinking” of femoral arteries increases systemic resistance and decreases right to left shunt and directs more blood from RV to lungs)

Physical Findings: Moderate pulmonary stenosis: mild cyanosis, especially on lips, mucus membranes, and digits. Severe pulmonary stenosis causes:
1. Profound cyanosis within a few days of birth
2. Clubbing of fingers and toes due to chronic hypoxemia
3. Palpable heave along left sternal border indicates RVH
4. Single S2 (pulmonary component is inaudible)
5. Systolic ejection murmur heard best at left upper sternal border (from PS)

Diagnostic Imaging and Testing:
A. Chest x-ray: “Boot-shaped heart,” prominence of RV, decrease in size of main pulmonary artery, decreased pulmonary vascular markings
B. ECG: RVH and Right axis deviation
C. Echo and Cardiac Cath: shows R ventricle tract anomaly, malaligned VSD, RVH

Treatment: Complete surgical correction at age 1: closure of VSD and enlargement of subpulmonary infundibulum. If need to delay complete correction until later in childhood, then palliative surgery in infancy: create connection between aorta and PA, results in L to R shunt and increases blood flow to lungs. Antibiotic prophylaxis.

Etiology: Abnormal anterior and superior displacement of the ventricular outflow tract (infundibular portion of the IV septum) resulting in four anomalies:
1. Ventricular Septal Defect due to septal malalignment
2. subvalvular pulmonic stenosis (misaligned infundibular septum obstructs outflow tract)
3. Overriding aorta that receives blood from both ventricles
4. RVH (due to increased pressure caused by pulmonary stenosis)

Pathology: see Etiology
Pathophysiology: Subvalvular pulmonary stenosis causes resistance to flow through right outflow tract. Most of the deoxygenated blood in the RV is diverted through VSD and into aorta, magnitude of shunt depends on severity of PS

Epidemiology: most common cyanotic congenital heart lesion seen AFTER infancy, associated with other defects, such as right-sided aortic arch and ASD
2. Transposition of the Great Arteries

*Clinical Presentation:* neonate presents on first day of life with cyanosis that increases as ductus arteriosus closes

*Physical Findings:*
1. Palpable right ventricular impulse at lower sternal border (because RV has to pump against systolic pressure)
2. Accentuated S2 (closure of aortic valve closer to chest wall)
3. No prominent murmurs unless there is an additional defect

*Diagnostic Imaging and Testing:*
   A. Chest x-ray: usually normal, base of heart may be narrow
   B. ECG: RVH
   C. Echo: shows abnormal orientation of great vessels (definitive diagnosis)

*Treatment:* TGA is a medical emergency. Give prostaglandin infusion to keep ductus arteriosus open. Also, use balloon catheter to create an opening in the interatrial septum. Permanent correction occurs via “arterial-switch:” transaction of great vessels above semilunar valves and ostia of coronary arteries. Great vessels switched, and coronary arteries relocated to “new” aorta

*Etiology:* great vessels arise from the opposite ventricle, cause is unknown but thought to be from failure of aorticopulmonary septum to spiral or from abnormal growth of subpulmonary and subaortic infundibuli

*Pathology:* RVH

*Pathophysiology:* pulmonary and systemic circulations are in parallel rather than in series, deoxygenated systemic blood passes into RA and RV and returns to circulation, oxygenated blood from lungs goes to LA and LV and returns to lungs. If no mixing of the two systems, then TGA is lethal. However, if ductus arteriosus and foramen ovale remain patent, then the two sides can communicate and deliver enough $O_2$ to the brain and vital organs.
3. Eisenmenger Syndrome

**Clinical Presentation:** Exertional dyspnea and fatigue in person with congenital heart defect. May have symptoms of hyperviscosity syndrome. Can present with hemoptysis due to rupture of pulmonary vessels.

**Physical Findings:**
1. cyanosis with clubbing in digits
2. prominent “a” wave in jugular venous pulsation
3. Loud P2 (pulmonic closure) sound
4. No murmur

**Diagnostic Imaging and Testing:**
A. Chest x-ray: proximal pulmonary artery dilation and calcification of pulmonary vasculature
B. ECG: RVH, RA enlargement
C. Echo+ Doppler: identifies underlying defect, estimates pulmonary artery systolic pressure

**Treatment:** avoid activities that increase right to left shunt (No exercise, high altitude, vasodilators, or pregnancy.) Antibiotic prophylaxis, supportive therapy. Only long-term treatment is heart-lung transplant.

**Etiology:** chronic left to right shunt through congenital heart defect causes severe pulmonary vascular obstruction, increased pulmonary pressure causes reversal of shunt, causing systemic cyanosis

**Pathology:** RVH, RA enlargement

**Pathophysiology:** increased pulmonary blood flow causes media to hypertrophy, decreases cross-sectional area of vascular bed. Vessels become thrombosed, increasing pulmonary vascular resistance causes reversal of shunt. Reduced hemoglobin saturation causes increase proliferation of bone marrow.
Stenotic Semilunar Valve Disease

Aortic Stenosis (AS)

Clinical Presentation:
- **Chest pain (angina):** median survival 5 years after chest pain starts
- **Syncope:** median survival 3 years
- **Dyspnea on exertion (CHF):** median survival 2 years
- **Atrial fibrillation (less common):** median survival 6 months
- Note: These symptoms may appear after many asymptomatic years of slowly progressing stenosis. Once the symptoms develop, they confer **decreased survival if surgical correction is not undertaken.**

Physical Exam: can permit accurate detection and estimation of the severity of the AS
- Typical findings:
  - **Auscultation:** coarse mid-systolic ejection murmur, S4 (atrial contraction into the stiff LV), split S2 with soft A2
    - **Specifics for auscultation based on severity:**
      - **Mild AS:** ejection click, early systolic murmur, split S2
      - **Moderate AS:** longer systolic murmur that peaks in mid-to-late systole (no ejection click because the valves are getting older)
      - **Severe AS:** even later peaking systolic murmur (don’t even hear the A2 part of S2 because the valve doesn’t even close)

  ![Early Peaking Murmur](image1)
  ![Late Peaking Murmur](image2)

- **Note:** If patient has AS and has an Ejection Click, that’s a good sign!!!
- **Differentials for auscultating in the three Congenital types of AS:**
  - With Congenital Valvular AS: aortic ejection click paradoxically heard at the heart’s apex
  - With Subvalvular AS: aortic systolic murmur with an associated diastolic aortic regurgitation
  - With Supravalvular AS – no associated aortic regurgitation and no ejection click

  - **Carotids:** weakened (“parvus”) & delayed, slow rising (“tardus”) upstroke, which peaks right before S2, and decreased volume due to obstructed LV outflow [note: normal carotid pressure peaks at same time as LV pressure peaks]. Can also have shudder/thrill during contraction, which reflects turbulence in LV outflow.
  - **Palpation:** suprasternal thrill, evidence of LVH in a sustained PMI
  - **Jugular Venous Pulse:** “v” should be the big rise, but with AS and associated LVH, get “a” as the dominant wave. Anything that causes concentric hypertrophy can show this large “a” wave in the JV Pulse.

- **Note:** In older patients, not uncommon to have murmur of calcific AS that is most audible in the mitral area. However, if you’ve appreciated the weakened, delayed carotid pulse before auscultating, you won’t miss the diagnosis of calcific AS even though it is heard in the mitral area.
  - If these same older patients have Ventricular Premature Beats, you may take advantage of varying diastolic filling periods – with larger end diastolic volume, you hear a larger murmur. Regurgitant murmurs (in the differential diagnosis), however, keep the same murmur intensity regardless of the increased filling period.
**Etiology:**

- **“Senile” calcific:** AS often caused by *age-related* degenerative calcific changes of the valve. Majority of patients diagnosed with AS after age 65 have this form.
- **Congenital:** Calcific changes that progress to AS may also develop in patients with congenitally deformed aortic valves (1-2% population born with bicuspid aortic valve). Majority of young patients with AS have calcification of congenital bicuspid valve.
  - Three types of congenital:
    - 1/ Congenitally malformed valve
    - 2/ Subvalvular AS
    - 3/ Supravalvular AS – associated with William’s Syndrome and is the rarest form of AS – these babies have low, wide-set eyes
- **Rheumatic:** AS can result from chronic rheumatic valve disease, although the prevalence of this as a cause in the US has been greatly decreased. 95% of patients with rheumatic AS also have rheumatic disease of the mitral valve.

**Pathology:**

- Path features of AS derived from etiology…
  - **“Senile” calcific:** *cumulative wear and tear* leads to endothelial and fibrous damage, which results in calcification of an otherwise normal trileaflet valve.
  - **Congenitally deformed valve:** *years of turbulent flow across the deformed valve* disrupt endothelium and collagen matrix of leaflets with result of gradual calcium deposition (like that in the “senile” form, but appearing decades earlier).
  - **Rheumatic:** *endocardial inflammation leads to organization and fibrosis of the valve*, resulting in fusion of the commissures and formation of calcified masses in the aortic cusps.
- Regardless of etiology, *all AS typified by calcification* deep within the fibrosa of the valve cusps, extending toward the surface and resulting in heaped up or nodular deposition extending into sinuses of Valsalva (the pockets that lead to the LCA and the RCA) of the aortic root.

**Pathophysiology:**

- **Normal aortic valve area** = 3-4 cm²
  - mild AS = 2 cm²
  - moderate AS = 1-1.5 cm²
  - critical AS = 0.8 cm²
- In AS, blood flow across aortic valve is obstructed during systole.
- This makes large pressure gradients between the LV and the aorta.
- AS develops over chronic course, so **LV undergoes concentric (pressure) hypertrophy** to compensate and overcome the large pressure gradient.
- With hypertrophy, stress on wall is relieved, but the LV becomes stiff as a result.
- LA contraction, though contributing little to LV stroke volume in normal individuals, contributes 25% of the stroke volume for the LV in AS patients. Thus, **LA hypertrophy can be beneficial for AS patients.**
- Because LA contraction contributes 25% volume to the LV in AS patients, it is dangerous and a poor clinical sign if they develop atrial fibrillation.
- Angina occurs because of an imbalance btw myocardial oxygen supply and demand.
  - Demand is greater because of an increased LV mass and because wall stress is greater due to increased pressure.
  - Supply is reduced in AS because the elevated LV diastolic pressure reduces the coronary perfusion pressure gradient between the aorta and the myocardium (I think this means that less blood is able to go into the sinuses of Valsalva…leading to the RCA and the LCA).
- **Syncope during exertion happens because the LV can't increase its CO during exercise due to the fixed stenotic aortic opening.** Also, exercise leads to vasodilatation of the peripheral muscle beds. These two factors lead to decreased cerebral perfusion pressure and a propensity to syncope upon exertion.
- Congestive heart failure symptoms happen late in the disease when markedly increased LV end diastolic volume and pressure lead to elevation of the LA and pulmonary venous pressures, which produces pulmonary alveolar congestion and symptoms of congestive heart failure (like dyspnea).
Diagnostic imaging/testing:

- **Electrocardiogram:**
  - LV hypertrophy is common in advanced AS.
  - With AS, get increased QRS voltage, get inverted T waves and get ST depression (due to pressure overload).

- **Echocardiography:**
  - Sensitive way to assess LV wall thickness.
  - Trans-valvular pressure gradient and aortic valve area can be calculated by Doppler echocardiography.

- **Cardiac Catheterization:**
  - Sometimes used to confirm the severity of AS and also to define the coronary anatomy, because concurrent coronary artery bypass surgery is often necessary at the time of aortic valve replacement in patients who have coronary disease in addition to their AS.

Treatment:

- **Natural history of severe, symptomatic, uncorrected AS is very poor.** (One year survival rate for patients with severe AS who don’t undergo surgery is 57%.)
- Only effective treatment for **advanced** AS is surgical replacement of the valve.
- **Aortic Valve Replacement (AVR):** indicated for AS when: 1/ patients with severe LV outflow obstruction develop symptoms or 2/ there’s evidence of progressive LV dysfunction in the absence of symptoms.
- After AVR, LV ejection fraction almost always increases.
- AVR gives a 10 year survival rate that exceeds 75%!
- **Percutaneous valvuloplasty:** unlike in MS, where it works pretty well, it doesn’t work well in AS
  - Balloon dilatation across the aortic valve orifice can fracture fused, calcified valve commissures providing some immediate outflow obstruction relief…BUT 50% of AS patients then undergo valve RE-stenosis within 6 months.
  - Valvuloplasty in AS patients is only used for patients who are poor surgical candidates or as a temporary fix in patients who are too sick to go directly into AVR surgery.
Regurgitant Semilunar Valve Disease

Aortic Regurgitation (AR)

Clinical Presentation:
- Dyspnea on exertion (CHF)
- Fatigue
- Decreased exercise tolerance
- Uncomfortable sensation of a forceful heartbeat associated with high pulse pressure
- Chest pain (occasionally)

Physical Exam:
Typical findings:
- **Auscultation:**
  - “blowing” early diastolic decrescendo murmur heard along left sternal border (heard best after patient exhales while leaning forward)
- **Blood Pressure:** HALLMARK of AR is wide pulse pressure \((PP = systolic - diastolic; \text{normal} = 30-40 \text{ mmHg}; \text{wide} > 40 \text{ mmHg})\) because a larger stroke volume produces a larger pulse pressure at any given aortic compliance
- **Pulse:** bounding pulses (strong, forceful pulses)
- **Carotids:** Depending on severity of the AR, might see bifid contour of the tall part of the carotid pulse and have a smaller contoured notch
- **Palpation:** hyperdynamic LV impulse (due to volume overload and eccentric hypertrophy)

**Note:**
- **Acute Aortic Regurgitation:** have no opportunity to dilate the LV, so it is relatively non-compliant and have a dramatic rise in pressure.
- **Chronic Aortic Regurgitation:** see wide pulse pressure, hyperdynamic apical impulse
  - Onset of symptoms in a chronic AR patient is usually an indication of the development of LV contractile dysfunction and the prognosis worsens once LV decompensation takes place.

Etiology:
- **Abnormalities of the aortic leaflets:** (that lead to stiffening and/or incomplete closure of the aortic valve)
  - **Rheumatic:** 25% of patients with rheumatic heart disease will develop AR
  - **Endocarditis:** freely multiplying organisms make and enlarge vegetations that lead to leaflet complications
  - **Congenital** (e.g. bicuspid valve)
- **Dilatation of the aortic root:**
  - **Aortic aneurysm/dissection:** aortic aneurysm is ballooning of the aorta; when aorta enlarges and stretches, it becomes prone to an aortic dissection, which is a separation or tear in the lining of the artery that allows blood to flow between the inner and outer walls of the vessel yet remains contained in the aorta.
  - **Marfan syndrome:** Think tall, thin people with spindly fingers. From an autosomal dominant connective tissue disease that appears in 4-6 of every 100,000 people. Marfan's syndrome causes deformations and defects in several body systems, most notably the ocular, skeletal, and cardiovascular (at least 90 percent of people with the Marfan syndrome will have heart involvement).
  - Also **Annulo-aortic actasia** and **Syphilis:** no details about these w/ respect to AR in book or lectures.
**Pathology:**
- Due to valve problems in AR, whether with the leaflet or aortic dilatation, get regurgitation of blood from aorta back into the LV during diastole.

**Pathophysiology:**
- With each contraction, the LV must pump out both extra, regurgitant volume and normal volume from the LA.
- Hemodynamic compensation due to Frank-Starling mechanism:
  - Increases stroke volume and maintains normal end-systolic volume
- Severity of AR depends on:
  1. Size of regurgitant aortic orifice
  2. Pressure gradient across aortic valve during diastole
  3. Duration of diastole

**Acute vs. Chronic AR:**
- **Acute AR:**
  - LV is normal size and relatively non-compliant
  - Volume load of regurg causes LV diastolic pressure to rise
  - Suddenly high diastolic pressure transmitted to LA and pulmonary circulation (can produce dyspnea and pulmonary edema)
  - Usually a surgical emergency requiring Aortic Valve Replacement.
- **Chronic AR:**
  - LV undergoes compensation due to long-standing regurgitation.
  - Get mostly LV volume overload, but also some pressure overload – so get both dilatation and some hypertrophy
  - Less pressure transmitted to the LA and the pulmonary circulation
  - Allowing aorta to regurgitate a large volume during diastole causes aortic (and systemic) diastolic pressure to drop substantially.
  - Combo of high LV stroke volume (inc systolic pressure) and reduced aortic diastolic pressure gives a widened pulse pressure.
  - Decreased aortic diastolic pressure → dec coronary perfusion pressure, reducing myocardial oxygen supply to the large LV…can produce angina (even without atherosclerotic coronaries)
  - (Chronic) left ventricular hypertrophy results in systolic dysfunction → less forward CO and increase in LA and pulmonary pressures → patient gets symptoms of CHF

**Diagnostic imaging/testing:**
- **Chest X-Ray:**
  - Chronic AR shows an enlarged LV silhouette.
  - Acute AR more likely to show pulmonary vascular congestion.
- **Echocardiography:** Doppler echocardiography can identify and quantify degree of AR and can often identify the cause of the AR.
- **Cardiac Catheterization:** used with contrast angiography for evaluation of LV function, quantification of the degree of AR, assessment of coexisting coronary artery diseases

**Treatment:** (surgical intervention not recommended till have regularly occurring symptoms and/or LV dysfunction)
- **Asymptomatic AR:**
  - 60% of patients with asymptomatic chronic AR and normal LV contractile function will still be asymptomatic at their 10-year follow-up.
  - Just need regular clinical evaluation, periodic assessment of LV function (by echo), and antibiotic prophylaxis for endocarditis.
- **Symptomatic AR with preserved LV function:**
  - May respond to diuretics and afterload reducing vasodilators (like ACE inhibitors).
  - Ca²⁺ channel blocker (nifedipine) shown to reduce LV enlargement, increase LV ejection fraction, delay need for valve surgery in patients.
- **Symptomatic patients w/ severe chronic AR or asymptomatic patients w/ impaired LV contractile function:**
  - Need surgical valve replacement (SVR) to prevent further deterioration of LV function.
Stenotic Atrioventricular Valve Disease

Mitral Stenosis (MS)

Clinical Presentation: (symptoms of L sided, then later R sided, heart failure)

- depends on degree of stenosis (mild=less stenosis/larger valve opening; severe=more stenosis/smaller valve opening)
- early symptoms: dyspnea, reduced exercise capacity
- mild MS: may lack dyspnea at rest; can develop it with exertion (or fever, anemia, hyperthyroid, pregnancy, etc.)
- severe MS: dyspnea at rest, fatigue, signs of pulmonary congestion (i.e. orthopnea, paroxysmal nocturnal dyspnea)
- advanced MS & pulmonary hypertension: progression to signs of right heart failure (JVD, hepatomegaly, ascites, peripheral edema), can compress recurrent laryngeal nerve w/ enlarged pulmonary artery or left atrium to cause hoarseness
- complications: atrial fibrillation, thromboembolism, infective endocarditis, hemoptysis

Physical Exam:

- Typical findings:
  - precordial palpation: right ventricular “tap”
  - auscultation: loud S1 in almost all cases, high-pitched “opening snap” (OS) after S2 – interval btw S2 and OS relates inversely to severity of the MS, OS followed by low-frequency decrescendo murmur (diastolic “rumble”) of which the duration relates to the MS severity
  - note that other valvular murmurs are often found in conjunction with MS (i.e. mitral regurgitation)

Etiology:

- MS almost always a sequela of rheumatic fever (50% cases); if a consequence of acute rheumatic fever (ARF), occurs on average 20 years post ARF.
- Also see rare cases of congenital mitral stenosis, calcifications of the mitral valve in elderly patients, or endocarditis with large vegetations that obstruct the valve orifice.

Pathology:

- Typical path features of rheumatic MS come from acute and recurrent inflammation – get fibrous thickening, calcification of valve leaflets, fusion of commissures of valves, and thickening and shortening of the chordae tendineae.

Pathophysiology:

- In MS, have obstruction to blood flow across the mitral valve – emptying of the LA is impeded and there’s an abnormal pressure gradient between the LA and LV.
- Get high LA pressure, normal LV pressure…sometimes reduced LV stroke volume and cardiac output.
- High LA pressure can be transmitted to the pulmonary circulation – can cause transudation of plasma into the lung interstitium and alveoli (causing the dyspnea) and can sometimes cause rupture of a bronchial vein into lung parenchyma, giving hemoptysis (coughing of blood).
- 60% of MS patients get passive pulmonary hypertension: an obligatory increase in pulmonary artery pressure that develops to preserve forward flow in the setting of increased left atrial and pulmonary venous pressures.
- 40% of MS patients get reactive pulmonary hypertension: medial hypertrophy and intimal fibrosis of the pulmonary arterioles – this causes decreased blood flow through the pulmonary vasculature, which results in increased right-side heart pressures and eventually right heart hypertrophy and failure.
- High LA pressure leads to LA enlargement, which stretches the atrial conduction fibers and may disrupt the cardiac conduction system…resulting in Atrial Fibrillation, and can predispose the patient for thrombus formation in the LA.
- Turbulent blood flow across the obstructed mitral valve can predispose patient to infective endocarditis – though not likely with MS.
Diagnostic imaging/testing:

- **Electrocardiogram:**
  - Typically shows **left atrial enlargement**; if pulmonary HTN has developed, right ventricular hypertrophy. Atrial fibrillation may be present. *Note: there is no LV enlargement here!*

- **Chest X-Ray:**
  - Reveals left atrial enlargement, pulmonary vascular redistribution, interstitial edema, Kerley B lines (due to edema within the pulmonary septae)
  - If have developed pulmonary HTN, right ventricular enlargement and prominence of pulmonary arteries also appears.

- **Echocardiography:**
  - MAJOR diagnostic value in MS. Reveals thickened mitral leaflets, abnormal fusion of their commissures with restricted separation during diastole.
  - Left atrial enlargement can be assessed and, if present, intra-atrial thrombus may be visualized
  - Mitral valve area can be measured from cross-sectional views or calculated from Doppler-echocardiographic velocity measurements (normal mitral valve area = 4-6 cm², mild MS ≤ 2 cm², critical MS ≤ 1 cm²).

- **Cardiac Catheterization:**
  - Not necessary to confirm diagnosis of MS, but can assist in assessing valve area and checking for the presence of mitral regurg, pulmonary HTN, or coronary artery disease.

Treatment:

- **Medications:**
  - **Prophylaxis against recurrent ARF in young patients.**
  - **Prophylaxis against infective endocarditis in all patients.**
  - Diuretics used to treat symptoms of vascular congestion.
  - Digoxin useful only if MS is accompanied by impaired LV contractile function or atrial fibrillation (it can slow the heart rate).
  - β-blockers or calcium channel antagonists may be useful to slow the heart rate.
  - Anticoagulant therapy is given to patients with MS and associated atrial fibrillation to prevent thromboembolism.

- **Mechanical correction (if meds don’t work):**
  - **Percutaneous balloon mitral valvuloplasty:** balloon catheter from femoral vein into the RA, through the atrial septum, into the mitral valve where the balloon is rapidly inflated to “crack” open the fused commissures (this procedure best in absence of complications such as MR, extensive calcification, or atrial thrombus). Better outcome than surgeries.
  - **Open mitral commissurotomy:** surgery – the stenotic commissures are separated under direct visualization.
  - **Mitral valve replacement:** only for severe disease – has a 1-2% perioperative mortality, but a 10 year survival rate exceeding 80%.
Regurgitant Atrioventricular Valve Disease

Mitral Regurgitation (MR)

Clinical Presentation: (most common valvular disease on a daily basis in clinics)
- Patients w/ acute MR usually present with symptoms of pulmonary edema (fluid accumulation and swelling in the lungs), such as: severe dyspnea, anxiety while struggling to breathe, tachycardia, cold & clammy skin (due to peripheral vasoconstriction from inc. sympathetic outflow), tachypnea, coughing “frothy” sputum, lung base rales.
- The symptoms of chronic MR are due to low cardiac output. Symptoms: fatigue and weakness on exertion.
- Patients w/ severe MR or those who develop LV contractile dysfunction may complain of: dyspnea, orthopnea (inability to breathe easily unless one is sitting up or standing), paroxysmal nocturnal dyspnea (awakening suddenly during the night feeling short of breath) – these patients may also have symptoms of right heart failure (increased abdominal girth, peripheral edema).

Physical Exam:
- Typical findings:
  - Auscultation: widely split S2 and apical holosystolic murmur (radiates to axilla) – note that some more rare subtypes of MR have alternate best-auscultation areas that can be confused with an Aortic Stenosis murmur.
  - 2 exceptions to holo-systolic murmur: 1/ Acute Severe MR = early systolic, 2/ mild MR = late systolic
  - To insure that the murmur is due to MR, have patient clench fists. As systemic vascular resistance rises, severity of the MR murmur will intensify.
  - Can also note the effect of varying cardiac cycle length (in pt w/ A. fib or freq premature beats) on the murmur: MR murmur does not vary significantly, but AS murmur intensifies after long cycles.
  - Auscultation also commonly reveals an S3, reflecting increased volume returning to the LV in early diastole.
  - Palpation: often reveals a laterally displaced apical impulse due to LV enlargement.

Etiology:
- MR may result from structural abnormalities of the mitral annulus, valve leaflets, chordae tendinae, or papillary muscles (all these structures must act in a coordinated fashion for normal closure to take place).
  - Myxomatous degeneration of the valve is called mitral valve prolapse (see next outline).
  - Ischemic heart disease can harm the papillary muscles.
  - Infective endocarditis can cause leaflet perforation or chordae rupture.
  - Can have primary rupture of the chordae – gives acute, severe valve incompetence.
  - Rheumatic fever can cause MR if shortening of chordae and retraction of leaflets occurs.
  - Hypertrophic cardiomyopathy (HCM) causes abnormal motion in the anterior mitral leaflet, causing MR in 50% of HCM patients.
  - Marked LV enlargement results in MR due to either 1/ spatial separation of papillary muscles or 2/ mitral annulus stretching to a larger diameter.
  - Calcification of the annulus can come with normal aging (common w/ HTN or aortic stenosis).

Pathophysiology:
- In MR, part of the LV stroke volume is ejected backward into the LA. Thus, the forward cardiac output (CO) is less than the LV’s total output.
- Direct consequences of MR:
  - Elevation of LA volume and pressure
  - Reduction of forward CO into the aorta
  - Volume-related stress on the LV when regurgitated volume returns to the LV in diastole along with the normal pulmonary venous return
- According to Frank-Starling, inc LV volume ⇒ inc myofiber stretch and inc stroke volume w/ each contraction.
- Severity of MR and ratio of forward/backward flow determined by 5 factors:
  1. size of mitral orifice during regurgitation
  2. systolic pressure gradient between the LV and the LA
  3. systemic vascular resistance opposing forward LV blood flow
  4. LA compliance
  5. duration of regurgitation with each systolic contraction
  - also see inc in pulmonary artery and right heart pressures to push flow forward through heart

Pathophysiology continued below…
Pathophysiology continued...

- regurgitant fraction = \[ \frac{\text{Volume of MR}}{\text{Total LV stroke volume}} \]
  - ratio rises when the resistance to aortic outflow is increased

- Extent to which LA pressure rises in response to regurgitated volume is determined by LA compliance.

- **Acute MR**: ex: caused by sudden rupture of chordae tendineae
  - LA compliance undergoes little change, so have a stiff chamber that causes great inc in LA pressure along with the inc in LA volume. Inc pressure helps prevent further regurgitation, but it is also transmitted to the pulmonary circulation...resulting in **rapid pulmonary congestion and edema**.
  - Measure LA pressure in acute MR and see a prominent “v” wave, which shows the increased LA filling during systole...

- **Chronic MR**: gradual development allows for LA to undergo compensatory changes to lessen the effects of regurgitation on the pulmonary circulation.
  - LA dilate to accommodate larger volumes without inc in pressure.
  - Get inadequate forward cardiac output because the **LA becomes a low pressure sink** for LV ejection compared to the high pressure aorta.
  - Main symptoms of chronic MR are those of **decreased forward CO** – fatigue and weakness
  - LA enlargement predisposes to atrial fibrillation
  - LV undergoes gradual compensatory dilatation (eccentric hypertrophy – hypertrophy of wall with dilatation of cavity) in response to volume load
  - Forward output preserved to near-normal through Frank-Starling mechanism (maintaining high SV).
  - Over time, chronic volume overload results in poor LV systolic function and poor forward CO → symptoms of heart failure.

**Summary Table for Acute vs. Chronic MR:**

<table>
<thead>
<tr>
<th></th>
<th>Acute MR</th>
<th>Chronic MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA size</td>
<td>normal</td>
<td>increased</td>
</tr>
<tr>
<td>LA compliance</td>
<td>normal</td>
<td>increased</td>
</tr>
<tr>
<td>LA pressure</td>
<td>high</td>
<td>close-to-normal</td>
</tr>
<tr>
<td>pulmonary venous pressure</td>
<td>high</td>
<td>normal</td>
</tr>
<tr>
<td>major complication</td>
<td>pulmonary congestion</td>
<td>low forward cardiac output</td>
</tr>
</tbody>
</table>

To the right is a Frank-Starling diagram highlighting the relationship between increased venous filling (inc volume and pressure) and stroke volume. This is how the forward CO is preserved in Chronic MR in spite of the enlarging LV.

*Figure 1. Frank-Starling mechanism. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (LVEDP) and volume, thereby increasing ventricular preload. This results in an increase in stroke volume (SV). The "normal" operating point is at a LVEDP of ~8 mmHg and a SV of ~70 ml/beat.*
Diagnostic imaging/testing:

- **Chest X-Ray:**
  - In Chronic MR: LV and LA enlargement, calcification of mitral annulus may be seen if it is the cause of MR

- **Electrocardiogram:**
  - Typically shows LA enlargement and signs of LV hypertrophy.

- **Echocardiography:**
  - Can often identify structural cause of MR.
  - Can grade its severity by color Doppler analysis.
  - LV size and function (stroke volume often increased due to Frank-Sterling compensation for the inc. volume)

- **Cardiac Catheterization:**
  - Useful for identifying a coronary ischemic cause and for grading the severity of the MR.

- The characteristic hemodynamic abnormality is a large “v” wave on the pulmonary capillary wedge pressure tracing (this reflects the LA pressure).

Treatment:

- **Aims of treatment are to augment forward CO, reduce regurgitation into the LA, and relieve pulmonary congestion.** Acute MR needs treatment IMMEDIATELY; Chronic MR is a wait and see deal.

- **Medications:**
  - MR w/ heart failure: I.V. diuretics to relieve pulmonary edema, vasodilators to reduce resistance to forward CO
  - In Chronic MR, give oral arteriolar vasodilators to improve forward CO

- **Mechanical correction:**
  - Mitral valve surgery: can have valve replacement or repair…either should be performed before heart failure comes about, but must delay surgery as long as possible due to operative mortality (8-10% for replacement; 2-4% for repair)
    - **Valve replacement:** drawbacks of prosthetic valves – timing for chronic MR replacement is difficult to determine as life with replacement is not always clearly better than the natural history of the disease. 10-year survival rate is 50%. Better for older patients with extensive pathology.
    - **Valve repair:** eliminates many problems due to artificial valves; involves surgical reconstruction of parts of valve responsible for the regurgitation. Postoperative survival rate seems to be better than natural history of MR…allows for earlier surgical intervention. 10-year survival rate is 80%. Better for young patients with myxomatous involvement of the mitral valve.
Mitral Valve Prolapse (MVP)
-aka “floppy” mitral valve, myxomatous mitral valve, or Barlow’s syndrome

Clinical Presentation:
- Usually asymptomatic
- Affected individuals may describe chest pains or palpitations because of associated arrhythmias
- Clinical course of MVP is often benign

- Most common complication: development of gradually progressive mitral regurgitation
- Rare complications:
  - rupture of myxomatous chordae to cause sudden severe regurgitation and pulmonary edema
  - infective endocarditis
  - peripheral emboli due to microthrombus formation behind the billowy valve tissue
  - atrial or ventricular arrhythmias

Physical Exam:
- Typical findings:
  - midsystolic “click”
  - late systolic murmur heard best at the cardiac apex
  - click and murmur are both altered with sudden squatting (click and murmur come later in systole due to increased volume in the LV) and with sudden standing (click and murmur occur earlier in systole due to decreased volume in the LV)

Etiology:
- condition may be inherited as a primary autosomal dominant disorder
- may occur as a part of other connective tissue diseases such as the Marfan or Ehlers-Danlos syndromes
- MVP occurs in about 2.4% of the population and is more common among women, especially those with a lean, thin body type

Pathology:
- Typical path features of MVP are:
  - Enlarged valve leaflets, especially the posterior leaflet
  - Instead of dense collage and elastin matrix, the valvular fibrosa is fragmented and replaced with loose, “myxomatous” connective tissue
  - In severe MVP, may find: elongated or ruptured chordae, annular enlargement, and/or thickened leaflets

Pathophysiology:
- The midsystolic click likely corresponds to sudden tensing of the involved mitral leaflet or chordae tendinae as the leaflet is forced back toward the LA.
- Late systolic murmur corresponds to regurgitant flow through the incompetent valve.

Diagnostic imaging/testing:
- Echocardiography:
  - Used to confirm diagnosis by demonstrating posterior displacement of one or both mitral leaflets into the LA during systole.
- Electrocardiogram & Chest X-Ray:
  - Usually normal (unless chronic MR has led to LA and LV enlargement).

Treatment:
- Reassure the patient about the usually good prognosis for MVP.
- Antibiotic prophylaxis for endocarditis, but only if substantial valve thickening or MR are present.
Stenotic Semilunar Valve Disease

Pulmonic Stenosis (PS)

Clinical Presentation:
- Only PS with moderate to severe gradients are symptomatic.
- PS patients live a normal life and have no real complications.

Physical Exam:
- Typical findings:
  - Auscultation: Pulmonic ejection sound at the pulmonic auscultatory area; becomes less obvious during inspiration and is very obvious during expiration (unusual for a pulmonic sound).
  - More severe PS gives wider S₂ split.
  - As with A₂, the worse the stenosis gets, the less likely you are to get/hear a P₂ sound – with to much stenosis, valve won’t even close to generate a sound.
  - Palpation: precordial heave or palpable impulse from the RV may be felt at the left lower sternal border, suggesting moderately severe to severe PS. In the left upper sternal border (2nd intercostals space), a systolic thrill may be palpable.

Etiology:
- PS is rare and it is almost always due to congenital deformity of the valve.
- Calcific valvular changes cause progression to PS.
- As with AS, PS has three possible types of congenital deformities of the valve:
  - 1/ Congenitally malformed valve
  - 2/ Subvalvular PS
  - 3/ Supravalvular PS

Pathophysiology:
- Pressure gradients between the RV and the pulmonary outflow tract determine the severity of the PS:
  - mild PS cases: gradient < 40 mmHg
  - moderate PS: gradient of 40 – 80 mmHg (may be symptomatic)
  - severe PS: gradient > 80 mmHg (symptomatic)

Diagnostic imaging/testing:
- Electrocardiogram:
  - Can show increased QRS voltage in V1, inverted T waves also over the right precordium
  - Can show RV hypertrophy by axis deviation – depending on the severity of the PS
- Chest X-ray:
  - with angiogram…see doming of the pulmonic valve.
  - Concentric hypertrophy of right heart, so no real heart size change seen.
  - May see a little bit of encroachment of the right ventricle on the mediastinal air space

Treatment:
- Cardiac Catheterization:
  - Transcatheter balloon valvuloplasty is usually effective therapy for patients with severe or symptomatic PS.
Regurgitant Semilunar Valve Disease

Pulmonic Regurgitation (PR)

Clinical Presentation: (most of these occur in patients with any cause of right-sided heart failure)
- Dyspnea on exertion is most common
- Easy fatigability
- light-headedness
- peripheral edema
- chest pain
- palpitations
- syncope
- Note: In more advanced presentations of right-sided heart failure, abdominal distension secondary to ascites, right upper quadrant pain secondary to hepatic distension, and early satiety may occur.

Physical Exam:
Typical findings:
- **Auscultation:**
  - High-pitched *decrescendo murmur* along the left sternal border – often indistinguishable from AR
  - In pulmonary hypertension with PR, P₂ is accentuated – with increased RV end-diastolic volume, ejection time is increased, P₂ is delayed, and S₂ split is widened.
- **Jugular venous pressure:** usually increased; increased “a” wave is often present
- **Palpation:** RV systolic pulsation sometimes noted at the left lower sternal border due to RV enlargement; palpable pulmonary artery pulsation at left upper sternal border if patient has significant pulmonary artery dilatation

Etiology:
- PR most commonly develops in setting of severe pulmonary hypertension and results from dilatation of the valve ring by the enlarged pulmonary artery.

Pathophysiology:
- Incompetence of the pulmonic valve occurs is caused three pathologic processes:
  1. dilatation of the pulmonic valve ring
  2. acquired alteration of pulmonic valve cusp morphology
  3. congenital absence or malformation

Diagnostic imaging/testing:
- **Chest X-Ray:**
  - If have PR with pulmonary hypertension, can see: prominent central pulmonary arteries w/ enlarged hilar vessels and loss of vascularity in peripheral lung fields ("pruning")
- **Echocardiography:** Doppler echocardiography can easily identify between AR and PR – as their murmurs sound the same and can be indistinguishable.
- **Electrocardiogram:** may show right axis deviation due to RVH; can also show RA dilation if back-up is happening

Treatment:
- PR seldom severe enough to warrant special treatment because RV normally adapts to low-pressure volume overload without difficulty.
Stenotic Atrioventricular Valve Disease

Tricuspid Stenosis (TS)

Clinical Presentation:
- Can be similar to the symptoms of MS...please refer back to the clinical presentation for MS.
- Note: TS and MS can be coexisting due to rheumatic heart disease.

Physical Exam:
- Typical findings:
  - auscultation: similar to MS...hear an “opening snap” (OS) after $S_2$; OS followed by low-frequency decrescendo diastolic murmur – the murmur of TS is heard closer to the sternum and intensifies on inspiration due to increased right heart blood flow (more volume over stenosis = louder murmur)
  - jugular venous pulse: neck waves are distended with a large “a” wave due to RA contraction against the stenotic tricuspid valve orifice

Pathology:
- Typical path features of rheumatic TS come from acute and recurrent inflammation – like with MS, get fibrous thickening, calcification of valve leaflets, fusion of valve commissures, and thickening and shortening of the chordae tendineae.

Etiology:
- TS is rare and usually a consequence of rheumatic heart disease.

Treatment:
- Mechanical correction
  - Surgical therapy usually required – either valvuloplasty or valve replacement.
Regurgitant Atrioventricular Valve Disease

Tricuspid Regurgitation (TR)

### Clinical Presentation:
- In absence of pulmonary hypertension, **TR is usually asymptomatic**.
- If pulmonary hypertension and moderate-to-severe tricuspid regurgitation coexist, symptoms may include:
  - active jugular vein pulsations
  - swelling of abdomen
  - edema
  - fatigue
  - weakness

### Physical Exam:
- Typical findings:
  - Auscultation: **systolic murmur** heard at lower left sternal border – soft but becomes **louder on inspiration**
  - Jugular venous pulse: **prominent “v” waves**

  ![Tricuspid Regurgitation](image)

  - Can also have a pulsatile liver because of regurgitation of the RV blood into the systemic veins.

### Etiology:
- TR usually “**functional”** rather than structural in that it **usually develops secondary to right ventricular enlargement**.
- In patients with rheumatic mitral stenosis, **20% have significant TR**.
  - Of that 20%:
    - 80% have “**functional”** TR due to pulmonary hypertension w/ RV enlargement
    - the other 20% have “**organic”** TR due to rheumatic involvement of the tricuspid valve
- Risk factor for TR is use of the diet medications called "Phen- fen" (phentermine and fenfluramine) or dexfenfluramine.

### Diagnostic imaging/testing:
- **Echocardiography**:
  - Doppler echo is sensitive for the detection and quantification of TR.

### Treatment:
- Primary therapy for functional TR is directed at the conditions responsible for elevated RV size/pressure.
- Diuretic therapy
- Surgical repair of valve is indicated in severe cases.
Atherosclerosis
Chapter 5, pp.111-129

**Definition:** “hardening of the arteries” as a result of the abnormal accumulation of lipids, cells, and ECM within the arterial wall, creating lesions known as atherosclerotic (fibrous) plaques.

- The formation of plaques can result in:
  - Stenosis or narrowing of the arteries
  - Rupture, which may then lead to thrombosis

*Note that in either event, that blood supply to tissues is limited, resulting in major complications like angina, MI, stroke, and/or impaired blood flow to the kidneys and lower body—thus, atherosclerosis is the leading cause of morbidity & mortality in the U.S.*

The following is a brief review of the normal arterial wall and its constituents...

**Arteries:** Consist of 3 layers (intima, media, & adventitia) that all play a role in the development of atherosclerosis

- **Intima**
  - Innermost layer, most “intimate” with the blood
  - Single layer of endothelial cells
  - Metabolically active barrier between the blood and vessel

- **Media**
  - Middle layer separated from the intima and adventitia by the internal & external elastic laminae respectively
  - Mostly SMCs with some ECM (produced by the SMCs)
  - Contractile (esp. small arteries & arterioles) → alterations in Resistance & Flow

*Recall: \( Q = \frac{P}{R} \) (Q=Flow; P=Pressure; R=Resistance)

  - Elastic (esp. large arteries like the aorta) → forward propulsion of blood

- **Adventitia**
  - Outermost layer
  - Has blood vessels (vasa vasorum), nerves & lymphatics that nourish the vessel
1. Identify the risk factors for atherosclerosis and their role in the pathogenesis of atherosclerosis

Major, potentially modifiable risk factors include the following:

- Dyslipidemia
- Hypertension
- Smoking
- Diabetes Mellitus
- Obesity
- Low levels of physical activity

**Dyslipidemia**

- Refers to abnormal circulating lipid levels
- Higher levels of total serum cholesterol & LDL → increased risk of atherosclerosis and ischemic heart disease...thus, LDL is often termed the “bad cholesterol.”
- Elevated LDL may result from diets high in saturated fat or genetics defects in the LDL receptor (familial hypercholesterolemia).
- All cholesterol-carrying lipoproteins aren’t harmful, though as HDL helps to transport excess cholesterol back to the liver (reverse cholesterol transport)...thus HDL is commonly known as “good cholesterol” since it protects against lipid accumulation.

**Tobacco Smoking**

- Studies have shown that smoking (in even minimal amounts) is correlated with an increased risk for atherosclerosis & ischemic heart disease.
- Fortunately, smoking cessation can reverse tobacco’s adverse effects and lower the risk for disease.
- Contributions to the development of atherosclerosis include:
  - Enhanced modification of LDL
  - Decreased levels of HDL
  - Tissue hypoxia & increased oxidant stress → endothelial dysfunction
  - Increased WBC adhesion molecules & other inflammatory markers
  - Inappropriate stimulation of the sympathetic NS via nicotine
  - Oxygen displacement from Hb by CO

**Hypertension**

- Elevated BP increases ones risk of developing atherosclerosis, coronary heart disease, and stroke
- Especially in the elderly, the higher the systolic pressure (since it predicts adverse events more reliably than diastolic pressure), the higher the risk
• **Contributions to the development of atherosclerosis include:**

  o Creating injury to the endothelium and increasing its permeability to lipoproteins
  o Increased numbers of scavenger receptors on macrophages, thus enhancing the formation of foam cells
  o Increased production of proteoglycans by the SMCs → accumulation of modified LDL
  o Promotion of inflammation via the presence of Angiotensin II, which serves as both a mediator of hypertension and as a proinflammatory cytokine.

**Diabetes Mellitus**

• Diabetics have a 3 to 5-fold increased risk of suffering cardiovascular events

• **Contributions to the development of atherosclerosis include:**

  o Non-enzymatic glycation of lipoproteins in diabetic patients → enhanced cholesterol uptake by macrophages
  o Prothrombotic or anti-fibrinolytic states common in diabetes
  o Impaired endothelial function as evidenced by low levels of NO & increased WBC adhesion

*Recall that diabetes (particularly insulin-resistant), dyslipidemia, obesity, and hypertension are all part of the “Metabolic Syndrome,” a condition that predisposes one to atherosclerosis.*

**Physical Activity**

• Low levels of physical activity correlate with obesity and an increased risk for cardiovascular events

• **Contributions to lowering the risk of atherosclerosis include:**

  o Improvements in the lipid profile
  o Improvements in blood pressure
  o Enhancement of insulin sensitivity
  o Increased production of NO by endothelial cells

**Major, nonmodifiable risk factors include the following:**

• Advanced age
• Male gender
• History of coronary disease among family members of a young age (specifically, males >55 years and/or females >65 years)
• Estrogen status
**Estrogen Status**

- Prior to menopause women have a lower incidence of coronary events compared to men.
- After menopause however, the risk is similar, suggesting a potentially atheroprotective property of estrogen...

**Other, “new” risk factors (note that these are still under evaluation) include the following:**

- Homocysteine
- Lipoprotein (a)
- C-reactive protein
- Infection

**Homocysteine**

- Abnormally high amounts (hyperhomocysteinemia) may promote thrombosis
- Hyperhomocysteinemia may result from:
  - Genetic defects in methionine metabolism
  - Insufficient dietary intake of folic acid

**Lipoprotein (a)**

- Associated with Apo(a), which structurally resembles the plasma protein plasminogen, which plays a role in the lysis of fibrin plots.

**C-reactive protein (CRP)**

- Marker of inflammation produced by the liver upon stimulation via IL-6; thus, CRP is thought to be a marker of low-grade systemic inflammation associated with atherosclerosis.
- May also be a mediator of atherogenesis as it has the ability to activate complement → inflammation

**Infection**

- Infectious agents like C. pneumoniae and Herpes have been detected in atherosclerotic lesions
2. *Describe the pathological lesion of atherosclerosis in the arterial wall*

*Considered a chronic, inflammatory process, atherogenesis (the formation of an atherosclerotic fibrous plaque) involves 3 key steps:*

1. Accumulation of lipids within the intima
2. Recruitment of WBCs and SMCs to the vessel wall
3. ECM deposition

1. **For lipids to accumulate in the intimal layer there must be some sort of breakdown in endothelial function.**

*Refer to Table 5.1 (p. 113) for a good compare/contrast of normal vs. abnormal endothelial function!*

**Factors causing endothelial dysfunction:**

- *Physical Forces:* These are typically created in arterial branch points, where laminar flow is disrupted. As a compensatory mechanism, the endothelium will typically express enzymes responsible for production of NO and superoxide dismutase, whose normal, atheroprotective function is subsequently altered as a result of the disturbed flow.

- *Toxic chemical environment exposure:* This includes smoking, dyslipidemia, and diabetes. These states, among other things, may lead to an increase in the production of reactive oxygen species by endothelial cells.

*In general, these factors can lead to endothelial dysfunction by:*

- Impairing the endothelial permeability barrier function
- Release of inflammatory cytokines by the endothelium
- Increased expression of WBC adhesion molecules
- Aberrant release of vasoactive chemicals (ie. prostacyclin & NO)
- Interference with endothelial antithrombotic properties

*With the endothelium no longer serving as an effective barrier, lipoproteins like LDL (transporters of fat in the blood) are able to penetrate the intima and accumulate in the subendothelial space.*

*LDL undergoes biochemical modifications (ie. oxidation) → mLDL*

*mLDL has major consequences that include:*

- Recruitment of monocytes to the vessel wall
- Increased endothelial expression of inflammatory mediators (ie. M-CSF)
- Ingestion of mLDL by macrophages via scavenger receptors → foam cells*
* Note that normally the intake of LDL is via LDL receptors on hepatic cells via negative feedback inhibition...however, because mLDL can’t be taken up by these receptors (LDL receptors), they’re taken up via scavenger receptors on macrophages which aren’t limited by negative feedback \( \rightarrow \text{foam cells} \)

2. After entry and modification of LDL, WBCs and SMCs migrate to the vessel wall where they contribute to the formation of the fibrous plaque.

**WBC Recruitment**

- WBCs (monocytes & T cells) are recruited as a result of:
  - Natural chemoattractant properties of mLDL
  - Expression of specific cytokines by the endothelium
  - Expression of WBC adhesion molecules on the surface of the injured endothelium, including ICAM-1 & VCAM-1

* Note that mLDL also helps to stimulate ICAM-1 & VCAM-1 expression, illustrating how lipid accumulation helps to promote subsequent inflammation.

- Once monocytes adhere, penetrate through, and are localized in the subendothelial space, they differentiate into macrophages.
- The macrophages engulf the mLDL and become foam cells, the main constituent of the fatty streak.

**Fatty Streak**

- Represents the earliest visible atherosclerotic lesion
- Appears as yellow discoloration along the arterial surface
- Does not protrude into the lumen and thus does not disturb blood flow
- Present in most individuals by age 20
- Asymptomatic
- May regress over time in some locations with exception of the coronary arteries, where they develop into fibrous plaques

- Although T cells represent only a fraction of the cells within the lesion, their activation typically results in the release of inflammatory cytokines.

**SMC Recruitment**

- SMCs normally found in the media layer migrate to the intima, undergo proliferation, and produce ECM material.
This process is mediated by substances secreted by foam cells, activated platelets, and endothelial cells. Examples of this include:

- **PDGF**, which is secreted by foam cells and helps to stimulate the migration of SMCs into the subendothelial space.
- **Cytokines (ie. TNF-α, IL-1, TGF-b)**, which are secreted by foam cells and along with activating WBCs, induces SMC proliferation and ECM protein synthesis.

*Altogether, it is the migration of SMCs from the media to the intima, the accumulation of WBCs and foam cells, and the formation of the ECM-derived fibrous cap that generates the **fibrous plaque** characteristic of advanced atherosclerosis.

**Fibrous Plaque**

- Localized in the same sites as fatty streaks
- Appear as firm, gray lesions
- May project into the lumen, and if large enough, create a significant stenosis or obstruction to blood flow
- Has a necrotic core of cellular debris, as a result of the toxic effects of mLDL and of free oxygen radicals & hydrolytic enzymes derived from foam cells and T cells
- Thrombogenic due to its necrotic core. This is attributed to:
  - Production of TF by foam cells → activation of coagulation
  - Release of PDGF by activated platelets → degradation of heparin sulfate, a compound normally involved in the inhibition of SMC migration and proliferation.

3. **Differentiate the clinical presentation and pathophysiology of coronary artery stenosis from coronary artery thrombosis**

...So, I couldn’t find any specifics in the book about this nor was there anything specific in the powerpoint lectures...I’ll email Dr. Smith for key points and get back to you...
**Acute Coronary Syndromes**  
Chapter 7, pp. 157-184

**Definition**: life-threatening conditions that punctuate the course of CAD at any time.

- Encompass a continuum ranging from unstable angina (UA) to the most severe form of acute MI (STEMI)
- In >90% of the time they all have the same underlying pathophysiology:

  Atherosclerotic plaque disruption → platelet aggregation → intracoronary thrombus formation

- Thrombus formation is the result of interactions b/t the plaque, endothelium, circulating platelets, & vasomotor tone of the vessel wall
- The thrombus transforms an original region of stenosis or narrowing into a region of complete coronary obstruction
- The result is impaired blood flow through the coronary artery → imbalance b/t myocardial O₂ supply and demand
- The type of ACS that results is dependent upon the degree of obstruction

  - *Partial* → UA & Non-ST elevation or non-Q wave MI (NSTEMI)  
    (These are distinguished based on the presence of myocardial necrosis)

  - *Complete or near complete* → ST elevation or Q wave MI (STEMI)  
    (Characterized by severe ischemia & myocardial necrosis)

**Pathogenesis of Coronary Thrombosis**

- Normally, mechanisms are in place to prevent spontaneous thrombus formation...However, in the presence of atherosclerotic lesions, these may be overwhelmed → coronary thrombus formation
- Atherosclerosis contributes to thrombus formation by:

  - *Plaque rupture* → exposure of prothrombotic substances
  - *Endothelial dysfunction* → loss of protective, antithrombotic & vasodilatory properties

**Plaque Rupture**

- Considered the **major trigger** of coronary thrombosis
- Underlying causes include:

  - Circulating chemical factors (inflammatory cytokines) → increased vulnerability of the plaque to rupture
• Substances released from WBCs within the plaque itself that impair the integrity of the fibrous cap surrounding the plaque
• Physical stresses (ie. physical activity or emotional stress) \( \rightarrow \) activation of the Sympathetic NS \( \rightarrow \) increases in HR, BP, & contractility \( \rightarrow \) plaque rupture

*Note that most MIs occur in the morning because many of these stressors (ie. systolic BP, circulating epinephrine, & blood viscosity) are elevated during this time of the day.

• Upon rupture, thrombus formation is triggered by:
  • Intraplaque hemorrhage \( \rightarrow \) vessel lumen narrowing
  • Turbulent blood flow \( \rightarrow \) platelet activation
  • Release of TF \( \rightarrow \) activation of coagulation (it’s VIIa’s cofactor!)
  • Exposure of subendothelial collagen \( \rightarrow \) platelet activation

  *Platelet activation* \( \rightarrow \) release of granular contents:
  • Facilitators of platelet aggregation (ie. ADP & fibrinogen)
  • Activators of coagulation (ie. Va)
  • Vasoconstrictors (ie. TXA₂ & serotonin)

*Dysfunctional Endothelium*

• Platelet-associated vascular response is impaired \( \rightarrow \) less release of NO & prostacyclins \( \rightarrow \) less vasodilatation & less inhibition of platelet aggregation
• Unopposed vasoconstriction (mediated by platelet-derived TXA₂ & serotonin and thrombin within the forming clot) \( \rightarrow \) thrombus formation

*REFER TO FIGURE 7.3 (p. 160) FOR A SCHEMATIC OF THIS!!!*

**Consequences of Coronary Thrombosis (what type of ACS to expect)**

• Dependent upon the size and the extent of thrombus occlusion
  • *Small:* Typically non-occlusive & self-limited; may grow into the growing atheromatous plaque, resulting in its enlargement; does NOT result in ECG changes
  • *Larger, Partially occlusive OR Transiently Totally Occlusive:* Characterized by ST depression &/or inverted T waves (no Q waves!); typical outcomes are either UA or NSTEMI, which are distinguished from each other by the presence of myocardial necrosis (positive serum biomarkers for NSTEMI & negative for UA)
  • *Larger, Totally Occlusive:* Characterized by ST elevation (w/Q waves developing later) & positive for serum biomarkers
Transient total occlusive thrombi are the result of spontaneous recanalization or vasospasm.

*REFER TO FIGURE 7.4 (p. 162) FOR A SCHEMATIC OF THIS!!*

**Non-Atherosclerotic causes of ACS**

- Rarely mechanisms other than intracoronary thrombus formation can cause ACS
- Suspect these in young children presenting with ischemic syndrome or in those without risk factors for CAD
- Potential causes include:
  - Thromboemboli from mechanical or infected valves
  - Valvulitis → coronary occlusion
  - Intense transient vasospasms
  - Cocaine abuse → blocks Uptake I of NE → accumulation of NE → intense vasospasms, increased HR, contractility, & BP

**Pathology & Pathophysiology of MI**

- MIs (both STEMI & NSTEMI) result when there's sufficient ischemia to cause necrosis
- UA can also lead to necrosis if its underlying cause isn't corrected
- Defined by the extent of necrosis they produce in the myocardial wall:
  - Transmural: spans the entire wall thickness; results from complete or prolonged occlusion of an epicardial artery
  - Subendocardial: involves only the innermost layers of myocardium; subendocardium is the most vulnerable to ischemia because it's:
    - Subjected to the highest ventricular pressures
    - Has few collateral vessels to help perfuse it
    - Perfused by vessels that must pass through the contracting wall
Lists taken from Dr. Smith’s lecture...

• **Subendocardial**
  
  – Inner 1/3 to 1/2 of LV wall is occluded
  – Multifocal, patchy (distributed throughout the LV)
  – Circumferential
  – Coronary thrombosis rare
  – Often result of shock
  – No epicarditis
  – Do not form aneurysms

• **Transmural**
  
  – Full thickness of the wall is occluded
  – Unifocal, solid
  – Coronary artery distribution
  – Coronary thrombosis common
  – Often cause of shock
  – Epicarditis common since it’s a full thickness infarct
  – May result in aneurysm
  – Volume of collateral flow is the main factor in transmural infarct progression

• Infarctions represent the progression from potentially reversible ischemia → irreversible myocardial necrosis

• Tissues supplied directly by the infarcted artery die first, then surrounding tissues if the imbalance b/t myocardial O₂ supply & demand isn’t fixed

• Infarcts involving the LV are more common & more extensive than the RV since the myocardium is thicker and thus harder to perfuse.

• The magnitude of the infarction depends on:
  
  • Amount of myocardium supplied by the occluded vessel
  • Magnitude & duration of obstruction
  • Oxygen demand of the affected region
  • Ability of collateral blood flow to supply the affected region
  • Degree of tissue response to modify the ischemia
**Early Changes** (changes occurring at the time of acute infarction)

- **Cellular Changes**: As myocardial O₂ levels fall:
  - Shift in aerobic → anaerobic metabolism
  - Inability to oxidize fats & products of glycolysis
  - Accumulation of lactic acid → low intracellular pH
  - Decreased production of ATP

*These events all lead to impaired function myocytes as:

Decreased ATP → impaired Na/K ATPase activity → increased intracellular [Na] & Extracellular [K] → altered membrane potential → **arrhythmias**

Increased intracellular [Na] → impaired Na/Ca exchanger activity → increased intracellular [Ca] → intracellular edema → **wavy myofibers**

Increased intracellular [Ca] → activation of proteases & lipases → **cell death** & release of serum biomarkers

- Decreases in myocardial function can occur as soon as 2 minutes following occlusive thrombosis
- Without intervention, irreversible cell injury can occur within 20 minutes as indicated by membrane defects
- Proteases & lipases leak across the altered membrane causing more damage and the subsequent release of serum biomarkers (of infarction)

*Taken from Dr. Smith’s lecture...*

**Microscopic Features of Infarction**

- <4 hours - None, variable wavy fibers at border
- 4-12 hours - Early ischemic necrosis, edema, hemorrhage
- 12-24 hours - Coagulative necrosis, nuclear pyknosis, hypereosinophilia, contraction band necrosis, early PMNs
- 1-3 days - Loss of nuclei and striations, interstitial PMNs
- 3-7 days - Early disintegration of dead myocytes, dying PMNs, macrophages at border
- 7-10 days - Phagocytosis of dead cells, early granulation tissue at margins
- 10-14 days - Granulation tissue, new vessels, collagen
- 2-8 weeks - Gradual loss of cellularity, increasing collagen
- >2 months - Dense collagenous scar
Macroscopic Features of Infarction

- <4 hours - No abnormality
- 4-12 hours - Occasional dark mottling
- 12-24 hours - Dark mottling
- 1-3 days - Mottling with yellow-tan necrotic center
- 3-7 days - Central yellow-tan softening with hyperemic border
- 7-10 days - Maximally yellow-tan and soft, depressed red-tan borders
- 10-14 days - Red-gray, depressed borders
- 2-8 weeks - Gray-white scar, progressive from border to core of infarct
- >2 months - Mature scar

Late Changes

- Characterized by 2 steps:
  - Removal of necrotic myocytes by macrophages (**yellow softening**)
  - Deposition of collagen → fibrous scar

- **Yellow Softening**: since irreversibly injured myocytes do NOT regenerate, they’re cleared by macrophages...this is a type of tissue reabsorption that for leaves the thin, dilated infarcted area susceptible for rupture for some time until fibrosis & scarring is complete

Functional Changes

- **Impaired ventricular contraction**: AKA “ventricular systolic dysfunction”; CO is compromised b/c of loss of synchronous myocyte contraction

- **Impaired ventricular compliance**: AKA “ventricular diastolic dysfunction”; results in elevated ventricular filling pressures

- **Stunned Myocardium**: transient prolonged periods of ventricular systolic dysfunction that’s gradually recovered over time b/c of restored blood flow; seen in UA & regions adjacent to areas of acute MI

- **Ischemic Preconditioning**: brief ischemic insults to a region of myocardium may allow it to be resistant to subsequent bouts of ischemia; possibly due to the expression of adenosine receptors

  *Clinical significance: patients who survive an MI with anginal symptoms will have less morbidity & mortality that those without angina
• **Ventricular Remodeling**: involves ventricular expansion (dilation) of both the infarcted and non-infarcted areas to increase CO; however, this bad b/c it can lead to:
  - Increased wall stress (Remember: Wall Stress = $P\cdot r/2h$)
  - Increased susceptibility to wall rupture
  - Heart failure
  - Ventricular arrhythmias

**Clinical Features of ACS**

Because ACS encompass a continuum, there’s overlap in their clinical features. Since they result in different outcomes and warrant different therapies, distinctions are made based on:

1. Clinical Presentation
2. ECG findings
3. Presence of serum biomarkers of myocardial necrosis

*The most important distinction to be made is b/t ACS that causes ST elevation (STEMI) from those that do not (NSTEMI & UA)!

**Unstable Angina**

*Please refer to Noel's Review on Ischemic Heart Diseases...although I have yet to go over those notes, there's no doubt in my mind that she's done a fantabulous job with that section! 😊*

• Presents in 1 of 3 ways:
  - Increase in frequency, duration, & intensity of ischemic episodes in a person with chronic, stable angina
  - Angina that occurs @ rest
  - New onset angina occurring in a person with no previous history of CAD

• Although not as severe, UA can progress to STEMI & NSTEMI if left untreated
Acute MI

- **Signs & Symptoms**

  * **Characteristic pain:**

    - Result of NO & adenosine’s actions on afferent nerve endings
    - Resembles angina qualitatively, but is more severe, longer in duration, & radiates more widely
    - Doesn’t wane with rest
    - Responds very little to sublingual nitroglycerin
    - Referred to the C7-T4 dermatome regions → referred pain to the neck, shoulders, & arms
    - May elicit a “feeling of doom”

  *Note however, that 25% of patients may be asymptomatic...this is especially common among diabetics with peripheral neuropathy*

  * **Sympathetic effect:**

    - Result of pain & baroreceptor unloading (if hypotension is present)
    - Cool, clammy skin (b/c of vasoconstriction)
    - Diaphoresis (AKA “sweating”)
    - Tachycardia

  * **Parasympathetic effect:**

    - Nausea & vomiting
    - Weakness

  * **LV systolic & diastolic dysfunction** → impaired contractility → reduced SV → increased LVEDV & LVEDP → LA backflow → pulmonary venous backflow → pulmonary congestion → decreased lung compliance → J receptor activation → rapid, shallow breathing & feelings of dyspnea

  * **Physical Exam Findings:**

    - S4 because of LA contraction into a stiffened LV
    - S3 because of volume overload & possible MR (b/c of LV hypertrophy)
    - Pansystolic (Holosystolic) murmur b/c of resulting MR or VSD
    - Pericardial friction rub b/c of resulting pericarditis

  *Note however, that all patients presenting with chest pain won’t have UA or an acute MI! You must be aware of such conditions and their differentiating features! REFER TO TABLE 7.4 (p. 169)*
Inflammatory Response: release of IL-1 & TNF from macrophages & endothelial cells in response to tissue injury

- **Diagnosis of ACS**

_A similar table can be seen on p. 170, Table 7.5_

*Key Features:* Aside from the differences detected at clinical presentation,

- UA & NSTEMI are distinguished based on the presence of serum biomarkers for myocardial necrosis
- NSTEMI & STEMI are distinguished based on the detection of ST elevation on the ECG

<table>
<thead>
<tr>
<th>Unstable Angina (UA)</th>
<th>Myocardial Infarction (MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>1) Crescendo from previous chronic, stable angina</td>
<td>Prolonged, “crushing” chest pain that’s more severe, last longer, &amp; radiates more widely than typical angina</td>
</tr>
<tr>
<td>2) Angina at rest</td>
<td></td>
</tr>
<tr>
<td>3) New onset without a previous history of CAD</td>
<td></td>
</tr>
<tr>
<td><strong>Serum Biomarkers</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>ECG initial findings</strong></td>
<td></td>
</tr>
<tr>
<td>ST depression &amp;/or T wave inversion</td>
<td>ST elevation with eventual T wave inversion &amp; late appearing Q waves</td>
</tr>
</tbody>
</table>

**Temporal Sequence of ECG findings for STEMI:**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Acute</th>
<th>Hours</th>
<th>Days</th>
<th>Days Later</th>
<th>Weeks Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Normal ST &amp; T wave</td>
<td>-ST Elevation</td>
<td>-ST Elevation</td>
<td>-ST Elevation</td>
<td>-ST normalizes</td>
<td>-Normal ST &amp; T wave</td>
</tr>
<tr>
<td>-NO Q waves present</td>
<td>-Dimished R wave</td>
<td>-Dimished R wave</td>
<td>-Q wave deepens</td>
<td>-T wave inversion</td>
<td>-T wave inversion</td>
</tr>
<tr>
<td></td>
<td>-Q wave</td>
<td>-Q wave</td>
<td>-T wave inversion</td>
<td>-Q wave</td>
<td>-Q wave</td>
</tr>
</tbody>
</table>
Serum Biomarkers

Myocardial necrosis → defective cell membranes → release of serum biomarkers

- Detection of serum biomarkers serve important diagnostic & prognostic roles
- These are higher than normal in ACS & are released in a specific temporal sequence (Myoglobin then CK-MB & Troponins)

Myoglobin

- Cytosolic, O₂ binding protein of the cardiac & skeletal muscle
- Earliest marker detected (released 2-4 hours after injury)
- Rapidly cleared via the kidneys
- Highly sensitive, but NOT specific since found in cardiac & skeletal muscle
- Of limited diagnostic value
- Improved specificity if combined with Carbonic Anhydrase III tests...however this is very expensive

CK-MB

- CK isoenzyme found mainly in the heart (although found in other places too, including the skeletal muscle, uterus, prostate, gut, etc.)
- Released 3-12 hours after injury
- Has a delayed peaking pattern distinct from other tissues with CK-MB
- Has a sensitivity & specificity similar to Tn (this is increased even more is tested together)
- To distinguish CK-MB released from the heart vs. skeletal muscle, determine the relative index...usually >2.5-5% if there’s myocardial injury

  Relative Index = CK-MB/total CK

Troponins (TnT & TnI)

- Unique TnT & TnI found in the heart vs. skeletal muscle b/c of regulation by different genes → slight, AA variations...Thus, these are considered to be the Gold Standard of biomarkers
- Absent in healthy patients
- Released 3-6 hours after injury (so typically see rising CK-MB & Tn levels)
- Have stability issues...you must get the sample to the lab ASAP!

LDH

- Nonspecific marker
- Peaks 3-5 days after MI
- Great specificity when tested with CK-MB
Serum Biomarker Time Course

Figure “borrowed” from Dr. Hammett-Staber’s lecture...Refer to that for extra info!

Reference ranges and time courses:
Myoglobin (myo): males, 28-72 ng/mL; females, 25-58 ng/mL. Time to increase 2-4 h; time to peak 5-12 h; return to normal 1-2 days

Troponin T (cTnT): <0.03 ng/mL   Time to increase 3-6 h; time to peak 12-28 h; return to normal 5-15 d

Troponin I (cTnI): <0.1 ng/mL.  Time to increase 3-6 h; time to peak 12-24 h; return to normal 5-7 d

CK (total): males, 70-185 U/L; females, 45-145 U/L.  Time to increase 3-8 h; time to peak 12-36 h; return to normal 1-4 d.

CK-MB: <6 ng/mL.  Time to increase 3-12 h; time to peak 12-24 h; return to normal 1-2 d.

Important points:
1. The rise in myoglobin occurs first.
2. Increases in CK-MB and Tn (either I or T) begins at about the same time for most patients.
3. Normally, troponin is not detectable in serum from cardiac healthy patients.
4. TnI and TnT remain elevated for several days to ~2 weeks after an MI. (The biphasic pattern for TnT is thought to reflect the initial release of either a cytosolic or “soluble” fraction followed by the release of the structurally bound fraction.) Should there be a second MI, the levels increase further.
Important Notes:

- Persistent, small increases in Tn and MB are thought to reflect on-going ischemia/injury and should be investigated. Patients with such increases are greater risk of MI or sudden cardiac death within the next 6-9 months.

- The diagnosis of MI may remain uncertain even after taking into account patient history, ECG, & serum biomarkers...to improve certainty, *echocardiography* is done to detect ventricular systolic dysfunction & ischemic/infarcted regions.
**Treatment of ACS**

- Focused on reducing myocardial damage & the risk of complications
- Addresses:
  - Inciting intracoronary thrombus
  - Imbalance b/t myocardial \(O_2\) supply & demand

- Although certain therapeutic aspects are common to all ACS, there’s a critical difference in how STEMI is treated compared to UA & NSTEMI

- General in-hospital measures for ACS include:
  - *Continuous ECG monitoring*—to detect arrhythmias
  - *Bed rest*—to reduce myocardial \(O_2\) demand
  - *Supplemental \(O_2\)*—to improve perfusion & increase \(O_2\) supply
  - *Analgesics (ie. morphine)*—to relieve chest pain & anxiety

**Acute Treatment of UA & NSTEMI**

- Treatment consists of:
  - *Antithrombotic Therapy*—stabilizes the thrombus & prevent its further intrusion into coronary lumen while facilitating its dissolution
  - *Antischemic Therapy*—restores the balance b/t myocardial \(O_2\) supply & demand
  - “*Early Invasive Approaches*”—includes cardiac catherization & coronary revascularization; most beneficial in patients with severe UA & NSTEMI (ie. patients presenting with ST-T deviations at presentation, elevated serum biomarkers, & multiple cardiac risk factors)

**Antithrombotic Therapy (includes anti-platelet & anticoagulants)**

**Anti-platelets**

- *Aspirin*Æ inhibition of TXA\(_2\) synthesis by plateletsÆ inhibition of further platelet activation

- *Thienopyridines (ie. Ticlopine & Clopidogrel)*Æ inhibition of ADP-mediated platelet activation
*Because they block platelet activation & aggregation via 2 different pathways, the combination of the two is better than when used alone. Thienopyridines are also used as a substitute for aspirin if a patient has an aspirin allergy.

*Once initiated, anti-platelet therapy should be continued daily

- **GP IIb-IIIa inhibitors (ie. Eptifibatide, Tirofiban, & Abciximab)**→inhibition of platelet aggregation

*These are especially useful in the high risk cases of UA & NSTEMI

**Anticoagulants**

- **Unfractionated or LMW Heparins**→binding & activation of ATIII→increased potency of ATIII for thrombin→inhibition of thrombin→inhibition of further clot formation

  **OR**

  **Unfractionated or LMW Heparins**→direct inactivation of Xa→inhibition of further clot formation

*LMWH preferentially blocks Xa & is preferred over Unfractionated Heparin as it’s easier to administer, has a predictable bioavailability, & doesn’t require repeated monitoring & dose adjustments (unlike Unfractionated Heparin)

**Antischemic Therapy**

- **Nitrates**→venodilatation→reduced venous return/preload→reduced myocardial O₂ demand

  **OR**

  **Nitrates**→vasodilatation→increased flow to the coronary arteries & reduced likelihood of vasospasms→improved myocardial O₂ supply

- **Beta-Blockers**→reduced sympathetic drive→negative inotrophy & chronotropy, & electrical stability

- **Non-dihydropyridine Ca Channel Blockers**→negative inotrophy & chronotrophy

*Nitrates are particularly useful in those patients with CHF

*Non-dihydropyridines Ca Channel Blockers are used only when Nitrate &/or Beta-Blocker therapy has failed
**Acute Treatment of STEMI**

- Aimed at saving myocardium at risk necrosis via restoring blood flow through occluded coronary artery
- Therapy decisions must be made early to save the most amount of myocardium, often before the appearance of biomarkers of necrosis

**Thrombolytics**

- Accelerates the lysis of the intracoronary thrombus to restore blood flow & limit subsequent myocardial injury
- These are NOT used to treat UA or NSTEMI as they can cause more harm than good
- Rapid initiation is crucial & has a profound effect on mortality rates
- Includes Steptokinase, tPA, rPA, TNK-tPA, etc.

*Thrombolytics* → activation of plasminogen into plasmin → fibrin clot lysis

- *Side effects*: Bleeding due to poor substrate specificity (esp. seen with the older Steptokinase), as a result of fibrinogen lysis
- *Successful reperfusion*: relief of chest pain; normal ST-T waves; earlier than usual peaking of serum biomarkers
- Transient reperfusion arrhythmias may be present, but usually don’t require treatment

**Primary Percutaneous Coronary Intervention**

- Performed in conjunction with cardiac catheterization
- Option for patients with contraindications for thrombolytics
- Has higher rates of coronary reperfusion & survival without bleeding complications
- *Drawbacks*: expensive & limited to hospitals with prior experience

**Antithrombotic & Antischemic Therapies**

- These agents are used to:
  - Maintain patency of the coronary vessel following thrombolysis
  - Restore the balance b/t myocardial O2 supply & demand
  - Relieve chest pain
  - Prevent complications of MI
• Antiplatelets (ie. Aspirin, Thienopyridine, & GP IIb-IIIa antagonists)
• Unfractionated Heparin—given for 1-2 days to prevent thromboembolism in patients with atrial fibrillation, LV thrombus, or large wall motion abnormality (b/c a thrombus can form there)
• Beta-Blockers
• Nitrates

For more detail on these agents, refer to “Acute Treatment of UA & NSTEMI”

Adjunctive Therapies for both STEMI & NSTEMI

• Ace Inhibitors: limits adverse ventricular remodeling & reduces the incidence of CHF, recurrent ischemia, & mortality following an MI

*The effects of ACE Inhibitors is additive to that of aspirin & Beta-Blockers & is extremely useful in high risk patients w/ LV systolic dysfunction

• Statins: cholesterol lowering; may also improve endothelial dysfunction, inhibit platelet aggregation, & impair thrombus formation
Hypertension

(Chapter 13, pages 289-310)

Objectives:

1. Describe age-related change in prevalence in hemodynamic characteristics in hypertension
2. Identify the symptoms, signs and laboratory abnormalities that are characteristic of various forms of secondary hypertension
3. Identify the pathological and clinical manifestations of end-organ complications of hypertension
4. Describe the lifestyle measures useful in treating high blood pressure
5. Develop the plan for initial diagnosis and treatment of an individual with elevated blood pressure; describe the rationale for diagnostic testing and mechanism of action of any recommended drugs

Intro and the basics:

• Lots of people have hypertension
• High BP is usually asymptomatic until something bad happens
• Most of the time (95%) we don’t know the cause of the high BP
  o THIS IS CALLED ESSENTIAL HYPERTENSION (OR PRIMARY HTN)
• When we know the cause for elevated BP, it’s called SECONDARY HTN
  o These cases are far less common, but are important because they have different treatment strategies and cure is often possible.

• Definition: current criteria = diastolic of > 90, systolic of > 140.
  o These are arbitrary cut off points.

Recall that BP = CO x TPR, and CO = SV x HR. We can infer that 3 systems are important in regulating BP: heart, vessel tone, and kidney, which regulates intravascular volume, and thus preload. The kidney is especially important, because it has the amazing property of being able to return BP to normal despite very high CO and constriction of the vessels by excreting volume.

Review of the baroreceptor reflex. Feel free to skip.

Also recall that the BARORECEPTOR REFLEX is important in regulating blood pressure. Located in walls of aortic arch and in carotid sinus, the receptors monitor changes in BP by sensing the stretch in the vessel. With increased BP, they increase their rate of firing. The signals from the carotid sinus are sent to the medulla via the glossopharyngeal nerve (CN IX), while signals from the aortic arch are sent via vagus. The fibers converge at the TRACTUS SOLITARIUS, where upon sensing increased BP, sympathetic impulses are inhibited, and parasympathetic impulses are excited. All this results in decreased vascular resistance and decreased CO, decreased HR and force of contraction.
The main effect of the baroreceptor reflex is to reduce moment-by-moment changes in BP. The reflex is not involved in long term BP control and cannot prevent chronic HTN, because it resets to a baseline pressure in order to consistently prevent momentary changes.

Secondary Hypertension:
- Relatively uncommon, but important to look at because of the potential to cure. Also if we wait too long to treat a cause of secondary HTN, the changes incurred may become permanent.
- Clues for suspecting a secondary HTN:
  - AGE: if hypertension develops before age 20 or after age 50
  - SEVERITY: more severe hypertension (Stage 3)
  - ONSET: abrupt onset in previously normotensive patient
  - SIGNS of the cause: ex = bruit from renal artery stenosis
  - FAMILY HISTORY: negative, usually occurs sporadically
- Causes of Secondary HTN
  1. exogenous (medications)
  2. renal causes (renal parenchymal disease and renal artery stenosis)
  3. mechanical causes (coarctation of the aorta)
  4. endocrine causes (pheochromocytoma, adrenocortical hormone excess, thyroid hormone excess)

~ The objectives suggest that we need to know signs, symptoms and lab findings for the 4 causes of secondary hypertension. Here we go. ~

1) Exogenous Causes: Medications
- oral contraceptives. Estrogens can increase hepatic synthesis of angiotensinogen, which leads to more ang II. More ang II causes vasoconstriction and increased aldosterone release, which will increase sodium retention = ↑ volume.
- Glucocorticoids
- Cyclosporine A
- Erythropoietin (increased blood viscosity)
- Sympathomimetic drugs (cold medicine)
- Cocaine
- Chronic alcohol consumption

2) Renal Causes: two types
   i. renal parenchymal disease
      - Increased intravascular volume causes damage to the kidney.
      - Damaged nephrons are unable to excrete normal amounts of water and Na, thereby increasing the volume further
      - Can also involve secretion of lots of renin
ii. “renovascular hypertension”: renal artery stenosis
   - Can be stenosis of one or both of the renal arteries
   - Can be caused by atherosclerosis
     - Atherosclerotic lesions arise from plaque formation in the renal artery or abdominal aorta near the renal artery.
     - Atherosclerotic lesions are most common in older men.
   - Can be caused by fibromuscular dysplasia
     - Fibromuscular dysplasia = lesions of fibrous material or muscle proliferation within the arterial media.
     - This type is more common in young women.
   - Elevated BP in renal artery is caused by reduced blood flow, so the kidney responds by secreting more renin.
   - Diagnosis: ABDOMINAL BRUIT, UNEXPLAINED HYPOKALEMIA (excessive excretion of K)
   - Treatment: catheter interventions, surgical reconstruction. ACE inhibitors are useful in unilateral stenosis

3) Mechanical Causes: Coarctation of the Aorta
   - Definition: narrowing of the aorta, usually near the subclavian artery
   - Can cause reduced blood flow to the kidneys, resulting in increased renin and VASOCONSTRICTION
   - Additionally, the narrowing can stiffen the aortic arch and prevent the baroreceptors from doing a good job
   - Clinical clues
     - Inadequate flow to the legs or left arm
     - Absent femoral pulse
     - Midsystolic murmur—best heard on the back between the scapula
     - Chest x-ray will show indentation of the aorta
     - Notched appearance of the ribs (enlargement of the intercostal arteries)
   - Treatment:
     - Angioplasty or surgery to correct the stenosis
     - HTN may not disappear completely→desensitization of baroreceptors

4) Endocrine Causes: 3 kinds
   - Pheochromocytoma
     - Catecholamine secreting tumors of neuroendocrine cells
     - Tumor is often in the adrenal medulla
     - Release lots of NE and EPI which causes vasoconstriction and tachycardia
     - PRESENTATION:
       - Autonomic attacks: severe headaches, profuse sweating, palpitations, tachycardia.
       - Most patients have elevated BP even between attacks
     - DIAGNOSIS:
       - Plasma catecholamine levels
       - Urine catecholamine metabolite levels (VMA)
• **TREATMENT:**
  - Pharm = alpha receptor blocker [phenytoxybenzamine] plus a beta blocker
  - Surgery = resection
  - Prevention of catecholamine synthesis [methyltyrosine]

- Adrenocortical Hormone Excess
  - Mineralocorticoids (aldosterone) increase blood volume by stim Na reabsorption, in exchange for K.
    - Can be primary aldosteronism → adrenal adenoma or bilateral hyperplasia of adrenal gland
    - Asymptomatic
    - Can be secondary aldosteronism → renin-secreting tumor (increased ang II)

- **DIAGNOSIS:**
  - Hypokalemia
  - Excess aldosterone secretion

- **THERAPY:**
  - Surgical removal
  - Aldosterone receptor antagonist (spironolactone)

- Glucocorticoids (cortisol)
  - Increased renin synthesis and increased blood volume
  - CUSHINGS SYNDROME
    - Round face, central obesity, muscle weakness, hirsutism
    - ACTH secreting tumor in the pituitary
    - Or ACTH secreting tumor in periphery
    - **DIAGNOSIS** = 24 urine collection → measure cortisol
    - Or dexamethasone test to see if cortisol secretion is stopped.

- Thyroid Hormone Abnormalities → either hyper or hypothyroidism
  - TH : Induce Na/K ATPase in the heart
  - TH : Increase blood volume
  - TH : Stim metabolism and O2 demand → cardiac hyperactivity and ↑ vol.

  - Too little TH: metabolic rate falls, and the vasodilator metabolites decrease, which causes vasoconstriction.

**Essential Hypertension:**
- Elevated BP with no definable reason.
- Diagnosis of exclusion → first rule out all the causes of secondary hypertension
- Most people have mild form (stage 1)
- Usual age of onset = 20-50
- Usually a combination of defects, both genetic and acquired.
- Although no genetic markers have been found, ET runs in families
• Uneven distribution in racial groups ➔ higher in blacks
• Lower socioeconomic and education status ➔ higher
• Older age ➔ higher prevalence. (more on this later)
• Defects in heart, blood vessels and kidney can be involved in ET
• Kidney is really important: it has to be messed up for the defects in other systems to produce sustained hypertension.
• Insulin resistance was mentioned: ↑ insulin can increase BP
• Obesity and leptin: increased leptin can increase BP

OBJECTIVE # 1: Changes in BP with Age
In younger patients (age 40 and younger), essential hypertension is driven by increased CO with normal resistance. This is called the **hyperkinetic phase** of ET. As we age, the increased CO tends to decline in importance and peripheral resistance increases. This is because the heart and vessels adapt to the stress: LV hypertrophy and medial hypertrophy of the vessels.

- Two stages: “hyperkinetic phase” at younger age ➔ high CO, low TPR
- Later stage ➔ normal CO and high TPR

Consequences of Hypertension

**Signs:**

- **mostly ASYMPTOMATIC**
- Headache ?
- Nosebleed ?
- Dizziness ?
- Flushing
- Sweating
- Blurred vision

**Organ Damage:** heart, cerebrovascular system, aorta, peripheral vasculature, kidney, retina

- **heart in brief**
  - problems result from increased afterload AND atherosclerosis in coronary arteries (HTN disrupts protective mechanisms)
    - **concentric** hypertrophy ➔ increased stiffness ➔ DIASTOLIC DYSFUNCTION ➔ pulm congestion
    - SYSTOLIC DYSFUNCTION ➔ reduced CO, coronary art disease
    - Coronary artery disease: accelerated atherosclerosis cause plaque formation in coronaries ➔ decreased supply of O2, increased demand for O2 (due to the increased workload) ➔ MI

- Cerebrovascular system
  - Hemorrhagic or atherothrombotic hypertension strokes
    - Atherothrombotic: bits of plaque from carotid break off
    - Cause lacunae: cavities in middle and posterior brain circ.
• Aorta
  o Accelerated atherosclerosis can cause lesions to form in the aorta
    ▪ Can lead to aortic aneurysms, especially in the abdomen (AAA), below the level of the renal arteries
    ▪ Big ones are more likely to rupture (> 6 cm)
  o Aortic Dissection
    ▪ I don’t understand how this works, but I think blood goes in a weird place within the aorta and prevents normal blood flow
    ▪ Very serious → emergency surgery is required
• Kidney
  o HTN induced kidney disease
    ▪ Vessel walls are thickened with hyaline atherosclerosis
    ▪ HTN can induce necrosis of capillary walls
    ▪ Usually not a problem with mild HTN
    ▪ But severe HTN → permanent damage, dialysis
    ▪ Progressive renal failure prevents it from regulating blood volume, so BP goes up = more HTN
• Retina
  o Not so much damage to the eye as a **clinical tool for assessing BP**
  o Hypertensive retinopathy
  o Acute severe HTN → burst small retinal vessel
    ▪ maybe some blurred vision
    ▪ Papilledema: swelling of optic disc resulting from high intracranial pressure
  o Chronic HTN
    ▪ NO PAPILLEDEMA
    ▪ Vasoconstriction, arterial narrowing with medial hypertrophy
    ▪ Arteries will “nick” crossing veins
    ▪ Increased reflection of light thru ophthalmoscope

**Hypertensive Crises**
= severe elevation in BP, caused by acute hemodynamic insults on top of chronic HTN
  - Symptoms
    o Increased intracranial pressure
    o Headache
    o Blurred vision
    o Confusion
    o Somnolence
    o Coma
    o Retinal exam: hemorrhages, exudates, papilledema
    o Angina
    o Pulm edema
TREATMENT:
1) lifestyle changes: cheaper with few side effects!
   - Weight reduction
   - Exercise → lower resting HR, decreased sym tone
   - Diet
   - Sodium → controversial, but may improve the efficacy of drugs
   - Potassium → deficiency can raise BP
   - Alcohol → decreases in chronic alcohol can lower BP
   - Low calcium intake → increase BP
   - Caffeine → increase BP
   - Smoking → questionable influence on BP. Don’t smoke
   - Relaxation therapy → increased BP is linked to stress. Effectiveness depend on patient

2) pharmacologic treatment
   - Four classes: diuretics, sympathomimetics, vasodilators, Renin-ang system antagonists
   - This is a review from pharm. I’m not going to write about all these drugs…. 
   - The recommendations are: diuretics and beta blockers. Addition or substitution of one of the other families of drugs can help in certain patients.
   - Drug regimen should fit patient → recall the changes in HTN with age…older patient may not need the beta blocker he needed when he was younger.
   - When using multiple agents, pick ones that act on different sites
Figure 13.9. Physiologic effects of antihypertensive medications. Note that some antihypertensive medications work at multiple sites. HR, heart rate; SV, stroke volume; CC, cardiac contractility; VR, venous return; RAS blockers, renin-angiotensin system blockers (i.e., angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers); CCB, Ca²⁺ channel blockers.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Types (see Chapter 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Thiazides, Aldosterone-antagonists</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td>β-blockers, Combined α-β-blockers, Central α₂-agonists, Peripheral α-blockers</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Calcium channel blockers, Direct vasodilators (e.g., hydralazine, minoxidil)</td>
</tr>
<tr>
<td>Renin-angiotensin system antagonists</td>
<td>Converting enzyme inhibitors, Angiotensin II receptor blockers</td>
</tr>
</tbody>
</table>
Summary and plan of action for patient with suspected hypertension

--because HTN is usually asymptomatic, screening is essential. (cheap, effective, etc.)

1) several elevated blood pressures on multiple occasions in various settings (avoid white coat phenomenon.)

2) First thing to do is rule out secondary causes of HTN.
   a. What is my patient’s age: are they older than 50 or younger than 20?
   b. Is the elevated BP very very high?
   c. Does my patient have family members with HTN?
   d. Is the patient taking any drugs that could cause an elevation in BP, such as oral contraceptives?
   e. Does she have an abdominal bruit on exam?
   f. Does she have adequate blood flow to her legs?
   g. Does she have urine catecholamines, excess aldosterone, hypokalemia, urine cortisol or a ROUND FACE?

3) If the above questions do NOT bring results, exclude secondary HTN and cautiously think about ESSENTIAL HTN

4) Next, you need to think about treatment plans

5) Is the patient experiencing any symptoms from her HTN?
   a. Make sure she is not in a hypertensive crisis
   b. Assess any organ damage
      i. Does she ever have symptoms of CAD?
      ii. Does she have an abdominal aortic aneurysm?
      iii. Ask her about her kidney function
      iv. Check her retinas for signs of PAPILLEDEMA (unlikely) or increased light reflection (?)

6) Counsel patient on lifestyle
   a. Does she smoke? She should not.
   b. Can she lose some weight?
   c. What are her exercise habits?
   d. Discuss caffeine, relaxation therapy and alcohol

7) After all that, you can begin to think about treating your patient with drugs. Keep in mind the goals of therapy: lower BP in order to prevent the consequences of elevated blood pressure. (I think. I made this up.)

8) FIRST LINE DRUGS FOR UNCOMPPLICATED HTN:
   a. Diuretics: recall that diuretics work by decreasing volume, thereby lowering MAP and CO. They should not be used in persons with kidney problems. There are several kinds of diuretics; most promote Na and Cl excretion.
   b. Beta blockers: lower BP by decreasing HR and CTY; decrease renin secretion which causes a decrease in TPR. (Recall that Ang II is a vasoconstrictor)

9) There are other drugs to choose from is our patient is unresponsive or suffers from side effects. Always keep in mind the patient’s specific needs and age. Remember the age-related changes in hypertension and pick your drugs accordingly.

10) If you choose more than one drug, make sure that the multiple drugs together act at different sites and do not oppose each other.
Ischemic Heart Disease
Chapter 6, pg.131-156

The Objectives for this assignment are combined with the ones from Chapter 5 on Atherosclerosis. The two subjects go hand-in-hand, but I’ll try not to overlap with Ashley too much. Here are the objectives restricted to my section:

1. Identify the major determinants of myocardial oxygen supply and demand; describe the rationale, pathophysiology and clinical utility of exercise stress testing
2. Describe the epidemiological characteristics of ischemic heart disease
3. Develop a rational plan for evaluation and management of a patient with chest pain

Intro and the basics:
• Angina = condition where you have a mismatch between myocardial oxygen supply and demand.
• The leading cause of angina is CORONARY ARTERY DISEASE
• CAD = reduced myocardial oxygen supply due to atherosclerotic narrowing of the coronary vessels
• Ischemic Heart Disease is the leading cause of death in the US

Objective # 1: The major determinants of myocardial oxygen supply and demand.

Oxygen supply depends on
• Oxygen carrying capacity of the blood
  o This term remains constant in the absence of anemia or lung disease
• Rate of coronary blood flow.
  o This is the important one
  o Recall that coronary artery flow (Q) is directly proportional to perfusion pressure (P) and inversely related to coronary vascular resistance (R)
  o \[ Q = \frac{P}{R} \]
  o For the coronary arteries, most of the perfusion HAPPENS DURING DIASTOLE!!
    o This is because during contraction of the myocardium during systole, the coronary vessels are mashed closed when the muscle contracts (and I think Dr. Faber said that the blood can’t enter the coronary vessels from the aorta when the velocity of systole is so great. Did I make that up?)
    o So, blood enters the vessels during diastole when the myocardium is relaxed and the vessels aren’t compressed.
    o We can approximate the perfusion pressure of the coronaries by measuring the aortic diastolic pressure
      ▪ Things that change the aortic diastolic pressure will thus change the perfusion pressure of the coronaries
      ▪ EX: hypertension, aortic regurg will decrease aortic diastolic press.
    o The other key determinant in blood flow is coronary vascular resistance
Things that affect resistance

- External compression
  - Greatest during systole, when the myocardium contracts and compresses the coronary vessels
  - SUBENDOTHELIUM is most susceptible to damage, because it is closest to the highest pressures

- Intrinsic control of coronary tone
  - The heart gets the max amount of O2 out of the blood with each cycle—there is not the reserve available as there is in other tissues.
  - **Any additional O2 requirements must be met by an increase in blood flow**!
  - It does this by changing the resistance.

Autoregulation of Coronary Vascular Resistance

- Metabolic factors
  - Local metabolites accumulate during times of HYPOXIA, when aerobic metabolism is inhibited
  - ADP and AMP accumulate because they can’t be made into ATP.
  - They are degraded into ADENOSINE, a potent VASODILATOR
  - Adenosine binds to vasc. smooth muscle and prevents Ca entry, leading to relaxation, vasodilation and increased blood flow

\[ O_2 \downarrow \quad \text{adenosine} \uparrow = \text{dilation} \]
• Endothelial factors
  o Vasoactive substances are produced by endothelial cells
  o Nitric Oxide
    - vasodilator
    - Released under normal conditions in response to ACh or sheer stress of blood flow
    - Utilizes a cGMP mechanism
  o Prostacyclin
    - vasodilator
    - Released from endothelial cells in response to hypoxia, ACh, sheer stress
    - Utilizes a cAMP mechanism
  o Endothelium-derived hyperpolarizing factor
    - Vasodilator
    - Does NOT involve a cGMP or cAMP mechanism
  o Endothelin-1
    - VASOCONSTRICTOR
    - Stimulated by Ang II, EPI, sheer stress of blood flow

Normally there is a balance between these factors, where the vasodilators predominate. In sick endothelium, the balance can be shifted towards the constrictors.

• Neural Factors
  o Recall both beta 2 and alpha receptors are on the coronary vessels
  o Beta 2 dilates, and alphas constrict.

The way all these factors work together determines the net coronary tone.

**OXYGEN DEMAND DEPENDS ON**

1. ventricular wall stress: increased wall stress increases O2 needs
   - definition: tangential force acting on the myocardial fibers tending to pull them apart; energy is needed to oppose that force.
   - Wall stress = intraventricular pressure (P) times the radius of the vent. (r) divided by 2 times the vent. wall thickness (h).
   - Wall stress = P x r / (2h)
   - Wall stress is increased with more LV filling (mitral or aortic regurg)
   - Wall stress also increases with increased systolic pressure in the LV (aortic stenosis or HTN)
   - Increased thickness of the vent. wall will decrease wall stress (hypertrophy)

2. heart rate
   - increasing HR consumes more ATP and O2 requirement increases

3. contractility
   - increasing force of contraction increases O2 utilization
In summary, the determinants of oxygen supply are:
1. carrying capacity of blood
2. blood flow, which is dependent on pressure and resistance

The determinants of oxygen demand are:
1. wall stress
2. heart rate
3. contractility

General Causes of Ischemia
- Atherosclerotic CAD
- Decreased aortic perfusion pressure (hypotension, aortic regurg)
- Decreased blood oxygen carrying capacity (anemia, blood loss)
- Increasing O2 demand: aortic stenosis (increased wall stress)

I did not find the epidemiology of ischemic heart disease. Maybe we will hear about it in class?

Pathophysiology of Ischemia
(not in objectives, but it’s gotta be important. Some overlaps with objective from Day 1, which merit review anyway)

--reduction in blood flow resulting from combination of fixed vessel narrowing and abnormal tone (endothelial cell dysfunction).

Fixed Vessel Narrowing
- the hemodynamic significance of stenotic lesion depends on its LENGTH but more importantly by the DEGREE OF VESSEL NARROWING (L/r^4)
- coronary vessels consist of proximal epicardial segment and distal resistance vessels
- plaque formation happens in the proximal segments
- resistance vessels try to compensate for any narrowing in the proximal vessel
- less than 60% occlusion is not significant...ie, max blood flow can still occur, even though the vessel is narrowed by 60%
- when the vessel diameter is narrowed by more than 70%, max blood flow is reduced, even with full dilation of the resistance vessels
- this results in coronary blood that is inadequate when oxygen demand increases (physical exertion).
- Here, there is a mismatch between oxygen supply and demand→ANGINA
- If the vessel is occluded by more than 90%, you can have angina at REST
Endothelial Cell Dysfunction:

- problems with inappropriate vasoconstriction and loss of antithrombic properties

  - Inappropriate vasoconstriction
    - With dysfunctional endothelium, release of NO (and others) is impaired
    - This **shifts the balance over to the vasoconstrictors**
    - Results in a decrease in coronary blood flow
    - In some patients with no evidence of plaque formation but with big risk factors for CAD, impaired vasodilation can be noted
      - Thought that endothelial dysfunction may happen early in the atherosclerotic process
    - When platelets being to aggregate after plaque disruption, they release metabolites (5-HT, ADP) that stimulate release of NO.
      - If NO release is impaired, then vasoconstriction predominates, and flow is further restricted.
  
  - Platelet aggregation
    - Endothelial cells release substances that interfere with platelet aggregation
    - The release of these substances is reduced with endo dysfunction

Consequences of Ischemia

- Dyspnea → transient reduction in systolic contraction = ↑ LV diastolic pressure, increased LA pressure, pulm congestion via pulm veins
- Pain → accumulation of metabolic products activates pain receptors (C7-T4)
- Arrhythmias
- MOSTLY DETERMINED BY SEVERITY AND DURATION OF IMBALANCE.

  - Options:
    - Irreversible myocardial necrosis
    - Rapid full recovery
    - Prolonged contractile dysfunction without necrosis, recovery possible
      - “stunned myocardium” = reversible, but only gradually
      - likely to be response to severe ischemia that just falls short of irreversible necrosis
    - “hibernating myocardium”
      - results from multivessel CAD
      - persistently reduced blood supply
      - readily reversed when blood flow is improved

This stuff is important in deciding on a treatment plan. In imaging, we can now tell the difference between these types of tissues. Since hibernating or stunned myocardium would respond well to surgery, but necrotic tissue would not, we would make a decision about surgery based on the imaging studies.
~REVIEW~
Different Types of Ischemic Syndromes:
1. Stable Angina: most common symptom
   - Fixed obstructive plaque in one or more coronary arteries
   - 70% → angina with exercise
   - 90% → angina at rest
   - chronic predictable transient angina
   - endothelial cell dysfunction → problems with vasodilation
   - variable threshold vs fixed threshold depending on degree of vascular tone
   - may have no pathologic findings if no necrosis has occurred
2. Unstable Angina
   - Precursor to acute MI
   - Acceleration of symptoms
   - Plaque rupture, platelet aggregation, thrombus formation, vasoconstriction
3. Variant Angina
   - Prinzmetal’s syndrome
   - Coronary artery spasm with no evidence of plaque
   - ?early atherosclerosis, with just endothelial dysfunction?
   - Occurs at rest → not a result in increased O2 demand
   - Vasospasm adjacent to area of plaque
4. Silent Angina
   - Asymptomatic
   - Problematic for diagnosis
   - Common among diabetics → impaired pain sensation?
5. Syndrome X
   - Typical angina, but no plaque formation
   - Problem with the resistance vessels of the heart → may not dilate properly
   - Good prognosis

Bottom line:
ACUTE PLAQUE CHANGE IS THE CRITICAL COMPONENT IN ACUTE SYNDROMES

uncomplicated. Disruption of plaque
Clinical Features of Stable Angina

- Quality of pain
  - Pressure
  - Tightness
  - Heaviness
  - Not really pain

This is in contrast to other causes, described as: stinging, itching, stabbing, shooting.

- Location of pain
  - Diffuse, not localized
  - Central, substernal chest
  - Arm, jaw, throat: radiating
  - Point to pain with clenched fist over sternum “LEVINE’s SIGN”

- Accompanying symptoms
  - Tachycardia
  - Sweating
  - Nausea
  - Dyspnea
  - Weakness

- Precipitating Factors
  - Physical exertion
  - Anger, excitement
  - Large meal
  - Cold weather

- Duration of Pain
  - Usually relieved within minutes
  - Lasts longer than a second or 2
  - If pain lasts for days, it is unlikely to be ischemia

Physical Exam:

- During anginal attack: may have no abnormal findings.
  - Increased HR, BP
  - Mitral regurg
  - Bulging impulse
  - S4 gallop, because ischemia decreases vent. compliance → stiff

Diagnostic Studies

- ECG—if during an ischemic attack, we would see
  - ST segment depression
  - T wave flattening or inversion
o Maybe ST segment elevation
o These changes quickly normalize with resolution of symptoms

- Exercise Stress Test ***Note: this is one of the objectives!***
We do this test when the ECG is normal. Because it is hard to catch someone at the time of an ischemic attack, their ECG will most likely be normal. Thus we cannot rule out ischemic heart disease based on ECG alone. The test is not useful for patients unable to exercise (severe arthritis).

- Patient exercises until angina develops, until there are signs of ischemia on the ECG (see above), target heart rate is achieved, patient gets too tired.
- **POSTIVE TEST:**
  - Patient’s typical angina is recreated
  - ECG shows signs of ischemia ➔ **ST segment depressions**, 1 mm

- **MARKEDLY POSITIVE:**—indication of severe multivessel disease
  - ECG changes seen within 3 minutes
  - Persist for more than 5 minutes after test is stopped
  - ST segment depressions > 2 mm
  - Systolic BP **DECREASES** during exercise
  - Ventricular arrhythmias develop
  - Patient cannot exercise for at least 2 minutes

When considering doing an exercise stress test, remember that several things can affect the results. If the patient is taking a beta-blocker, then optimal heart rate may never be reached. If you are doing the test to see if ischemic heart disease is present, ask the patient to stop taking the beta-blocker for 24-48 hours before the test. If you already know the patient has ischemic heart disease, you can use the test as a means of assessing current medical regimen.

Other diagnostic studies—briefly:
- **Nuclear Exercise Study:**
  - look at areas of poor perfusion during exercise
  - allows determination between ischemic areas and necrotic/infarcted areas.
  - Expensive

- **Exercise Echocardiography:**
  - LV contractile function is assess, at baseline and after exercise

- **Pharmacologic Stress Tests**
  - Used for folks who can’t exercise
  - DOBUTAMINE – increases force of contraction
  - DIPYRIDMOLE or ADENOSINE—vasodilators
    - Dipyrimidole blocks uptake of adenosine so there is more circulating ➔ vasodilation.
Ischemic regions are already max dilated, so this drug-induced vasodilation increases flow to health arteries and promotes stealing of blood from diseased segments to perfuse other parts
- Cold spots are visible in image

- Coronary Angiography
  - Contrast material injected into artery → regions of stenosis are visible
  - Low risk, but more than the non-invasive tests
  - Gold standard for CAD diagnosis
  - But you always have to think about the functional effects on the patient
  - Does not tell you anything about the composition of the plaque and whether it is likely to rupture

Natural History:
- We don’t know why some plaques rupture and some don’t.
- Location and extent of stenosis relates to mortality
- Some predictors of mortality =
  - Degree of impaired LV contractile function
  - Poor exercise capacity
  - Anginal symptoms
- Stop smoking, eat less fat, lower cholesterol, control BP, control diabetes mellitus, get more exercise

Treatment: goal of treatment is to reduce the frequency of anginal attacks by restoring balance of supply and demand, prevent MI, prolong survival.

Acute Anginal Attack
- Stop physical activity
- Sublingual nitroglycerin = drug of choice
  - Works mostly through venodilation = ↓ preload, ↓ O2 consumption
  - Also dilates coronary arteries → may not help much of the vessels are already max dilated

Preventing Recurrent Ischemic Episodes: decrease cardiac workload and reduce demand
- Organic Nitrates
  - SYMPTOMATIC RELIEF ONLY → will not prolong survival
  - Venodilation
  - Sublingual or spray = rapid onset
  - Can be used prophylactically
  - Longer acting options
    - Isosorbide dinitrate or transdermal patches of nitroglycerin
    - Drug tolerance limits effectiveness
  - Side effects = headache, palpitations, tachycardia

- Beta Blockers
  - Reduce myocardial oxygen demand
Beta antagonists: decrease force of contraction, decrease HR, relieve ischemia, increase time spent in diastole

- Decrease rates of recurrent infarction following acute MI
- FIRST LINE TREATMENT FOR CAD
- Side effects and contraindications:
  - Bronchospasm, if non-selective is used
  - Avoid any type of beta blocker in pts w/ obstructive airway disease
  - Avoid using them with decompenated LV dysfunction (reduced CTY)
  - Avoid using them in patients with bradycardia
  - Avoid using them in patients with diabetes mellitus
  - Cause fatigue
  - Cause sexual dysfunction

- Calcium Channel Blockers: antagonize voltage gated L-type calcium channels
  - Dihydropyridines
    - VASODILATOR (↓ oxygen demand—reduce wall stress, ↑ oxygen supply—coronary dilation)
  - Nondihydropyridines (verapamil, diltiazem)
    - Less potent vasodilator
    - Decrease force of contraction
    - Slow heart rate
  - Short acting calcium channel blockers
    - Associated with increased risk of MI
    - Avoid

No drugs have been found to slow or reverse the process of arterial lesions in CAD. Although beta blockers have been shown to increase survival after an MI, none of these drugs will improve survival for patients with chronic stable angina.

Prevention of MI and Death:
- Antiplatelet therapy (aspirin)
  - STANDARD ADDITION to the drugs used in treating CAD
  - Substitute with clopidogrel in patients allergic to aspirin

- Lipid Lowering Therapy
  - Statins: can improve endothelial cell dysfunction
  - Get LDL below 100 mg/dL in patients with CAD

- ACE inhibitors
  - Reduce risk of MI and death in patients with CAD
  - Improve ventricular function

More intensive interventions
- Mechanical revascularization: 2 types
Consider when patients are not responding to the drugs
  o Too many side effects of the drugs
  o Patient has type of CAD that respond esp. well to interventions

1) Percutaneous coronary intervention (PCI)
  o Done under fluoroscopy
  o Balloon tipped catheter into peripheral artery
  o Balloon is inflated once into the coronary vessel
  o Then removed

This helps by increasing the size of the lumen, which increases perfusion and O2 supply. The effect is to compress the plaque and stretch the vessel underneath. Drawbacks = most patients have restenosis within a short period of time.

Stents can now be placed at the time of PCI which reduces the chance of restenosis. Left permanently in the vessel and acts as a scaffold to maintain patency.

Problem: thrombogenic → must give oral anti-platelet agents afterward.

Also, at time of PCI, we can attempt to get rid of some of the plaque: directional coronary atherectomy shaves the plaque down and fragments are collected. Rotational atherectomy uses a spinning burr to get rid of the plaque.

PCI has not been shown to reduce the risk of MI or death from CAD.

2) Coronary Artery Bypass Graft (CABG)
  o Native veins are grafted onto the coronary vessels to bypass the obstruction (saphenous vein is commonly used)
  o Arterial grafts can also be used, by reconnecting the internal mammary artery to the coronary vessel
  o The arterial grafts tend to stay patent longer—more resistant to atherosclerosis.

Plan for patient with chest pain:
First, get a good history. Ask all the questions about quality of pain/discomfort, location, accompanying symptoms, precipitating factors, what made it go away.

After you establish that the patient’s history is consistent with that of angina, you will want to do an ECG. Although you might not find anything if the patient is no longer experiencing the discomfort, it’s an easy test that could potentially show something.

Once you see that the ECG is not helpful, you will want to get an exercise stress test if the patient is able to exercise. You find ST segment depression, so you have a potential diagnosis.

Begin by counseling the patient on smoking cessation, diet and exercise. Then move into prescribing medications. First, aspirin. Then, prescribe NTG for acute attacks. Ask about asthma and then prescribe a beta blocker and an ACE inhibitor. Look at the patient’s LDL level and consider offering a statin. Keeping cost of medications in your mind, maybe you could wait on the Ca-channel blocker, as its effectiveness has not been proven.
DISEASES of the PERICARDIUM
(from readings on Monday, Sept 27th - pgs 311-324)

Objectives: (see last 2 pages of this study guide for specific summaries tailored to objectives)
- Recognize the clinical symptoms, physical findings, electrocardiographic changes, and diagnostic imaging abnormalities in cardiac tamponade
- Contrast and differentiate the pathophysiology and clinical findings in cardiac tamponade from pericardial constriction
- Recognize indications and develop a rational therapeutic plan for medical and surgical treatment of pericardial disease

What is the pericardium?
- A 2 layered sac holding the heart → inner visceral and outer parietal layers

Acute Pericarditis
Most common disease of the pericardium = inflammation of its layers

ETIOLOGY
- Lots of causes, some of the more common are listed below (sorry, this is long...)
- Infectious
  - Idiopathic and Viral pericarditis
    - Most common cause
  - Tuberculous Pericarditis
  - Nontuberculous Bacterial Pericarditis (Purulent)
- Noninfectious
  - Pericarditis Following Myocardial Infarction
  - Uremic Pericarditis
  - Neoplastic Pericarditis
    - Tumor w/in pericarditis - usually from metastatic spread... usually large and hemorrhagic and can lead to cardiac tamponade.
  - Radiation-induced Pericarditis
  - Pericarditis Associated with Connective Tissue Disease
  - Drug Induced Pericarditis

PATHOLOGY
- Serous Pericarditis - early inflammatory response; exudate is thin fluid w/ scant leukocytes
- Serofibrinous pericarditis - most common; plasma proteins in exudates → "bread and butter" pericarditis; portions of the pericardium may become thickened and fused... may lead to scar that restricts diastolic filling of heart
• **Suppurative (purulent) pericarditis** - intense inflammatory response (most assoc with bacterial infection)
• **Hemorrhagic pericarditis** - grossly bloody form due to TB or malignancy

**PRESENTATION**
• **Chest pain and fever!**
  • Differentiate from MI b/c pain is sharp and *pleuritic* (meaning aggravated by inspiration and coughing) and *positional* (sitting and leaning forward make it feel better)
  • May have *dyspnea* but not exertional -- usually b/c it just hurts to breathe deeply

**PHYSICAL EXAM**
• **Friction rub** → scratchy sound from inflamed layers moving against each other (heard best with diaphragm and patient leaning forward while exhaling)
  • Rub is evanescent → comes and goes from one exam to the other

**TESTS and IMAGING**
• **ECG** → abnormal in 90%
  o **diffuse ST segment elevation** in most leads except aVR and V1
  o **PR segment depression** (pg 315 for good examples)
  o Contrast to MI where ST segments only elevated in leads overlying infarction and no PR depression
• Echocardiography → for presence and hemodynamic significance of pericardial effusion
• Additional studies for finding cause (like PPD, serology, search for malignancy, etc)

**TREATMENT**
• Idiopathic/viral usually self limited → **rest and pain relief w/ NSAIDs** (not steroids)
• Pericarditis after MI also treated similarly w/ rest and aspirin (try to stay away from other NSAIDs b/c delays healing of MI)
• Purulent pericarditis needs drainage and intensive antibiotic therapy.

**Pericardial Effusion**

Normally only 15-50 mL of pericardial fluid... more may accumulate in assoc w/ above types of pericarditis or also noninflammatory serous effusions may occur

**PATHOPHYS**
• So whether you get cardiac compression symptoms depends on:
  o Volume of fluid
  o Rate of fluid accumulation
  o Compliance characteristics of pericardium
• If **sudden increase of volume** results in big elevation of pericardial pressure and potential for severe cardiac chamber compression (even more so if pericardium is even less compliant than normal... like in presence of tumor or fibrosis of sac)
• If **slow accumulation of volume** (like over weeks to months), the pericardium gradually stretches so that with adaptation, it can accommodate even up to 1-2 liters (!!!) of fluid w/out raising the pressure much

**PRESENTATION**
- Spectrum from **asymptomatic to cardiac tamponade**
- **Symptoms of compression:**
  - Dysphagia (difficulty in swallowing)
  - Dyspnea (pushing on the lungs)
  - Hoarseness (recurrent laryngeal nerve compression)
  - Hiccups (phrenic nerve stimulation)

**PHYSICAL EXAM**
- **Muffled heart sounds** b/c large pericardial fluid insulates heart
- **Reduced intensity of friction rub** if volume is large enough to have separated the 2 inflamed layers completely
- **Ewart’s sign** → dullness to percussion of the left lung over the angle of the scapula

**TEST and IMAGING**
- Chest x-ray → normal if small effusion. W/ more than 250 mL, cardiac silhouette enlarges in globular symmetric fashion.
- ECG → **reduced voltage of complexes**... w/ really large effusions, height of QRS may vary from beat to beat (electrical alternans) b/c it’s like the heart is swinging side-to-side in a big water balloon, so electrical axis is always changing.
- Echocardiography → most useful. Identifies volumes as small as 20 mL... can quantify volume, determine whether ventricular filling is compromised and help guide placement of a pericardiocentesis needle.

**TREATMENT**
- If cause of effusion is known, get rid of cause
- If cause is unknown, **clinical state determines** whether or not to do a pericardiocentesis
- If asymptomatic, even large volume could be observed for years...
- But if there is a sudden rise in pericardial volume or cardiac compression is seen, then do a pericardiocentesis (drain the pericardium).

**Cardiac Tamponade**
This is just a really really bad pericardial effusion. The fluid accumulates under high pressure and smooshes the cardiac chambers so that cardiac filling is limited giving rise to low SV and CO and hypotension... hypotensive shock... and ... death. (I told you it's bad).
ETIOLOGY

- Any acute pericarditis can progress to tamponade, but most commonly it’s from neoplastic, postviral and uremic pericarditis.
- Acute hemorrhage into pericardium can also cause tamponade
  - Blunt or penetrating chest trauma (a good reason not to get stabbed in the chest)
  - Rupture of LV free wall after an MI
  - Complication of a dissecting aortic aneurysm

PATHOPHYS

- B/c of surrounding tense pericardial fluid, heart is compressed and diastolic pressure w/in each chamber becomes elevated and equal to the pericardial pressure.
- Thus, normal venous return can’t be accommodated in heart so both systemic and pulmonic pressure rise (giving R-sided heart failure symptoms i.e. systemic venous congestion... and L-sided heart failure symptoms i.e. pulmonary congestion symptoms )
- That’s not all... reduced filling of ventricles during diastole decreases SV and CO declines
- This then triggers dangerous compensatory mechs to try to keep tissues perfused (initially thru Symp NS activation), but eventually you can’t keep up and you go into shock and... die (unless you treat it).

PRESENTATION

- Suspect tamponade in anyone w/ known pericarditis, pericardial effusion, or chest trauma who develop signs/symptoms of vascular congestion and decr CO.
- If tamponade happens suddenly, profound hypotension symptoms are prevalent (e.g. confusion, agitation)... if gradual, then fatigue (from low CO) and peripheral edema (from R-sided failure) may be presenting complaints

PHYSICAL EXAM

- Key findings:
  - JVD
  - Systemic hypotension
  - “small quiet heart” -- quiet precordium upon palpation b/c of insulation
- other signs
  - sinus tachycardia (reflex to hypotension)
  - pulsus paradoxus → important sign in tamponade... it’s the cyclical decrease of systolic blood pressure (more than 10 mmHg) during normal inspiration. (this is actually just an exaggeration of normal cardiac physiology... when we inspire, systemic venous return is facilitated and the RV fills which pushes on the interventricular septum and causes a transient decr in LV size... thus, the SV and systolic BP is transiently reduced right after inspiration)... also see pulsus paradoxus in obstructive airway diseases and severe asthma...
TESTS and IMAGING

- **Echocardiography** → **most useful noninvasive tech.** Evaluate whether effusion led to tamponade... important indicator of high pressure fluid is compression of RV and RA during diastole (good pic of what echo image will look like on pg 56 - fig 3.12)... echo can differentiate b/t tamponade and other causes of low CO
- **Cardiac catheterization** → **definitive diagnostic** procedure. Measures intracardiac and intrapericardial pressures... (below is a measure of RA pressures)
  - In early diastole (the dotted line), normally, the tricuspid opens and there is a rapid decline (the y descent) in RA pressure as blood flows into the RV... in cardiac tamponade, the pericardial fluid is pushing on the RV during diastole, so it can’t fill as easily, so the RA can’t empty as quickly, and thus, the y descent is blunted in cardiac tamponade.

![Diagram of Right Atrial Pressure](image)

**Figure 14.5. Schematic diagrams of right atrial (or jugular venous) pressure recordings. A. Normal. The initial a wave represents atrial contraction. The y wave reflects passive filling of the atria during systole, when the tricuspid and mitral valves are closed. After the tricuspid valve opens, the right atrial pressure falls (y descent) as blood empties into the right ventricle. B. Cardiac tamponade. High-pressure pericardial fluid compresses the heart, impeding right ventricular filling, so that the y descent is blunted. C. Constrictive pericarditis. The earliest phase of diastolic filling is not impaired so that the y descent is not blunted. The y descent appears accentuated because it descends from a higher than normal right atrial pressure. The right atrial c wave (described in Chapter 2) is not shown.**

- Can also do a pericardiocentises along with the catheterization...and after pericardiocentises, you’ll want to keep some pericardial fluid for diagnostic purposes → stain for bacteria, fungi... get cell counts... protein levels... adenosine deaminase levels (high levels are sens and spec for TB)

**TREATMENT**

- **Pericardiocentises** is the only intervention that can save the patient’s life.
Patient is head up at 45 deg angle, needle inserted into pericardial space below xiphoid process... catheter inserted into pericardial space and another catheter into right side of heart... both hooked up to a transducer for pressure readings

In tamponade, intrapericardial and diastolic intracardiac pressures will be high and equal... after pericardiocentesis, pericardial pressure goes to normal and is no longer equal to pressures w/in heart (which also decline to normal levels)

Can repeat procedure if tamponade recurs

- Sometimes you may need to remove part or all of the pericardium (surgery) to prevent reoccurrences...

**Constrictive Pericarditis**

Doesn’t happen too often, but important b/c it can masquerade as other common disorders... also, it’s really bad, but correctable - like tamponade.

**ETIOLOGY**

- Used to be TB, but that’s not common anymore, so now most freq cause is idiopathic → months to yrs after an idiopathic/viral acute pericarditis... but any pericarditis can lead to this

**PATHOPHYS**

- Normally, after an acute pericarditis, the effusion usually gets gradually resorbed...
- In constrictive pericarditis, the fluid undergoes organization and fuses with the pericardial layers and later forms scars... sometimes you also get calcification...
- So now a rigid, scarred pericardium encircles the heart and inhibits normal filling of the cardiac chambers... the abnormalities occur during diastole; systolic contraction of the ventricles are normal
- During diastole, blood goes from RA → RV and RV size expands and quickly reaches its limit imposed by the hard pericardium... at this pt, further filling is abruptly stopped and venous return to the right heart stops.
- Thus, systemic venous pressure rises (R-sided heart failure systems) and also since the LV is impaired as well, you get decr SV → decr CO → decr BP
- The way I see it, to understand the physical difference b/c tamponade and constrictive pericarditis, think of the heart up against a big water balloon that is pushing on the chambers not letting them fill as much... that’s tamponade. Now think of the heart in a very small, hard, container... the heart will fill in the beginning just fine but only until it reaches the confines of the container... then no more... that’s constrictive pericarditis.

**PRESENTATION**

- Signs and symptoms develop over months to years
- Often resemble symptoms of tamponade
- Reduced CO
  - Fatigue
Hypotension
  - Reflex tachy
- Elevated systemic venous pressures
  - JVD
  - Hepatomegaly and ascites
  - Peripheral edema

When pts come in w/ hepatomegaly and ascites you may think it’s hepatic cirrhosis or intra-abdominal tumor… carefully inspect jugular veins to rule out this cardiac problem

**PHYSICAL EXAM**
- **early diastolic “knock”** following S2 → the ventricle suddenly stops filling when it hits the rigid pericardium
- **no pulsus paradoxus** → this is b/c the neg intrathoracic pressure from inspiration is not transmitted thru rigid pericardial shell to right heart… thus, the blood is pulled up but can’t enter right heart so increased venous return accumulates in the intrathoracic veins → jugular veins become more distended during inspiration (Kussmaul’s sign)… **opposite of normal physiology**

**TESTS and IMAGING**
- Chest x-ray → normal or mildly enlarged cardiac silhouette
- ECG → nonspecific ST and T wave abnormalities; atrial arrhythmias are common
- Echocardiography → subtle findings…
- **Computed tomography or MRI** → superior to echo in assessment of pericardial anatomy and thickness… good for ruling out constrictive pericarditis
- **Cardiac catherization** → confirms diagnosis… will show 3 key features:
  - elevation and equalization of diastolic pressures in each of the cardiac chambers
  - the RA tracing will show a **prominent y descent** (see prev. fig)
    - after the tricuspid opens, the RV quickly fills before it hits the pericardial restriction and stops filling… diff than in tamponade which causes an external compression throughout the cardiac cycle and so it prevents rapid filling of the ventricles and thus blunts the y descent… (think of the water balloon vs. hard container analogy if it helps)
  - R and L ventricular tracings show **early “dip and plateau” configuration** → the early diastolic ventricular filling stops abruptly as the volume in each ventricle reaches the limit imposed by the constricting pericardium… *(see on next page)*
*** FYI: the clinical and hemodynamic findings of constrictive pericarditis are often similar to those of restrictive cardiomyopathy… (next study guide)... this pericarditis is correctable but the cardiomyopathy one is not... may need to do endomyocardial biopsy to distinguish.

TREATMENT

- Only effective treatment is **surgical removal of the pericardium**
  - Symptoms may not resolve immediately but eventually they improve in majority of pts.
Summary keeping Objectives in mind:

- Know all the info I included for cardiac tamponade.
- Focus on the similarities and differences b/t cardiac tamponade and constrictive pericarditis
  - SIMILARITIES: symptoms and signs are similar b/c they arise from impaired diastolic filling of the ventricles in both disorders... so I would word it as such: the pathophysiology (the mechanisms that lead to the symptoms) is similar in both diseases but the pathology is different (pericardial fluid under pressure in tamponade; and scarred, rigid pericardium in constrictive pericarditis)... also cardio-cath is most reliable diagnostic tool for both...

<table>
<thead>
<tr>
<th>Cardiac Tamponade</th>
<th>Constrictive Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsus paradoxus present</td>
<td>No pulsus paradoxus</td>
</tr>
<tr>
<td>No Kussmaul’s sign</td>
<td>Kussmaul’s sign present</td>
</tr>
<tr>
<td>Y descent blunted in RV pressure reading</td>
<td>Accentuated Y descent in RV</td>
</tr>
<tr>
<td>Echocardiography pretty useful</td>
<td>Echo gives subtle results (MRI better)</td>
</tr>
<tr>
<td>Treat w/ pericardiocentesis</td>
<td>Treat w/ removal of pericardium</td>
</tr>
<tr>
<td>Pathology = high pressure fluid compression</td>
<td>Pathology = stiff, fibrotic, scarred pericardium</td>
</tr>
</tbody>
</table>
TREATMENT PLAN for ACUTE PERICARDITIS
- Idiopathic/viral usually self limited → rest and pain relief w/ NSAIDs (not steroids)
- Pericarditis after MI also treated similarly w/ rest and aspirin (try to stay away from other NSAIDs b/c delays healing of MI)
- Purulent pericarditis needs drainage and intensive antibiotic therapy.

TREATMENT PLAN for PERICARDIAL EFFUSION
- If cause of effusion is known, get rid of cause
- If cause is unknown, clinical state determines whether or not to do a pericardiocentesis
- If asymptomatic, even large volume could be observed for years...
- But if there is a sudden rise in pericardial volume or cardiac compression is seen, then do a pericardiocentesis (drain the pericardium).

TREATMENT PLAN for CARDIAC TAMPONADE
- Pericardiocentesis is the only intervention that can save the patient’s life.
  - Patient is head up at 45 deg angle, needle inserted into pericardial space below xiphoid process... catheter inserted into pericardial space and another catheter into right side of heart... both hooked up to a transducer for pressure readings
  - In tamponade, intrapericardial and diastolic intracardiac pressures will be high and equal... after pericardiocentesis, pericardial pressure goes to normal and is no longer equal to pressures w/in heart (which also decline to normal levels)
  - Can repeat procedure if tamponade recurs
- Sometimes you may need to remove part or all of the pericardium (surgery) to prevent reoccurrences...

TREATMENT PLAN for CONSTRICTIVE PERICARDITIS
- Only effective treatment is surgical removal of the pericardium
  - Symptoms may not resolve immediately but eventually they improve in majority of pts.
  - Also make sure that prior to this, you have ruled out restrictive cardiomyopathy which can have very similar presentations... (do myocardial biopsy)

*** all these treatment plans are also located in the outline w/ their respective diseases... I just cut and pasted them here for easier reference as they specifically have to do with the last objective for the reading...
Heart Failure: inability of the heart to pump blood forward at a sufficient rate to meet the metabolic demands of the body (forward failure), or the ability to do so only if the cardiac filling pressures are abnormally high (backward failure), or both. Impaired left ventricular function is the most common cause of heart failure.

**Review of cardiac physiology:**

Frank-Starling Relationship: The higher the preload, the greater the ventricular output. In English, an increase in the amount of blood in the ventricle before contraction (during diastole) results in an increase in the amount of blood the ventricle pumps into the aorta during systole. This relationship is a good thing because it allows the ventricle to pump more blood when it sees an increased volume (like during exercise).

Why this happens: think of the ventricles as a new balloon. The more air you put in the balloon, the more the balloon has to stretch to hold the air. In the heart, this stretching comes from the overlap of actin and myosin filaments and a subsequent increase in the number of crossbridges linking the two filaments. An increase in crossbridges results in an increase in the force of contraction and an increase in Ca²⁺ sensitivity, which further increases the force of contraction. Again, think of the balloon. If you blow the balloon up a lot and let it go, it flies around the room because the air comes out with a lot of force. But if you only blow the balloon up a little bit, the air leaves with less force, and it’s no fun because the balloon just falls on the floor. :0) See p.215 Fig 9.3

![Frank-Starling Mechanism](image1.png)

**Figure 1.** Frank-Starling mechanism. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (LVEDP) and volume, thereby increasing ventricular preload. This results in an increase in stroke volume (SV). The “normal” operating point is at a LVEDP of ~8 mmHg and a SV of ~70 ml/beat.

![Family of Frank-Starling Curves](image2.png)

**Figure 2.** Family of Frank-Starling curves. Changes in afterload and inotropy shift the Frank-Starling curve up or down.
Determinants of Contractile Function in the Intact Heart

Cardiac Output = Stroke Volume × Heart Rate

\[ CO = SV \times HR \]

The three major determinants of stroke volume are preload, afterload, and contractility.

**Preload:** stretch on the myocardial fibers before contraction. In a healthy heart, the higher the preload, the higher the SV.

**Afterload:** the load or force the ventricle must contract against. For the LV, the afterload is the pressure in the aorta that the ventricle must overcome to open the aortic valve and eject blood. Afterload is independent from preload. The higher the afterload, the lower the SV.

Afterload is also defined as the wall stress that develops during systolic ejection. Represented by the Laplace relationship:

\[ \sigma = \frac{P \cdot r}{2 \cdot h} \]  
(wall tension = LV pressure × LV radius / 2 × LV wall thickness)

Increased arterial pressure increases wall tension. Increased wall thickness decreases wall tension.

**Contractility** (inotrophy): the contractile force of the ventricles at a given preload and afterload. Can be enhanced physiological or pharmacologically. The higher the CTY, the higher the SV. Increased CTY shifts the Frank-Starling curve upwards, which increases SV for a given preload and afterload. (See second figure above)

A few more terms:

**Ejection Fraction:** fraction of end-diastolic volume ejected during systole (normal 55-75%)

**Compliance:** ease or difficulty with which the chamber can be filled. If ventricular compliance is reduced, as in severe LVH, then it accepts less volume from the atria, resulting in lower end-diastolic volume (AKA lower preload) and subsequently, a lower SV.

Three important concepts:
1. **Ventricular SV** is a function of preload, afterload, and contractility. SV rises with an increase in preload and contractility and a decrease in afterload.
2. **Ventricular end-diastolic volume** is a measure of preload and is influenced by a compliance of the atria and ventricles.
3. **Ventricular end-systolic volume** depends on afterload and contractility, but not on preload (because of Frank-Starling relationship.)
Pathophysiology of Heart Failure

Divided into systolic and diastolic dysfunction.

**Systolic Dysfunction**: heart failure that results from an abnormality of ventricular emptying. Results in decreased ability of ventricle to eject blood
- Caused by *impaired contractility* or *excessive afterload*
- Accounts for 2/3 of heart failure
- Conditions that impaire CTY: MI, myocardial ischemia, volume overload (MR and AR), dilated cardiomyopathy
- Conditions that increase afterload: Aortic stenosis and hypertension

**Etiology**: Impaired contractility is caused by:
1. destruction of myocytes
2. abnormal myocyte function
3. fibrosis

Increased afterload is caused by pressure overload, which ↑ resistance to flow

**Pathophysiology**: a decrease in contractility causes a decrease in SV and an increase in end-systolic volume and pressure. During the next cardiac cycle, the ventricle receives a normal amount of blood from the lungs, resulting in an increased end-diastolic volume and pressure (increased preload.) Increased preload results in an increase in SV (Frank-Starling) and a reduction in end-systolic volume. However, increased preload cannot completely compensate for the decreased CTY and ejection fraction, so end-systolic volume remains higher than normal. The increased diastolic pressure is transmitted to the LA and the pulmonary veins and capillaries. If pulmonary capillary hydrostatic pressure rises above 20mmHg, then fluid collects in the interstitium of the lungs and causes pulmonary congestion.

↓ CTY → ↓ SV → ↑↑ ESV → ↑↑ preload → ↑ SV → ↓ ESV. However, ESV is still higher than normal, therefore: ↑ EDP and V → ↑ pulm hydrostatic P → congestion

For increased afterload, increased resistance to flow results in pressure overload, which causes a decrease in stroke volume and an increase in end-systolic volume and a subsequent increase in end-diastolic volume and pressure. Leads to increased pulmonary capillary hydrostatic pressure and pulmonary congestion.

↑ afterload → ↑ resistance → ↓ SV → ↑ ESV → ↑ EDV / P → ↑ pulm hydrostatic P → congestion

Remember: systolic dysfunction results from problem with ventricular emptying (↑ ESV)
**Diastolic Dysfunction**: heart failure that results from an abnormality in diastolic relaxation or ventricular filling.

- Accounts for 1/3 of heart failure
- Causes of impaired ventricular relaxation: LVH, hypertrophic cardiomyopathy, restrictive cardiomyopathy, myocardial ischemia, fibrosis
- Causes of impaired filling: Mitral Stenosis, pericardial constriction to tamponade

**Etiology**: Impaired diastolic relaxation is an active, energy-dependent process. Any condition that inhibits energy delivery to ventricles will impair diastolic relaxation (ex: acute myocardial ischemia.)

Impaired ventricular filling is caused by increased stiffness of the ventricular wall (ex: fibrosis, LVH)

**Pathophysiology**: decreased compliance of ventricle requires higher pressure to push blood from the atria into the ventricles during diastole. Elevated pressure is transmitted to the pulmonary vasculature (causing pulmonary congestion) or systemic vasculature (causing peripheral edema.)

\[ \downarrow \text{Compliance} \rightarrow \uparrow \text{EDP} \rightarrow \uparrow \text{hydrostatic P} \rightarrow \text{pulmonary congestion or edema} \]

**Both systolic and diastolic dysfunction can result in right and left-sided heart failure.**

**Right-sided heart failure**: Key differences from left-sided failure

1. RV has thin walls and is very compliant. Therefore, it can accept lots of blood without big increases in pressure
2. RV ejects against the low-pressure pulmonary vasculature. Therefore, it cannot tolerate large increases in afterload, and conditions that cause sudden increase in afterload (ex: pulmonary embolism) will cause right-sided heart failure.
3. Most common cause of R-sided heart failure: left-sided heart failure (increased pulmonary pressure)
4. Cor pulmonale: right-sided heart disease secondary to pulmonary dysfunction, major cause of isolated right heart failure
5. Right heart failure causes left heart failure: decreased outflow from right ventricle results in decreased flow to the LA, causing decreased SV

**Compensatory Mechanisms**

Heart failure results in a decrease in SV and CO. As a result, BP falls (hypotension.) All of the following compensatory mechanisms are things that the body does to raise BP.
1. **Frank-Starling Mechanism**: Heart failure causes a downward shift in the Frank-Starling curve, which causes a decrease in SV. (See figure below and Fig 9.3 on page 215) Decrease in SV causes increase in preload, which subsequently increases SV. Helps to empty LV and preserve CO. However, if patient is in the flat part of the curve, an increase in preload does not have much impact on cardiac output. But, increased preload (or increased end-diastolic volume) does cause an increase in end-diastolic pressure, which is transmitted to the pulmonary vasculature and causes congestion (or edema if right heart failure.)

![Frank-Starling curves](image)

2. **Neurohormonal Alterations**: In response to ↓ CO, these mechanisms maintain BP by increasing total peripheral resistance and increasing intravascular (increases SV.)

\[ \text{BP} = \text{CO} \times \text{TPR} \]

These mechanisms are helpful initially, but chronic activation contributes to heart failure.

**A. Adrenergic Nervous System**: ↓ CO → ↓ BP → ↓ baroreceptor firing → ↑ sympathetic outflow and ↓ parasympathetic outflow. Causes an ↑ HR, ↑ CTY (β1), and vasoconstriction (α1).

- Increased HR and CTY causes increase in CO
- Vasoconstriction increases venous return to the heart, which increases preload and therefore increases SV, but only IF the ventricle is operating on the ascending portion of the curve (see figure above.)
- Vasoconstriction also increases TPR and helps maintain BP

**B. Renin-Angiotensin-Aldosterone System**: release of renin stimulated by:
1. decreased renal artery perfusion
2. decreased salt delivery to kidneys
3. direct stimulation of β2 receptors by adrenergic NS
How renin works:

- renin results in formation of **angiotensin II, a potent vasoconstrictor**, which increases TPR (renin converts angiotensinogen to angiotensin I, which is converted to angiotensin II via ACE)
- AII stimulates thirst, increases water intake (↑ intravascular volume)
- AII causes adrenal cortex to release aldosterone, which causes sodium and water to be absorbed from the distal tubule (↑ intravascular volume)
- Increase in TPR and intravascular volume causes increased CO

C. Anti-diuretic hormone (ADH, vasopressin)

- Release stimulated by AII and baroreceptors
- Promotes water reabsorption from the collecting duct, increasing intravascular volume

Negative Effects of Neurohormonal Compensatory Mechanisms

A. Increased Volume in the heart without substantial increases in SV exacerbates pulmonary congestion
B. Increased TPR increases afterload and impairs SV and CO
C. Increased HR causes increased metabolic demand, which reduces heart function (because heart can’t increase CO to meet demand)
D. Increased Sympathetic drive causes downregulation of beta receptors, resulting in decreased CTY
E. AII and Aldosterone stimulate fibrosis and heart remodeling via activation of cytokines

**Treatments for heart failure decrease compensatory mechanisms**

Role of ANP and BNP: atrial and B-type natriuretic peptides: beneficial hormones, released in response to cardiac stress and counteract compensatory mechanisms

3. Ventricular Hypertrophy and Remodeling

- In heart failure, wall stress is increased from either volume or pressure overload. \( \sigma = \frac{P r}{2 h} \) Chronically increased wall stress stimulates ventricular hypertrophy. Helps maintain contractile force and decreases wall stress, but hypertrophy causes an increased diastolic pressure.
- **Volume overload**: LV is dilated due to increased volume in the heart. Results in eccentric hypertrophy, characterized by elongation of myocytes (series)
- **Pressure overload**: increased afterload causes in higher systolic pressure. Results in concentric hypertrophy, characterized by increase in wall thickness without chamber dilation (parallel)
• Over time, ventricular function declines, causing chamber to dilate out of proportion with wall thickness. Increased wall stress → decompensation → downward spiral → heart failure
• Decrease in ventricular function seen in heart failure is caused by myocyte loss and dysfunction. Loss of myocytes results from necrosis and apoptosis secondary to catecholamines, AII, cytokines, and mechanical strain. Myocyte dysfunction causes decreased Ca homeostasis and ATP utilization

Factors that cause compensated heart failure to decompensate: (Table 9.3)
A. Increased metabolic demand: fever, hyperthyroid, tachycardia, pregnancy
B. Increased Volume: ingesting lots of salt and water, renal failure
C. Increased Afterload: HTN, pulm embolism
D. Decreased CTY: negative inotrophic meds, MI, Ethanol
E. Slow heart rate
F. Failure to take heart failure meds

Clinical Manifestations of Heart Disease

Left heart failure

Pathophysiology: impaired CO and elevated venous pressure due to failure of left ventricle. ↑ work of the breathing and can cause transudation of fluid into lungs.

Clinical Presentation:
1. dyspnea (can occur even if congestion is absent)
2. nocturia
3. dulled mental status
4. fatigue
5. orthopnea (labored breathing while lying down that is relieved by sitting upright, measured by number of pillows person sleeps on at night)
6. paroxysmal noctural dyspnea (severe breathlessness that awakens patients from sleep 2-3 hours after going to bed)
7. nocturnal cough
8. hemoptysis

Physical Findings:
General
1. cachexia (frail, wasted appearance from ↓ appetite and ↑ metabolic demand)
2. dusky appearance (↓ CO)
3. diaphoresis (↑ Sympathetic drive)
4. Cool extremities (↑ vasoconstriction)
**Pulmonary Exam:** Pulmonary rales, rhonchi, wheezing, pleural effusion, tachypnea, and Cheyne-Stokes respiration (alternating periods of hyperventilation and apnea due to ↑ circulation time between lungs and respiratory centers in the brain)

**Cardiac Exam:**
1. variation in apical impulse
   a. diffuse PMI: dilated cardiomyopathy
   b. sustained PMI: pressure overload from aortic stenosis or HTN
   c. “lifting” PMI: volume overload from mitral regurgitation
2. loud P2
3. S3 from abnormal filling of dilated chamber
4. S4 from atrial contraction into stiff ventricle
5. murmur of mitral regurgitation present if left ventricle is very dilated
6. sinus tachycardia (↑ Sympathetic drive)
7. pulsus alternans (alternating strong and weak peripheral pulses)

**Diagnostic Imaging and Testing:**
A. Chest x-ray: increased cardiothoracic ratio. When P > 15 mmHg, diameter of blood vessels supplying upper lung greater than those supplying lower lung (normally vessels to lower lungs are larger). When P > 20 mmHg, indistinct vessels and Kerley B lines (short linear markings at in lower peripheral lung) indicate interlobular edema. When P > 25 mmHg, opacification of the air space (alveolar edema.) May see pleural effusion.
B. Echo: assesses ventricular function
C. Cardiac Cath: determines valvular and ischemic causes of heart failure

**Right heart failure**

**Pathophysiology:** impaired CO and elevated venous pressure due to failure of right ventricle. Increases work of the breathing and can cause peripheral edema.

**Clinical Presentation:**
1. abdominal discomfort (because liver becomes enlarged)
2. anorexia (edema in GI tract)
3. peripheral edema, especially in ankles and feet
4. unexpected weight gain (due to increase in interstitial fluid)
Physical Findings:

General:
1. cachexia (frail, wasted appearance from ↓ appetite and ↑ metabolic demand)
2. dusky appearance (↓ CO)
3. diaphoresis (↑ Sympathetic drive)
4. Cool extremities (↑ vasoconstriction)

Pulmonary Exam: pleural effusion, tachypnea, Cheyne-Stokes respiration

Abdominal Exam: hepatic enlargement with Right Upper Quadrant tenderness

Cardiac Exam:
1. RV heave from RV enlargement
2. S3 or S4
3. murmur of tricuspid regurgitation
4. distention of jugular veins
5. edema

Diagnostic Imaging and Testing:
Chest x-ray: increased cardiothoracic ratio and enlargement of azygous vein due to increased right atrial pressure, may see pleural effusion

Prognosis and Treatment of Left and Right Heart Failure

Prognosis: Poor in the absence of correctable underlying causes
- 5 year survival from diagnosis is 50%
- if patient has severe symptoms, 1 year survival is 40%
- mortality due to refractory heart failure and ventricular arrhythmias
- ventricular arrhythmias caused by ventricular dysfunction, which is perpetuated by cytokines and neurohormones. Prognosis correlates with concentration of these substances in the body

Treatment: 5 main goals of therapy
1. Identify and correct underlying condition causing heart failure
2. Eliminate acute precipitating factors
3. Manage symptoms: treat pulmonary and systemic congestion and increase CO
4. Decrease neurohormonal response
5. Improve long term survival

Say YES to Drugs:
A. Diuretics:
- Mechanism of action: reduce volume causing reduced preload. End-diastolic volume and pressure fall, preventing pulmonary congestion.
- If patient is on the flat part of the Frank-Starling curve, then decrease in preload will not significantly reduce CO. Must monitor dosage carefully to ensure diuretic does NOT significantly ↓ CO.
- Only used if there is evidence of pulmonary congestion (rales) or edema
- Since patients with heart failure have reduced renal perfusion, they must be treated with LOOP diuretics (furosemide, torsemide, bumetanide), thiazide diuretics can also be used
- Caution: overdiuresis decreases CO and causes hypokalemia and hypomagnesia, which can precipitate arrhythmias.
- If patient has purely diastolic dysfunction, then they need high diastolic filling pressures, therefore must be careful with diuretics

B. Vasodilators:
- Mechanism of action: counteract vasoconstriction of neurohormonal mechanisms, results in reduced volume and ↓ ventricular remodeling
- Venous vasodilators (nitrates): decrease venous return to the heart, reducing LV diastolic filling pressure and pulmonary capillary hydrostatic pressure, results in decreased pulmonary congestion
- Arteriolar vasodilators (hydralazine): decrease systemic vascular resistance, therefore decreases afterload and increases SV. Increased CO balances decreased TPR, causing BP to stay the same.
- Balanced vasodilators (ACE inhibitors): affects both veins and arteries. ACE inhibitors reduce AII, which 1. reduces vasoconstriction 2. reduces aldosterone promoting sodium and water excretion and decreasing volume 3. increases bradykinin, a vasodilator 4. limits ventricular remodeling
- ACE inhibitors increase survival and are the standard first line therapy for patients with LV systolic dysfunction.
- What if patient can't tolerate ACE inhibitors? Angiotensin II receptor blockers (ARB) also block AII and do not cause cough associated with ACE Inhibitors. Can also use H-ISDN (combo of venous dilator isosorbide dinitrate and arteriolar dilator hydralazine). Third choice is Nesiritide (recombinant BNP), but administered IV and is expensive.
C. Inotropic Drugs

- Mechanism of action: increase intracellular Ca, increasing force of contraction, decreases end-diastolic volume and increases SV and CO
- Used to treat systolic ventricular dysfunction (not diastolic dysfxn)
- Beta agonists (dobutamine and dopamine): limited use because only IV form and drug resistance common
- Digitalis: IV or oral, increases contractility and improves symptoms, also decreases sympathetic drive, reducing afterload. Good for patients with heart failure and concurrent atrial fib because it treats arrhythmias too. Treats symptoms, but does NOT improve survival.

D. Beta Blockers

- Mechanism of action: unclear, but have been shown to decrease HR, increase CO and improve survival
- Use with caution to prevent decreased contractility

E. Spironolactone

- Mechanism of action: aldosterone antagonist, K-sparing diuretic
- Aldosterone contributes to fibrosis and remodeling of the heart, spironolactone counteracts
- Increases survival and relieves symptoms
- Must monitor to ensure hyperkalemia does not develop

F. Summary of Drug Therapy for chronic congestive heart failure

**Left Ventricular Systolic dysfunction:** ACE inhibitor + beta blocker
+ congestion (pulm or systemic): add diuretic
+ volume overload/ clinical deterioration: subtract beta blocker
+ persistent symptoms: add digoxin
+ advanced heart failure: add spironolactone
If can’t tolerate ACEI: ARB or H-ISDN
Other drugs to consider: anticoagulants and anti-arrhythmics (getting back to sinus rhythm increases CO)

**Diastolic dysfunction:** treat underlying cause! Then, use diuretics to decrease edema and pulmonary congestion, being careful not to substantially decrease end-diastolic pressure, use Ca channel blockers when diastolic dysfunction caused by HTN or hypertrophic cardiomyopathy

G. Other therapies for chronic heart failure: resynchronization of the ventricles using a pacemaker (indicated when ventricles do not contract
together) or cardiac transplant (indicated for patients with severe LV dysfunction whose condition is refractory to medical treatment)

**Acute Pulmonary Edema**

**Etiology:** Acute, left sided failure results from an MI or from a precipitating event in a patient with chronic compensated congestive heart failure

**Pathophysiology:** Acute, severe left sided heart failure causes elevated capillary hydrostatic pressure, rapid accumulation of fluid in the lungs

**Clinical Presentation:** Severe dyspnea and anxiety

**Physical Findings:** hypoxemia, cold, clammy skin, tachypnea, coughing up “frothy” sputum, rales, wheezing

**Treatment:** eliminate underlying cause and think “LMNOP”

- **L:** Lasix (furosemide): fast-acting diuretic ↓ preload and pulm capillary pressure
- **M:** Morphine: reduces anxiety and ↑ venous dilation (pooling of blood in periphery)
- **N:** Nitrates: reduces preload
- **O:** Oxygen: via face-mask
- **P:** Position: patient should be seated upright to allow pooling of blood in lower body, decreasing venous return to the heart

**Objectives:**

1. Identify the pathophysiologic mechanisms of clinical symptoms in heart failure (pages 3-8)
2. Develop a rationale initial medical regimen for a patient with heart failure based on underlying pathophysiology (pages 9-10)
3. Recognize clinical indications for device therapy and surgical intervention (bottom of page 11, top of page 12)
THE CARDIOMYOPATHIES
(from readings on Tuesday, Sept 28th - pgs 237-252)

Objectives:
Recognize common clinical presentations, including symptoms, physical findings, electrocardiographic changes and diagnostic imaging abnormalities in patients with primary myocardial disease

General Info on the Cardiomyopathies:
• Group of heart disorders where major abnormality is with myocardium... often results in symptoms of heart failure
• Often etiology is unknown
• Classification into 3 types: (based on anatomic appearance and abnormal phys of the LV)
  o Dilated cardiomyopathies → big ventricle and impaired systolic contraction
  o Hypertrophic cardiomyopathies → thick ventricle wall and abnormal diastolic relaxation but intact systolic fxn
  o Restrictive cardiomyopathies → very stiff myocardium and impaired diastolic relaxation but normal/near normal systolic fxn

Dilated Cardiomyopathy (DCM):

ETIOLOGY
• Myocyte damage causes ventricular dilation w/ only a little hypertrophy
  o While the majority of the causes for myocyte damage are idiopathic, commonly recognized causes are viral myocarditis, alcohol toxicity and gene mutations
  o DCM from Acute Viral Myocarditis → in youngsters, from Coxsackie group B or echo viruses, usually self limiting with full recovery... however some progress to DCM... (Hypothesis that myocardial destruction is immune-mediated, but not sure)
  o Alcoholic cardiomyopathy → only in small number of alcoholics, EtOH impairs cellular fxn, important b/c it’s one of the few reversible causes of DCM... stop EtOH and you get dramatic improvement of ventricular fxn
  o Several familial forms of DCM recently been discovered

PATHOLOGY
• Marked enlargement of all 4 chambers (though sometimes limited to R or L side)
• Chamber dilatation is out of proportion to hypertrophy
• Microscopically → myocyte degeneration w/ irreg hypertrophy and atrophy of myofibrils...
• Interstitial and perivascular fibrosis often extensive
• pic on pg 239 (fig 10.2) of the dilation of both ventricles
PATHOPHYS

- It starts from myocyte injury → decr contractility → decr SV
- Hallmark = ventricular dilation (volume overload) w/ decr contractile fxn ...
- As SV and CO impaired, 2 compensatory effects:
  - Frank-Starling mech where elevated EDV increases stretch on myofibers and thus incr subsequent SV
  - Neurohormonal activation
    - Primarily sympathetic NS → incr HR and CTLY
    - Kidneys spit out renin b/c of decline in renal blood flow → activation of renin-angiotensin-aldosterone axis → incr TPR and intravascular volume
- B/c of compensation, pt may be asymptomatic in early stages... but ...
- Compensation can actually be harmful in long run
  - Constant arteriolar vasoconstriction and incr systemic resistance make afterload bigger and so harder for LV to eject blood forward... and rise in intravascular volume further burdens ventricles → end result is pulmonary and systemic congestion
  - Chronically elevated ang II and aldosterone contributes to myocardial/vascular remodeling with fibrosis
- As ventricles enlarge over time, the mitral and tricuspid valves may fail to close together properly in systole → valvular regurg...
- 3 detrimental conseq of valvular regurg:
  - Excessive volume and pressure loads on atria → atria dilate → atrial fibrillation
  - Regurg into LA further decr forward SV into aorta
  - When regurg volume returns to LV during diastole, it adds to the volume overload

Figure 10.3. Pathophysiology of dilated cardiomyopathy. The reduced ventricular stroke volume results in decreased forward cardiac output and increased ventricular filling pressures. The listed clinical manifestations follow: JVD, jugular venous distention.
PRESENTATION
- manifestations of CHF (symptoms associated w/ low CO, pulmonary congestion and systemic congestion)
- see symptoms in boxes from diagram in last page
- b/c symptoms are insidious, pt may complain only of weight gain (edema) and SOB on exertion

PHYSICAL EXAM
- Signs of decr CO → cool extremities (vasoconstriction), low BP, tachycardia
- If sig RV failure develops → signs of systemic venous congestion → JVD, etc.
- Pulmonary exam → crackles and basilar chest dullness on percussion (from possible pleural effusions)
- Cardiac exam → enlarged heart w/ leftward displacement of diffuse apical impulse
- Auscultation:
  - S3 common (poor systolic fxn)
  - Murmur of mitral valve regurg (holosystolic) is common if sig LV dilation
  - Murmur of tricuspid valve regurg (also holosystolic) will be added if sig RV dilation

TESTS and IMAGING
- Chest x-ray → enlarged cardiac silhouette; possible pulmonary vascular redistribution, alveolar edema and pleural effusions...
- ECG → a whole bunch of things...
  - Atrial and ventricular enlargement (pg 92 and 93 give expls)
  - Wide array of arrhythmias but particularly a-fib and ventricular tachy
  - Conduction defects common (L or RBBB) -- (pg 94 for expl)
  - Diffuse repolarization (ST and T wave) abnormalities common
  - Localized Q waves from myofibrosis (resembles pattern of a previous MI)
- Echocardiography → valuable in diagnosis of DCM → demonstrates 4 chamber dilation w/ little hypertrophy and global reduction of systolic contractile fxn... can see the regurgs sometimes
- Cardiac cath → to see if coexistent coronary artery disease is contributing... can also look at pressure differences ...

TREATMENT (there is nothing in the objectives about treatment...it is so extensive and so detailed in the book - far more than I think we will need to know, so if you want extra info, look at pgs 241-243, but the main pts are as follows):
- Goal of therapy is:
  - Relieve symptoms
  - Prevent complications
  - Improve long-term survival
- Prognosis is poor
Hypertrophic Cardiomyopathy (HCM)

- Most common cardiac abnormality found in young athletes who die suddenly during vigorous physical exertion.
- Septal or LV hypertrophy that is NOT due to chronic pressure overload
- A.k.a → hypertrophic obstructive cardiomyopathy (HOCM) and idiopathic hypertrophic subaortic stenosis (IHSS)

ETIOLOGY
- Familial disease... (genetic)... autosomal dominant
- Mutation causes impaired contractile fxn → incr myocyte stress → compensatory hypertrophy and proliferation of fibroblasts
- Precise mutation determines age of onset of hypertrophy, extent and pattern of cardiac remodeling, and individual's risk of developing symptomatic heart failure or sudden death

PATHOLOGY
- Hypertrophy of any portion of the ventricles, but asymmetric hypertrophy of the ventricular septum is most common
- Histology is unusual and doesn't reflect normal hypertrophy of myocytes... myocyte disarray and fibrosis = diagnostic of HCM and play role in stiffness and arrhythmias

PATHOPHYS
- Predominant feature = ventricular hypertrophy that reduces compliance and relaxation (diastolic fxn) of the chamber such that filling becomes impaired
- Myocyte disarray → arrhythmias
- Can have HCM w/ or w/out an outflow tract obstruction depending on where hypertrophy is and how bad it is:

![Diagram of heart showing early systole and mid-late systole](image-url)

Figure 10.7: Pathophysiology of left ventricular (LV) outflow obstruction and mitral regurgitation in hypertrophic cardiomyopathy (HCM). Left panel: The LV outflow tract is abnormally narrowed between the hypertrophied interventricular septum and the anterior leaflet of the mitral valve (AML). It is thought that the rapid ejection velocity along the narrowed tract in early systole draws the AML toward the septum (small arrow). Right panel: As the mitral valve abnormally moves anteriorly and contacts the septum, outflow into the aorta is transiently obstructed. Because the mitral leaflets do not coapt normally in systole, mitral regurgitation (MR) also results.
PRESENTATION

- Symptoms vary widely from asymptomatic to really bad
- Avg age of presentation is **mid 20s**
- **Dyspnea** is most common symptom (due to elevated diastolic LV pressures)
  - Further exacerbated by high systolic LV pressure and mitral regurg in those with outflow tract obstruction
- **Angina** is common even in absence of CAD... myocardial ischemia from:
  - high oxy demand of increased muscle mass (hypertrophy)
  - narrowed small branches of coronary arteries w/in hypertrophied area
  - if outflow obstruction is present, high systolic ventricular pressure → incr wall stress → also increases myocardial oxy demand
- **Syncope**
  - from arrhythmias (caused by abnormal myofibers)
  - if outflow obstruction is present, CO falls transiently during exertion due to the increased pressure gradient b/t the LV and the outflow tract distal to the obstruction... this can lead to syncope
- **Sudden Death**
  - Arrhythmias can exaxerbate symptoms of HCM... A-fib is not well tolerated b/c of the loss of the end-diastolic atrial contraction and further impairment of diastolic filling... Ventricular fib is BAD and can cause sudden cardiac death w/out any of the other symptoms as warning.
Risk factors for sudden death = history of syncope, family history of sudden death, high risk mutations and extreme hypertrophy of the LV wall

PHYSICAL EXAM

- May be normal if asymptomatic
- \( S4 \) from left atrial contraction into the stiffened LV
- **Double apical impulse** \( \rightarrow \) palpable presystolic impulse over the cardiac apex from the forceful atrial contraction
- For those with systolic outflow obstruction:
  - **Carotid pulse** rises briskly in early systole, but then quickly declines as obstruction to cardiac outflow appears
  - **LV outflow obstructive murmur** (cresc-decresc) \( \rightarrow \) heard best at L lower sternal border
    - Heard best when using some maneuvers to differentiate it from an aortic stenosis murmur:

<table>
<thead>
<tr>
<th></th>
<th>Valsalva</th>
<th>Squatting</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preload</td>
<td>Decr</td>
<td>Incr</td>
<td>Decr</td>
</tr>
<tr>
<td>Afterload</td>
<td>Decr</td>
<td>Incr</td>
<td>Decr</td>
</tr>
<tr>
<td>HCM murmur</td>
<td>Incr</td>
<td>Decr</td>
<td>Incr</td>
</tr>
<tr>
<td>AS murmur</td>
<td>Decr</td>
<td>Incr (usually)</td>
<td>Decr</td>
</tr>
</tbody>
</table>

- FYI: **Valsalva method** is when pt “bears down” like if they were pooping... causes HCM murmur to increase in intensity...

- **Mitral regurg murmur** (holosystolic) \( \rightarrow \) heard best at apex

TESTS and IMAGING

- **ECG**
  - LV hypertrophy an LA enlargement
  - Prominent Q waves common in inferior and lateral leads b/c of depolarization thru hypertrophied septum
  - Diffuse T waves inversions \( \rightarrow \) can predate clinical, echo, or other manifestations of HCM
  - Atrial and ventricular arrhythmias common
- **Echocardiography** \( \rightarrow \) most helpful
  - Degree of LV hypertrophy can be measured
  - Identify regions of asymmetric wall thickness
  - Signs of ventricular outflow obstruction and imaging of the mitral valve
  - Doppler recordings during echo \( \rightarrow \) quantify regurg
  - Used as serial assessment in children with mild HCM to monitor
• Cardiac Cath → reserved for pts for whom diagnosis is uncertain or if cardiac surgery is planned
  o Major feature is for those with obstruction → finding a pressure gradient w/in outflow portion of LV

TREATMENT (again, we don’t need this for objectives, but in case you want it…)
• Beta blockers is standard therapy
• Ca channel antagonists
• Anti-arrhythmics
• Avoid strenuous exercise
• Antibiotic prophylaxis to ward off infective endocarditis
• Myomectomy (surgical removal of parts of hypertrophied muscle mass)
• Genetic counseling

Restrictive Cardiomyopathy (RCM)
• Less common than DCM and HCM
• Abnormally rigid (but not necessarily thickened) ventricles with impaired diastolic filling but usual systolic fxn
• Causes:
  o Fibrosis or scarring of endomyocardium
  o Infiltration of the myocardium by an abnormal substance, like amyloid

PATHOPHYS
• Rigid myocardium
  o Incr diastolic ventricular pressure → venous congestion → JVD, hepatomegaly and ascites, peripheral edema
  o Decr ventricular filling → decreased CO → weakness and fatigue

PRESENTATION
• Signs of both L and R sided heart failure (as stated just above)

PHYSICAL EXAM
• Signs of CHF → pulmonary rales, JVD, ascites
• Kussmaul’s sign → similar to constrictive pericarditis → JVD worsens with inspiration b/c RV can’t accommodate the incr venous return

TESTS and IMAGING
• Chest x-ray → normal sized heart w/ signs of pulmonary congestion
• ECG → nonspecific ST and T wave abnormalities; conduction disturbances such as AV block or BBB
• Transvenous endomyocardial biopsy, CT and MRI → very useful to differentiate RCM from constrictive pericarditis (RCM will not show a thickened pericardium)
THERAPY

- Poor prognosis... not really treatable unless you can get at underlying cause and if it's not too late...
- Symptom alleviation

**SUMMARY keeping Objectives in mind:**

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**TABLE 10.4. Summary of the Cardiomyopathies**

<table>
<thead>
<tr>
<th>Dilated Cardiomyopathy</th>
<th>Hypertrophic Cardiomyopathy</th>
<th>Restrictive Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular morphology</strong></td>
<td>Dilated LV with little hypertrophy</td>
<td>Marked hypertrophy, often asymmetric</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Fatigue, weakness, dyspnea, orthopnea, PND (symptoms of congestive heart failure)</td>
<td>Dyspnea, angina, syncope</td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td>Pulmonary rales, S3; if RV failure present: JVD, hepatomegaly, peripheral edema</td>
<td>S4; if outflow obstruction present: systolic murmur loudest at left sternal border, accompanied by mitral regurgitation</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Impaired systolic contraction</td>
<td>Impaired diastolic relaxation; LV systolic function vigorous, often with dynamic obstruction</td>
</tr>
<tr>
<td><strong>Cardiac size on chest radiograph</strong></td>
<td>Dilated</td>
<td>Normal or dilated</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td>Dilated, poorly contractile LV</td>
<td>LV hypertrophy, often more pronounced in septum; systolic anterior movement of MV with mitral regurgitation</td>
</tr>
</tbody>
</table>

LV, left ventricle; PND, paroxysmal nocturnal dyspnea; RV, right ventricle; JVD, jugular venous distension; MV, mitral valve.

---

hehehe... yes, a little crooked, I know...
General Info:

**Peripheral Vascular Disease:** umbrella term for pathologic entities that affect arteries, veins, lymphatics. Disease states of the peripheral vasculature interfere with the critical functions of blood vessels...

**Critical functions of blood vessels:**
- Regulate differential distribution of blood to tissues
- Actively synthesize and secrete vasoactive substances that regulate vascular tone
- Actively synthesize and secrete antithrombotic substances that maintain fluidity of blood and vessel patency
- Have an integral role in the transport and distribution of immune cells to traumatized or infected tissues

**Pathophysiologic causes processes of PVD can be placed in three categories:**
1. structural changes in vessel walls  
2. narrowing of the vascular lumen  
3. spasm of vascular smooth muscle

I’ll break these diseases down into types, which I’ll make as separate files (so they’ll hopefully be more easily accessible if you have questions about specific diseases).

**The peripheral vasculature disease types** as broken down in our book and my study guides are:

<table>
<thead>
<tr>
<th>Diseases of the Aorta</th>
<th>Occlusive Arterial Diseases</th>
<th>Disease Causing Arterial Spasm</th>
<th>Venous Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Study Guide Section 1)</td>
<td>(Study Guide Section 2)</td>
<td>(Study Guide Section 3)</td>
<td>(Study Guide Section 4)</td>
</tr>
<tr>
<td>Aortic Aneurysms</td>
<td>Peripheral Arterial Disease</td>
<td>Raynaud’s Phenomenon</td>
<td>Varicose Veins</td>
</tr>
<tr>
<td>Aortic Dissection</td>
<td>Acute Arterial Occlusion</td>
<td></td>
<td>Venous Thrombosis</td>
</tr>
<tr>
<td></td>
<td>Vascularitic Syndromes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Objectives to consider for each disease of the peripheral vasculature:**
- Recognize common clinical presentations – including symptoms, physical findings, ECG changes, and diagnostic imaging abnormalities in patients.
Peripheral Vasculature Diseases – Section 1
DISEASES OF THE AORTA

First, some general review of the aorta:
- The largest conductance vessel of the vascular system
- Can break it down into four sections:

<table>
<thead>
<tr>
<th>Section of Aorta</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aorta</td>
<td>• 3 cm diameter at base of heart (LA)</td>
</tr>
<tr>
<td></td>
<td>• 5-6 cm in length</td>
</tr>
</tbody>
</table>
| Aortic arch            | • three major branches
                          | o brachiocephalic (bifurcates to give right common carotid and right subclavian)
                          | o left common carotid
                          | o left subclavian                                                      |
| Descending aorta       | • from arch, the diameter narrows to 2-2.5 cm                           |
| Abdominal aorta        | • subdiaphragmatic
                          | • provides arteries to abdominal viscera
                          | • bifurcates into left and right common iliacs, which supply the pelvic organs and lower extremities |

- Aorta is an artery…it is composed of:
  1. intima
     a. endothelial layer
  2. media
     a. internal elastic lamina
     b. smooth muscle cells
     c. matrix including elastic fibers and collagen, respectively for stretching and strength – in aorta, ratio of elastin to collagen is 2:1, allowing aorta to expand during systole and recoil during diastole
     d. external elastic lamina
  3. adventitia
     a. collagen fibers
     b. perivascular nerves
     c. vasa vasorum supplies oxygenated blood to the aorta

- Aorta’s recoil against the closed aortic valve during diastole is what promotes forward propagation of blood flow.
  o with age, get degeneration of the elastic fibers of the aorta and its branches – collagen becomes more prominent and arteries stiffen
  o stiffer arteries → increased systolic blood pressure
  o Aorta, thus, with age is subject to injury from mechanical trauma due to high pulsatile pressure and shear stress.

- Diseases of the aorta commonly appear as aneurysm, dissection, or obstruction.
  o Aneurysm and dissection are discussed in the text…I will elaborate on them in colored text boxes (的笑容) below…
Aortic Aneurysms (AA)

Clinical Presentation:
- Often asymptomatic
- Patient may be aware of a pulsatile mass (especially if abdominal aorta is involved)
- Patient may have symptoms caused by compression of other structures by the aneurysm… examples:
  - Back pain (erosion of the vertebrae by large abdominal aneurysm)
  - Dysphagia/hemoptysis/respiratory problems (esophagus or trachea compressed by thoracic aneurysm)
  - Hoarseness (stretching of the left recurrent laryngeal due to aortic aneurysm)
  - Heart failure (aortic regurgitation from dilation of the aortic ring by aneurysm of the ascending thoracic aorta)

Physical Findings:
- Aneurysms of the abdominal aorta may be discovered by careful abdominal palpation – one would feel a large, pulsatile mass.
- Aortic aneurysms most often seen incidentally on chest or abdominal x-rays, especially if the aneurysm’s walls are calcified.

Etiology and Pathogenesis:
- Atherosclerosis is implicated in approximately 90% of abdominal aortic aneurysms.
  - Atherosclerosis more common in descending aorta than ascending portion.
- Atherosclerotic aneurysms rarely develop before age 50 and are more common in men
  - Development is accelerated by smoking, hypertension, dyslipidemia (and other factors that predispose to atherosclerosis in general)

- Ascending aortic aneurysms are uncommonly atherosclerotic; instead they are related to cystic medial degeneration.
  - Cystic medial degeneration (aka cystic medial necrosis) involves degeneration and fragmentation of elastic fibers – w/ later accumulation of collagenous and mucoid material in the medial layer.
  - This condition affects ascending aorta due to greatest pulsatile expansions happening there

- Medial degeneration can also happen with connective tissue disorders:
  - Marfan syndrome
  - Ehlers-Danlos
- Medial degeneration can happen in response to hypertension and aging.

- Pseudoaneurysm: may develop at sites of vessel injury caused by infection or trauma (puncture of vessel during surgery or percutaneous catheterization)

- Vessel wall can also be weakened by the likes of: syphilis, TB, staph, strep, salmonella, inflammatory diseases, genetic defects of connective tissue fibers (approx 5-10% of patients have an affected first-degree relative)
Pathology:
- General terminology: Aneurysm = abnormal, localized dilatation of an artery

- In the aorta, must distinguish aneurysm from diffuse ectasia, a lesser increase of aortic diameter due to fragmentation of elastic fibers, decrease number of smooth muscle cells, increase in acid mucopolysaccharide.

- To have aortic aneurysm, either:
  1. the diameter of a portion of the aorta has increased by 50% or more…or
  2. a portion of the abdominal aorta has enlarged to greater than 3.5-4cm in diameter

- True aneurysm: a dilatation of all three layers of the aorta (gives a bulge in the vessel wall) – two types:
  - True fusiform: entire circumference of a segment of the aorta is dilated (most common)
  - True saccular: localized outpouching involving only a portion of the circumference

- Aortic aneurysms may be confined to the abdominal aorta (most common), the thoracic aorta, or both.

- Pseudoaneurysm (aka false aneurysm): a contained rupture of the vessel wall that mimics the appearance of a true aneurysm – this develops when blood leaks out of lumen through a hole in the intimal and medial layers and is contained by merely the adventitia or perivascular organized thrombus.
  - Very unstable lesion and is prone to rupture.

Pathophysiology:
- Most devastating consequence of aortic aneurysm is rupture…often fatal.
- Aneurysm may rupture suddenly or may leak slowly, extravasating blood into the vessel walls and causing pain and local tenderness.
- Risk of rupture is related to the size of the aneurysm – LaPlace Law: the larger the vessel radius, the larger the wall tension required to withstand a given internal fluid pressure.

- 5 year risk of rupture of an abdominal aortic aneurysm
  - <5cm in diameter is 1-2%
  - >5cm in diameter is 20-40%

Diagnostic tests/Imaging:
- Chest or Abdominal X-ray: Aortic aneurysms often first suspected when dilation is incidentally observed on an x-ray that was being taken for something else – particularly visible on x-ray if aneurysm’s walls are calcified.
- US, CT, MRI, or conventional arteriography: used to confirm aortic aneurysm diagnosis

Treatment:
1. Transabdominal surgical repair w/ placement of a prosthetic graft: gold standard for treatment (when diameter is >4.5-5cm or is expanding at a rate of more than 1cm/year)
2. Percutaneous deployment of an endovascular graft: less invasive, cost-effective, with similar morbidity and mortality to open repair.
- Of these treatments, if aneurysm exceeds 6cm in diameter, surgical repair is recommended.
- For Marfan syndrome patients, surgical repair is often recommended at a lower threshold.
**Aortic Dissection (ADis)**

**Clinical Presentation:**
- **Sudden, severe pain with a “ripping” or “tearing” quality**
  - In anterior chest: **type A dissection** (involves the ascending aorta)
  - Between the scapulae: **type B dissection** (involves descending thoracic and/or abdominal aorta)
- **Pain travels** as the dissection propagates along the aorta
- **Other symptoms are those relating to the complications of ADIs:**
  - Rupture
    - pericardial tamponade
    - hemomediatinum
    - hemothorax (usually left sided)
  - Occlusion of aortic branch vessels
    - carotid (stroke)
    - coronary (MI)
  - Distortion of aortic annulus
    - splanchic (organ infarction)
    - renal (acute renal failure)

**Physical Findings:**
- **Vitals:** Hypertension often found either as the underlying cause of dissection, resulting from diminished renal vascular flow (renin-angiotensin system activation), or due to sympathetic nervous system response to severe pain
  - If dissection has occluded flow to one of the subclavian arteries, will see different systolic BPs in each arm
- **Neurologic:** deficits (related to stroke) may be present if carotids are affected
- **Auscultation:** If have Type A dissection (involving ascending aorta), may get aortic regurgitation, which means may hear an early diastolic murmur.

**Etiology:**
- **Two postulated origins:**
  1. ADIs might arise from a tear in the intimal layer, allowing blood from lumen to enter into the media and propagate along the plane of the muscle layer.
  2. ADIs might arise from rupture of the vasa vasorum (in the adventitia) w/ subsequent hemorrhage into the media, forming a hematoma in the arterial wall that then tears through the intima and into the vessel’s lumen.
- **Predisposition to ADIs can come from any condition that interferes with the normal integrity of the elastic or muscular components of the medial layer.** Some conditions that can predispose are:
  - Chronic HTN (more than 2/3 of ADis patients have HTN history)
  - Aging
  - Cystic medial degeneration (a feature of diseases including Marfan and Ehlers-Danlos)
- Traumatic insult to the aorta may also incite dissection.
- **ADIs is most common in ages 50-60 and in men.**

**Pathology:**
- **Two possible types of Aortic Dissection:**
  1. Type A: involves the ascending aorta (is most common with 65%) and may involve the arch (10%)
  2. Type B: involves the descending thoracic aorta (20%) and/or abdominal aorta (5%)
- **Distinction of type A or B is important as is influences treatment strategy and prognosis.**
- **Type A ADis tends to be more devastating due to potential extension into the coronaries, arch vessels, and aortic valve support structures.**
- **Dissections can be classified as acute or chronic:**
  - Acute: present with duration of symptoms less than 2 weeks
Pathophysiology:
- In aortic dissection, a blood filled channel divides the medial layers of the aorta, (bluntly) dissecting the intima from the adventitia along various lengths of the vessel.
- ADIs is definitely a life-threatening condition.

Diagnostic tests/Imaging:
- **Diagnosis of ADIs must not be delayed!** Death may ensue.
- **Transesophageal Echocardiography:** one of the most useful tests; often the initial diagnostic test because of its universality (most hospitals can do this), great sensitivity and specificity, and reasonable cost.
- **MRI and contrast angiography:** also useful for detecting ADIs

Treatment:
- Treatment of ADIs must have **aim to stop the dissection that’s taking place.**
- If acute ADIs, **must reduce systolic BP and decrease LV contraction force** to minimize aortic wall shear stress.
  - Drugs to use: **Beta-blockers** (to reduce force of LV contraction and to lower BP), **vasodilators** (to rapidly reduce BP).
- Surgical therapy: repairing intimal tear, suturing edges of false channel, sometimes inserting a synthetic aortic graft
- **Type A dissections:** early surgical correction shown to improve outcome compared with drugs alone.
- **Type B dissections:** if uncomplicated and subacute, managed with **aggressive drugs alone** – early surgical intervention does not improve patient outcome.
  - If develop evidence of propagation of ADIs, compromise of major branches of aorta, impending rupture, or continuing pain, then do surgery.
- Catheter based repair with endovascular stent-grafts is being explored as an alternative to surgical intervention.
Peripheral Vasculature Diseases – Section 2

OCCLUSIVE ARTERIAL DISEASES

- These diseases may be caused by atherosclerosis, thromboembolism, or vasculitis (inflammation of the vessel wall).
- Clinical presentation of occlusive arterial diseases results from decreased blood flow to the affected limbs or organs.

This section will summarize:
1/ Peripheral Arterial Disease
2/ Acute Arterial Occlusion
3/ Vasculitic Syndromes (four of these)

---

Peripheral Arterial Disease (PAD)

Clinical Presentation:
- **Claudication**: symptom of exertional limb fatigue and pain
  - Patients with PAD often report discomfort of buttock, thigh, or calf that is precipitated by walking and relieved with rest.
- **Severe PAD patient may report pain at rest in the feet or toes.**
- Can have **ulceration**, infection, skin necrosis, and even gangrene (threatening viability of a limb).

Physical Findings:
- **Loss of pulses distal to the stenotic segment**
- **Bruit**s (swishing sounds that indicates turbulent blood flow) may be audible in abdomen (renal or mesenteric arteries) or over iliac, femoral, or subclavian arterial stenoses.
- Can see muscle atrophy, pallor, cyanotic discoloration, hair loss, occasional gangrene and necrosis of foot/digits.
- **Ischemic ulcers** start as small traumatic wounds on **tips of toes or lateral malleolus** – as opposed to diabetic ulcers, which are found more proximally and on the medial malleolus.

- Compare blood pressure measure from ankle to BP measure from arm – called **Ankle-Brachial Index (ABI)**.
  - Use BP cuff and a Doppler instrument to detect blood flow
  - **Normal**: ABI (ankleBP/armBP) ≥ 1.0
  - **Claudication**: ABI < 0.9
  - Patient with pain at rest and severe arterial compromise: ABI < 0.5

Etiology:
- PAD may result from **atherosclerotic plaques in large and medium size arteries.**
- **PAD is most prevalent vascular disorder** – 0.3% of total population, 5.2% of population over age 70
- **Risk factors**: smoking, dyslipidemia, diabetes mellitus, hypertension
- 40% of patients with symptomatic PAD also have significant coronary artery disease

Pathology:
- Generally, **atherosclerotic disease in arteries of pelvis or lower limbs**
- **Identical pathology to that of atherosclerotic coronary artery disease (CAD)**
- have **progressive stenosis** and obstruction of blood flow
Pathophysiology:

- Complications from ischemia distal to stenosis.
- Imbalance between oxygen supply and demand: exercise raises demand, stenosed/obstructed artery can’t supply.
- Rest improves symptoms as supply-demand balance is restored.
- Amount of blood flow reduction is very closely linked to the amount of vessel narrowing, length of stenosis, and viscosity of blood…
- Poiseuille’s Law: volume rate of flow is \( Q = \frac{(\Delta P \pi r^4)}{(8 \eta L)} \)
  - Where \( \Delta P \) is pressure difference between the ends of the stenosis, \( L \) is the length of the stenosis, \( r \) is the radius or the vessel, and \( \eta \) is the viscosity of the blood.
  - The most important component of the system is the radius \( r \) as it is present in the calculation of blood flow to the power of 4! So, when the vessel’s radius is decreased by ½, the vessel’s flow is decreased by \( (\frac{1}{2})^4 = \frac{1}{16} \).
  - Note that higher flow \( (Q) \) rates across a stenosis with a fixed length \( (L) \) and radius \( (r) \) indicate a larger pressure gradient \( (\Delta P) \) – blood turbulence results in a loss of energy and thus a decreased perfusion pressure post stenosis.
  - What’s the point? We can use this law to show how blood flow is limited to structures distal to the stenosis.

- In PAD, obstructed arteries can’t respond to vasodilating stimuli during exercise – blood flow is further limited.
- Dysfunctional atherosclerotic endothelium doesn’t release normal amounts of vasodilators – blood flow limited again.

- Due to ischemia, can see changes in physical and biochemical state of muscles distal to the stenosis.
  - Denervation and dropout of muscle fibers \( \rightarrow \) reduced muscle strength and atrophy
  - Abnormalities of mitochondrial oxidative metabolism in viable muscle fibers \( \rightarrow \) muscle weakness

Diagnostic tests/Imaging:
- Duplex Ultrasonography: might be used to visualize and assess extent of arterial stenoses and corresponding reductions in blood flow

Treatment:
- Lifestyle/Risk Factor Modification…
  - Quit smoking
  - Lower lipids
  - Control diabetes
  - Control hypertension
  - Start an exercise program

- Drug Therapies: goals are symptomatic relief and improved exercise capacity; in severe PAD, goals are healing ulcers and preventing limb loss
  - Anti-platelet therapy: not actually proven to reduce symptoms or prevent thrombotic complications, but given to all PAD patients
  - Phosphodiesterase inhibitor (cilostazol): thought to improve claudication by inducing vasodilatation and inhibiting platelet aggregation (note, however, that most vasodilators are not helpful in relieving claudication)
  - Drugs that improve RBC and WBC deformability (pentoxifylline): may improve symptoms

- Medical Procedures:
  - Mechanical revascularization: indicated when drugs didn’t relieve disabling claudication or when have severe leg ischemia
  - Catheter-based interventions: percutaneous transluminal angioplasty and stent implantation can be done on selected patients with few complications
  - Bypass operations: go around occluded arteries with prosthetic or saphenous vein grafts
  - Amputation: needed in severe limb ischemia if blood flow can’t be reestablished
Acute Arterial Occlusion (AAO)

Clinical Presentation:
- Symptoms are related to reduced blood supply to tissues and are known as the “five P’s”:
  - Pain
  - Pallor
  - Paralysis
  - Paresthesia
  - Pulselessness
- A sixth “P” is sometimes present:
  - Poikilothermia (coolness)

Etiology:
- AAO has two possible causes:
  1. Embolization from a cardiac or vascular site
  2. Thrombus formation in situ

- The origins of arterial emboli are:

<table>
<thead>
<tr>
<th>Cardiac Origin</th>
<th>Aortic origin</th>
<th>Venous origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>From stagnant LA flow (like in atrial fibrillation, mitral stenosis)</td>
<td>From thrombus material overlying an atherosclerotic segment</td>
<td>From a paradoxical embolism, that travels through an abnormal intracardiac shunt (e.g. an ASD)</td>
</tr>
<tr>
<td>From LV mural thrombus (e.g. dilated cardiomyopathy, MI, ventricular aneurysm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From valvular lesions (endocarditis, mitral stenosis, thrombus on prosthetic valve)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From LA myxoma (a mobile tumor in the LA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Thrombus formation in the arteries may appear at sites of endothelial damage, atherosclerotic stenoses, or within bypass grafts.

Pathophysiology:
- Extent of tissue damage from thromboembolism in AAO relates to:
  - site of occluded artery
  - degree of collateral circulation serving the tissue distal to the obstruction.

Treatment:
- Anticoagulation
  - Often heparin to prevent propagation of the clot and reduce likelihood of additional emboli.
- Intra-arterial thrombolysis
  - Can use tissue plasminogen activator (TPA) to eliminate acute thrombi
- Catheter-based thrombectomy
  - Also used to eliminate acute thrombi
- Surgery (removal of the thrombus or arterial bypass)
  - Done only to improve severely compromised blood flow
Vasculitic Syndromes

Our book introduces four syndromes that fall into this category. Before outlining these syndromes, I’ll recap the relevant general information:

Vasculitis: inflammation of the vessel wall

- Can result from:
  1. Immune complex deposition
  2. Cell-mediated immune reactions against the vessel wall

  1. Immune complexes activate complement cascade → get release of chemoattractants and anaphylatoxins → get increased vascular permeability → neutrophils come to the vessel wall → neutrophils injure the vessel with their lysosomal contents and toxic oxygen-derived free radicals.

  2. Cell-mediated immune reactions: T cells bind vascular antigens → release lymphokines → attract additional lymphocytes and macrophages to the vessel wall.

- These inflammatory processes can cause end-organ ischemia because of either vascular necrosis or local thrombosis.
- Most Vasculitic Syndromes do not have known causes…they’re distinguished from each other by pattern of vessels involved and histologic characteristics.

Table of Vasculitic Syndromes (modified from p.336):

<table>
<thead>
<tr>
<th>Arteries Commonly Affected</th>
<th>Polyarteritis nodosa</th>
<th>Takayasu’s arteritis</th>
<th>Giant cell arteritis</th>
<th>Thromboangitis obliterans (Buerger’s disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries Commonly Affected</td>
<td>small to medium size (esp. renal, coronary, hepatic, skel musc)</td>
<td>aorta and its branches</td>
<td>medium to large size (esp. cranial, aortic arch &amp; branches)</td>
<td>small size (esp. distal arteries of extremities)</td>
</tr>
<tr>
<td>Histology</td>
<td>PMNs, acute fibrinoid necrosis, aneurismal dilatation</td>
<td>Granulomatous arteritis w/ fibrosis; significant luminal narrowing</td>
<td>lymphocytes, intimal fibrosis, granuloma formation</td>
<td>inflammation and thrombosis without necrosis</td>
</tr>
</tbody>
</table>
Vasculitic Syndrome: Polyarteritis nodosa (PAN)

Clinical Presentation:
- **Generalized inflammatory symptoms:**
  - Fever
  - Malaise
  - Musculoskeletal pains
- Symptoms may also relate to decreased organ blood flow:
  - Hypertension (due to reduced flow into the renal arteries and, thus, renin-angiotensin system activation)

Etiology & some Epidemiology:
- PAN may be idiopathic (from an obscure or unknown cause).
- Is also seen with Hepatitis B infection (30% of PAN cases).
- Prevalence of 6/100,000 – **more common in males**

Pathology:
- Many **nodules found along course of vessels**.
- **Histologic examination of affected areas of arteries shows:**
  - PMNs in all three vessel layers (intima, media, adventitia)
  - **Intimal proliferation and degeneration**
    - Fibrinoid necrosis with occlusion of the lumen
- **Grossly, the vessel wall (including elastic lamina) is disrupted and leads to aneurismal dilatation.**

Pathophysiology:
- Distal to the involved vessel, **get ischemia that damages tissues and visceral organs**; kidney, heart, liver are commonly affected.

Diagnostic Imaging/Testing:
- **Biopsy of involved vessel: used to diagnose PAN**
- Blood test: **Antineutrophil cytoplasmic antibodies (ANCAs)** circulating – suggests necrotizing vasculitis

Treatment:
- **Prednisone** and other **Immunosuppressive Agents** (with treatment, good prognosis: 5 year prognosis of up to 80%)
- If disease goes **untreated, prognosis is poor** (5 year = 15%)
Vasculitic Syndrome: Takayasu’s Arteritis

Clinical Presentation:
- General symptoms:
  - Fever
  - Malaise
- Focal symptoms related to inflammation of affected vessel:
  - Cerebrovascular ischemia (brachiocephalic or carotid a.)
  - MI (coronary a.)
  - Arm claudication [remember this is a symptom of exertional limb fatigue and pain] (brachiocephalic or subclavian a.)
  - Hypertension (renal a.)

Physical Findings:
- Takayasu’s Arteritis called “Pulseless disease”...
  - Carotid and limb pulses diminished or absent (85% patients) at time of diagnosis.
- Possible finding of aortic aneurysm with palpation.

Etiology & some Epidemiology:
- Idiopathic (from an obscure or unknown cause).
- Occurs worldwide, but most commonly reported from Asia and Africa
- Most often seen in women < 40 years old.

Pathology:
- Takayasu’s arteritis targets the aorta and its major branches.
- Uncommonly causes aortic aneurysm or aortic dissection.
- Histologic examination of affected areas of arteries shows:
  - Plasma cells and lymphocytes infiltrating media and adventitia
  - Giant cells
  - Intimal proliferation
  - Disruption of elastic lamina
  - Fibrosis

Pathophysiology:
- Distal to the involved vessel, get ischemia that damages tissues.

Treatment:
- Steroid and cytotoxic drugs may reduce vascular inflammation and give symptomatic relief.
- Surgical bypass of obstructed vessels may be helpful for severe cases.
**Vasculitic Syndrome: Giant Cell Arteritis (aka Temporal Arteritis)**

**Clinical Presentation:**
- Symptoms depend on distribution of affected arteries…may include:
  - Prominent headache (from temporal a. involvement)
  - Facial pain
  - Claudication of jaw while chewing (facial a. involvement)
  - 50% patients have visual impairment (ophthalmic a. involvement) – irreversible blindness can result

**Physical Findings:**
- With Giant Cell Arteritis, may find **diminished temporal pulses**.

**Etiology & some Epidemiology:**
- Associated with Polymyalgia Rheumatica (an inflammatory condition)
- Uncommon disease (24/100,000).
- Most often seen in patients > 55 years old.
- 65% patients are females.
- Giant Cell Arteritis is usually a self-limiting disease of 1-5 years.

**Pathology:**
- **Giant Cell Arteritis** is a disease of **medium to large size arteries**: common involvement of **cranial vessels, aortic arch and its branches**.
- **Histologic examination of affected areas of arteries shows:**
  - Lymphocytes infiltrating
  - Intimal fibrosis
  - Focal necrosis with Granulomas containing Multinucleated Giant Cells

**Pathophysiology:**
- Distal to the involved vessel, **get ischemia that damages tissues**.

**Diagnostic Imaging/Testing:**
- **Erythrocyte Sedimentation Rate**: elevated (marker of inflammation)
- **C-reactive Protein**: elevated (marker of inflammation)
- **Biopsy of involved vessel (usually a temporal artery)**: used to diagnose Giant Cell Arteritis
- **Ultrasound (US)**: can support diagnosis if see a hypoechoic (def: region in US image where echoes are weaker or fewer than normal) halo around lumen with arterial stenosis and/or occlusion

**Treatment:**
- **DON’T WAIT FOR BIOPSY RESULTS BEFORE TREATING.**
- Go ahead and give **high-dose systemic steroids** to treat vasculitis and prevent visual damage
**Vasculitic Syndrome:** Thromboangiitis Obliterans (aka Buerger’s Disease)

**Clinical Presentation:**
- **Triad** of symptoms/signs:
  1. **Distal arterial occlusion**
     - Leads to arm and foot claudication
     - Ischemia of the digits
  2. **Raynaud’s phenomenon** (see Diseases Causing Arterial Spasm study guide)
  3. **Migrating superficial vein thrombophlebitis** (inflammation of a vein caused by a blood clot)

**Etiology & some Epidemiology:**
- **Strongly associated with smoking.**
- Increased incidence of HLA-A9 and HLA-B5 in Thromboangiitis Obliterans patients.
- Most common in **men < 40 years old.**
- Only 2% of cases in females.

**Pathology:**
- Thromboangiitis Obliterans is an **inflammatory disease of small and medium size arteries, veins, and nerves.**
- It involves **distal vessels of upper and lower extremities.**
- **Histologic** examination of affected areas of arteries shows:
  - Inflammation and thrombosis without necrosis
  - Preservation of internal elastic lamina

**Pathophysiology:**
- Distal to the involved vessel, **get ischemia that damages tissues.**

**Diagnostic Imaging/Testing:**
- Cannot detect and thus **cannot use traditional lab markers** for inflammation and autoimmune disease.
- **Arteriograph:** see **areas of stenosis** interspersed w/ normal appearing vessels; **more severe disease distally**;
  - collateral vessels with “corkscrew” appearance around stenotic regions; no atherosclerosis in proximal arteries
- **Tissue Biopsy:** diagnosis can be established this way – but **rarely need to do this**
- Biopsy of involved vessel: reveals an **occlusive, highly cellular, inflammatory thrombus** – limited vessel wall involvement, preservation of the internal elastic lamina

**Treatment:**
- **Only treatment is to STOP SMOKING…**
  - Prevents progression of disease and complications
**Raynaud’s Phenomenon**

**Clinical Presentation:**
- **Color change in the fingers or toes that comes with cold temperature settings or emotional stress**
- Usually get a **triphasic color response** in the fingers (or toes):

<table>
<thead>
<tr>
<th>Phase</th>
<th>Color</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>distinct white</td>
<td>blood flow is interrupted</td>
</tr>
<tr>
<td>Phase 2</td>
<td>blue (cyanotic)</td>
<td>local accumulation of desaturated hemoglobin</td>
</tr>
<tr>
<td>Phase 3</td>
<td>reddish (ruddy)</td>
<td>blood flow begins to resume</td>
</tr>
</tbody>
</table>

- Color changes may be accompanied by **numbness, paresthesias, or pain of the affected digits.**
- Only 16% of patients report worsening of their symptoms over an extended time, so prognosis is usually benign.

**Etiology:**
- **Primary Raynaud’s Phenomenon** (aka Raynaud’s Disease): occurs as an **isolated disorder**
  - Patients are **majority females between 20-40 years old**
  - Apparently no genetic component
- **Secondary Raynaud’s Phenomenon**: appears as a **component of other conditions**, such as…
  - Connective tissue diseases: like scleroderma, SLE
  - Arterial occlusive disorders: (see Section 2 study guide for Peripheral Vasculature Diseases)
  - Carpal tunnel syndrome: tunnel protects the median nerve and nine tendons; pressure placed on the nerve produces the numbness, pain, and eventually hand weakness
  - Thoracic outlet syndrome: compression of the neurovascular structures at the superior aperture of the thorax; the brachial plexus (95%), subclavian vein (4%), and subclavian artery (1%) are affected
  - Blood dyscrasias: a general term used to describe any abnormality in blood or bone marrow's cellular components, such as low WBC count, low RBC count, or low platelet count
  - Certain drugs: like…beta-blockers, ergotamine preparations (used for migraine headaches), some chemotherapy agents, and vasoconstrictor drugs (such as some OTC cold meds and narcotics)
  - Thermal or vibration injury: like with workers who operate vibrating tools

**Pathology:**
- Raynaud’s Phenomenon is a **vasospastic disease of the digital arteries** (usually of the fingers, but 40% of patients also have involvement of their toes).
- People with this condition can experience vasospasm, an **extreme vasoconstrictor response** when they’re in **cold temperature settings** or under **emotional stress.**
- Vasospasm causes **temporary blockage** of vascular lumen, which blocks blood flow.
Pathophysiology:
- Even in non-Raynaud’s people, the body responds to cold by activating the sympathetic nervous system.
- Fingers and toes only have α-receptors – which means they can only vasoconstrict in the presence of NE.
- In healthy people, get moderate vasoconstriction in fingers and toes – in Raynaud’s patients, get severe vasoconstriction (in cold environment or when under emotional stress).

- Possible mechanisms for overactive/severe vasoconstriction in Primary Raynaud’s:
  - Exaggerated sympathetic discharge in response to cold
  - Heightened vascular sensitivity to adrenergic stimuli
  - Excessive release of vasoconstrictor stimuli (serotonin, thromboxane, endothelin)

- Possible mechanisms for overactive/severe vasoconstriction in Secondary Raynaud’s:
  - With connective tissue diseases or arterial occlusive diseases, digital lumen is largely obstructed by sclerosis or inflammation → higher susceptibility to sympathetically mediated vasoconstriction.

Treatment:
- **Lifestyle**…
  - Avoid cold places.
  - Wear warm clothing.
  - If have to be in cold place, use insulated gloves or footwear.

- **Meds**…
  - Some success in preventing vasospasm with drugs that relax vascular tone…
    - α-adrenergic blockers
    - calcium channel blockers
Peripheral Vasculature Diseases – Section 4
VENOUS DISEASE (p. 339-345)

General Info about veins and such…

Veins: high-capacitance vessels that carry blood from the capillaries toward the heart; have thinner walls than arteries; often have one-way valves at intervals to prevent reflux of the blood, which flows in a steady stream and is in most cases dark-colored due to the presence of reduced hemoglobin.

- Veins hold more than 70% of the total blood volume.
- They’re not as muscular in structure as the arteries are…
  - The subendothelial layer of veins is thin
  - Compared to arteries, tunica media has fewer, smaller bundles of smooth muscle cells intermixed with reticular and elastic fibers.

*Note that as this section is part of the Peripheral Vasculature Diseases, the veins we will discuss are mostly veins in the extremities! That said…*

- Veins of extremities have intrinsic vasomotor activity, but transport of blood back to the heart does require external compression from surrounding skeletal muscles as well as one-way valves to keep the blood moving toward the heart.

- Deep vs. Superficial Veins of the Extremities:

<table>
<thead>
<tr>
<th>Course in body…</th>
<th>Deep Veins</th>
<th>Superficial Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>generally course along the arteries and return blood to the heart</td>
<td>located subcutaneously and eventually drain into the deeper veins through a perforating connectors</td>
<td></td>
</tr>
</tbody>
</table>

This study guide will follow the book by breaking Venous Diseases down into three sub-types:
1/ Varicose Veins
2/ Venous Thrombosis – Deep Venous Thrombosis
3/ Venous Thrombosis – Superficial Thrombophlebitis

Here I go with color co-ordinated boxes again…hope they help!
**Varicose Veins**

Clinical Presentation:
- Patient with **dilated, tortuous superficial vessels** – usually involving legs
  - Most often occur along the saphenous veins, but can occur in any vein…for example:
    - Hemorrhoids (ano-rectal varicose veins)
    - Varicocele (spermatic cord varicose vein)
    - Esophageal varices (esophageal varicose veins): associated with portal hypertension
- Many patients are asymptomatic, but seek clinical help for cosmetic reasons.

- If have symptoms, they can include:
  - Dull ache or pressure sensation in legs after prolonged standing
  - Swelling and skin ulceration, usually near ankle: due to superficial insufficiency when venous valves can’t function normally due to dilation of the veins
  - Superficial vein thrombosis: due to stasis of blood in a varicosity
  - Localized hematoma: due to rupture of a varicosity

Etiology, Classification, & some Epidemiology:
- In legs, varicose veins are **classified as Primary or Secondary**:

<table>
<thead>
<tr>
<th>Primary Varicose Veins</th>
<th>Secondary Varicose Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem originates from...</td>
<td>underlying problem in the deep venous system</td>
</tr>
<tr>
<td>the superficial system</td>
<td></td>
</tr>
<tr>
<td>Predisposing factors</td>
<td></td>
</tr>
<tr>
<td>pregnancy</td>
<td>deep venous insufficiency</td>
</tr>
<tr>
<td>prolonged standing</td>
<td>deep venous occlusion</td>
</tr>
<tr>
<td>obesity</td>
<td>perforating veins incompetent</td>
</tr>
<tr>
<td>Explanations about condition</td>
<td></td>
</tr>
<tr>
<td>pregnancy or prolonged standing: high venous pressure in legs</td>
<td>deep venous blood shunted retrograde via perforating channels into superficial veins</td>
</tr>
<tr>
<td>varicosities in people with weak-walled vessels</td>
<td>increase luminal pressure and volume there</td>
</tr>
<tr>
<td>obesity: adipose tissue can’t support veins as well as lean mass could</td>
<td>cause dilatation and varicosities</td>
</tr>
</tbody>
</table>

- 10-20% of population has clinically apparent varicose veins
- Affect women 2-3 times more than men
- Half of affected patients have **family history** of varicose veins

Pathology:
- Thought to result from **intrinsic weakness of venous wall**, caused by one of the following:
  - Increased intraluminal pressure
  - Congenital defects in the venous valves…impairing flow toward the heart

Treatment:
- Usually treated conservatively:
  - have patients **elevate legs while laying down**
  - **avoid prolonged standing**
  - **wear compression hose** (to counterbalance increased venous hydrostatic pressure)
- **Injection of sclerosing solution**: for small, symptomatic varicose veins
- **Laser treatments**: improves cosmetic appearance for small, symptomatic varicose veins
- **Surgical therapy**: vein ligation and removal **only** done for patients who are very symptomatic, suffer recurrent superficial vein thrombosis, or develop skin ulcerations
**Venous Thrombosis**

First, some general info…

Definition:
- **Venous thrombosis/thrombophlebitis**: both these terms are used to describe the inflammatory response of a vessel wall that is caused by thrombus inside a superficial or deep vein

**Classification**:
- Thrombi in the legs are classified as either **deep venous thrombi** or **superficial venous thrombi**.

**Composition of thrombus over time**:
- **Early**: venous thrombus composed of **platelets and fibrin**
- **Later**: RBCs become interspersed in the fibrin and **thrombus starts to propagate** in the direction of blood flow.

Vessel changes due to thrombosis:
- **Vessel structural changes** can be minimal or can involve granulocyte infiltration, loss of endothelium, and/or edema.
- **Vessel flow** may be diminished or obstructed by thrombi. **Thrombi may dislodge, forming thromboemboli**.

Now, onward to the disorders…

---

**Venous Thrombosis – Deep Venous Thrombosis (DVT)**

**Clinical Presentation**:
- **May be asymptomatic**.
- **Symptoms can include**:
  - **Calf or thigh discomfort**, esp when standing or walking
  - **Unilateral leg swelling**

**Complication of post phlebitic syndrome** may present with:
- **Chronic leg swelling**
- **Stasis pigmentation**
- **Skin ulcerations**

**Complication of pulmonary embolism (PE)** may present with:
- **Pleuritic chest pain**
- **Tachypnea**
- **Cough**
- **dyspnea**
Physical Findings:
- With proximal DVT, will see edema of involved leg.
- May see erythema.
- May feel localized warmth.
- When palpate, may find:
  - tenderness over the course of the phlebitic vein
  - deep venous cord (stiff cord-like quality along the thrombosed vessel)
- Homan’s Sign: non-specific/unreliable finding of DVT that when dorsiflex patient’s foot, they have calf pain

Pathogenesis:
- Remember good ‘ol Virchow and his triad of factors that predispose to venous thrombosis:
  1. stasis of blood flow: disrupts laminar flow and puts platelets in contact w/ endothelium allowing coagulation factors to accumulate and slowing influx of clotting inhibitors
  2. hypercoagulability: often from genetic disorders or cancers
  3. vascular damage: “peels back” (denudes) the endothelium to expose subendothelial collagen, which is a substrate for binding von Willebrand’s factor and platelets → initiates clotting cascades and leads to clot formation.
    - Even if endothelium isn’t denuded, but is only injured, can get endothelial dysfunction, which can prevent synthesis and secretion of endothelial vasodilating substances and allow thrombosis to happen
- Note: Refer to the etiology section directly below to see what can precipitate problems in each part of the triad.

- DVT occurs most commonly in the veins of calves – may also develop in proximal veins (popliteal, femoral, iliac)
- Left untreated, 20-30% of DVTs occurring in calves propagate to proximal veins.
- Two major consequences of DVT:
  1. Pulmonary Embolism: a clot dislodges and travels through the IVC and right heart into the pulmonary circulation, where it causes obstruction.
  2. Postphlebitic syndrome: chronic deep venous insufficiency – persistent occlusion by DVT

Etiology & some Epidemiology:
- Predisposing factors: related to… stasis of blood flow (red), hypercoagulable states (purple), vascular damage (blue)
  - Prolonged immobilization/inactivity (after surgery, long travel in car or plane)
  - Immobilization of an extremity (after bone fracture)
  - Cardiac failure
  - Hyperviscosity syndromes
  - Inherited coagulation disorders (e.g. Factor V Leiden)
  - Antiphospholipid antibodies/lupus anticoagulant
  - Neoplastic disease (pancreatic, lung, stomach, breast cancers)
  - Pregnancy
  - Oral contraceptive use (or other high estrogen states)
  - Myeloproliferative diseases
  - Smoking
  - Instrumentation (intravenous catheters)
  - Trauma (external injury)

- PEs are the main complication of DVT; the incidence of PE in the US is 600,000 per year.
- 30-40% of PEs are fatal if untreated.
**Diagnostic tests/Imaging:**

- **Serum D-dimer:** byproduct of fibrin degradation that can be measured from peripheral blood; using enzyme-linked immunoassay, **D-dimer assay is highly sensitive for diagnosis of DVT** (and/or acute pulmonary embolism).
  - D-dimer also elevated in cancer, inflammation, infection, necrosis – positive test is, thus, not specific for DVT.
  - Normal D-dimer value helps exclude DVT; elevated level does not confirm DVT.

- **Venous compression duplex ultrasonography:** available, noninvasive test that is **97% sensitive and 97% specific** for diagnosis of **symptomatic DVT in a proximal vein** (not as good for a calf vein).
  - Vein is imaged with real-time US and pulsed by Doppler US to assess blood flow
  - To diagnose, must have: inability to compress vein w/ direct pressure, direct visualization of thrombus, absence of blood flow in the vein.

- Magnetic resonance venography: less frequently used – aids in diagnosis of proximal, particularly pelvic, DVT
- Contrast venography: less frequently used – **invasive** imaging technique that can provide definitive diagnosis

**Treatment:**

- **Treat patients in order to prevent pulmonary embolism (PE).**
- **Elevate the affected extremity** above level of heart to reduce edema and tenderness.
- **Anticoagulation** to prevent extension of thrombus.
  - First, use sub-cutaneous LMW Heparin (I.V. unfractionated heparin is more cost-effective)
  - Long term, use warfarin (advantage in that it is oral)

- Catheter-based thrombolysis: seldom used – but is for patients with ileofemoral DVT
- Intravascular filter in IVC: only used for patients who can’t take anticoagulants due to a bleeding disorder

- **Treatment for calf vein thrombosis is controversial** – may not need to treat as is less likely to get PEs from calf.
  - Monitor patient to determine if thrombus propagates into proximal veins…then treat.

- **DVT Prophylaxis is mandatory when risk of DVT is high** (i.e. when have bed rest after surgery): prophylax with one of the heparins, with low-dose warfarin, with compression stockings, or with pneumatic compression of legs
## Venous Thrombosis – Superficial Thrombophlebitis

### Clinical Presentation:
- **Erythema, tenderness, edema** over involved vein.

### Physical Findings:
- **Palpation:** may reveal a firm, thickened, thrombosed vein. Palpable thrombosed vessels are almost always superficial.

### Etiology:
- Can occur, for example, as a **complication of an indwelling intravenous catheter**.

### Pathology:
- A **benign** disorder associated with **inflammation and thrombosis of a superficial vein** (just below the skin).
- Much less serious than DVT! Superficial Thrombophlebitis **does NOT lead to pulmonary edema**.

### Treatment:
- **Local heat**
- **Rest of involved extremity**
- **Aspirin**/other anti-inflammatory medication: may relieve the associated discomfort
ST elevation causes in ECG

ELEVATION:
- Electrolytes
- LBBB
- Early repolarization
- Ventricular hypertrophy
- Aneurysm
- Treatment (eg pericardiocentesis)
- Injury (AMI, contusion)
- Osborne waves (hypothermia)
- Non-occlusive vasospasm

Pericarditis: EKG
"Pericarditis":
- PR depression in precordial leads.
- ST elevation.

Depressed ST-segment: causes

DEPRESSED ST:
- Drooping valve (MVP)
- Enlargement of LV with strain
- Potassium loss (hypokalemia)
- Reciprocal ST- depression (in I/W AMI)
- Embolism in lungs (pulmonary embolism)
- Subendocardial ischemia
- Subendocardial infarct
- Encephalon haemorrhage (intracranial haemorrhage)
- Dilated cardiomyopathy
- Shock
- Toxicity of digitalis, quinidine

ECG: T wave inversion causes

INVERT:
- Ischemia
- Normality [esp. young, AFAM]
- Ventricular hypertrophy
Ectopic foci [eg calcified plaques]
RBBB, LBBB
Treatments [digoxin]

**Murmurs: systolic**

**MR PV TRAPS:**
- Mitral
- Regurgitation and
- Prolaspe
- VSD
- Tricuspid
- Regurgitation
- Aortic and
- Pulmonary
- Stenosis

**Murmurs: louder with inspiration vs expiration**
- Left sided murmurs louder with **Expiration**
- Right sided murmurs louder with **Inspiration**.

**Murmurs: right vs. left loudness**

"RILE":
- Right sided heart murmurs are louder on Inspiration.
- Left sided heart murmurs are loudest on **Expiration**.