

Cardiac Pathology

Aaron Auerbach, MD, MPH

Armed Forces Institute of Pathology

Notes prepared by Keith J. Kaplan, MD, Walter Reed Army Medical Center

I. Cardiovascular Pathology

A. Atherosclerosis

1. Primary cause of morbidity and mortality in developed world
2. Focal intimal disorder of medium and large arteries characterized by focal accumulations of **lipid** and **matrix** (smooth muscle proliferation) producing **plaques (atheromas)**
3. **Composition of plaques** rather than size (stenosis severity) is primary determinant for development of acute coronary syndromes.
4. Atherosclerosis (AS) and arteriosclerosis are not synonymous terms.

B. Plaque morphology and classification

1. Many of the current concepts of AS are based on work of Stary HC. *Virchows Archiv A Pathol Anat* 1992;421:277-290.
2. Adaptive intimal thickening develops at young age at points of branching; migration of SMC from media into intima.
3. Initial lesion of AS is characterized by microscopic collections of macrophages including foam cells in intima (type I).
4. **Fatty streaks** (type II) are visible intimal collections of lipid-laden macrophages forming dots/streaks.
 - a. Intimal remains intact; lesions may regress.
5. **Preatheroma** (type III) represents bridge between minimal and advanced lesions; cause minimal intimal thickening.
6. Characterized by extracellular lipid ill-defined pools
7. **Atheroma** (type IV) displays disruption and disorganization of intima as lipid cores develop from coalescence of pools.
 - a. Crescentric lipid cores are composed of esterified and crystalline cholesterol resulting in pultaceous, soft consistency.
 - b. Vessel wall is thickened but minimal lumen reduction.
8. **Fibroatheroma** (type V) is composed of lipid core and fibrous cap containing collagen and smooth muscle cells; + lumen reduction.
9. Complicated (type VI) lesions consist of fissures, erosions, ulcerations, hematoma/hemorrhage or thrombotic deposits on type IV or type V lesions.

10. **Type VII** lesions are primarily **calcific**; **type VIII** are primarily **fibrotic**.

C. Pathogenesis of human atherosclerosis

1. Response-to-injury hypothesis
 - a. AS represents a protective, inflammatory-fibroproliferative response to intimal injury.
 - b. Variety of injurious sources include Ox LDL, mechanical, immunologic, toxins, viruses, homocysteine.
 - c. Injury leads to monocyte/macrophage and T-cell adherence.
 - d. Migration to subendothelial sites, conversion of monocytes to macrophages, gene activation and production of cytokines and growth factors resulting in SMC migration and proliferation.
 - e. SMC proliferation is part of the reparative response to inflammation.

D. Mediators in the development of atherosclerosis

1. Endothelial injury: oxidized LDL, viruses (CMV), toxins (nicotine), mechanical/shear stress, immunologic, homocysteine
2. Lipid peroxidation at endothelial cell produces Ox LDL and inflammation
3. Leukocyte adhesion and migration involves E-selectin (monocytes) and ICAM-1/VCAM-1 (monocytes and lymphocytes).
4. Growth factors: PDGF-A/-B), M-CSF, GM-CSF, bFGF, IGF-I, TGF-beta, CK: IL-1 and TNF-alpha
5. Components of intrinsic and extrinsic coagulation cascade and role of thrombin and fibrinogen in damaged vessels.

E. Risk factors for atherosclerosis

1. **Major risk factors:** hypertension, hyper- and dyslipidemia, diabetes mellitus, family history, cigarette smoking.
2. **Other risk factors:** older age, male gender, obesity, homocystinuria, increased lipoprotein (a), increased plasma fibrinogen, factor VII, leukocyte levels (WBC).
 - a. These risk factors are based on population studies; disease development and progression for individual patients is variable and often unpredictable.

F. Morphologic patterns of atherosclerotic plaques

1. A practical clinicopathologic approach to AS is based on concept of **stable** and **unstable plaques**.
2. **Stable plaques** correspond to types IV-V in the Stary scheme.
3. Plaques involve epicardial vessels and **not** intramyocardial.

4. Distribution includes proximal half of LAD (including diagonal) and circumflex (including obtuse marginal branches); RCA distribution may be proximal or distal; LCA obstruction rarely occurs as an isolated lesion.
5. 70-75% of coronary lesions are eccentric; 25-30% are concentric.
6. Vascular remodeling (dilatation) is an important compensatory mechanism in AS and is associated with medial atrophy.

G. Unstable atherosclerotic plaques

1. Defined as acute luminal alteration secondary to medial spasm, or plaque rupture, hemorrhage or thrombosis (Stary VI)
2. Risk factors for spontaneous plaque rupture include
 - a. Soft plaque with a necrotic core
 - b. Atheroma with a thin fibrous cap
 - c. Clusters of foam cells within fibrous cap
 - d. Atherophagocytosis by giant cells
 - e. Intimal clusters of leukocytes
 - f. Adventitial bands of mononuclear leukocytes

(Modified from Edwards WD. *Cardiovascular Pathology*. (Eds Schoen & Gimbrone) Williams & Wilkins. p13)

H. Morphology of unstable atherosclerotic plaques

1. Plaque rupture
 - a. Common sequelum with lesions ranging from minimal erosions to deep tears
 - b. Lesions result in exposure of luminal blood to thrombogenic subendothelial materials.
 - c. Junction of plaque with adjacent "normal" wall is frequent site of involvement.
 - d. Possible outcomes of rupture include fibrous healing, atheroembolization to distal vessels, thrombosis.
2. Plaque hemorrhage
 - a. Deep intimal tears lead to hemorrhage into the core of plaques, progressing to accelerated plaque enlargement and luminal reduction.
 - b. Plaque hemorrhage may occasionally be restricted to bleeding within the plaque itself (without surface tears).
 - c. Mechanism of plaque progression with intraplaque thrombosis stimulating SMC proliferation
3. Thrombosis
 - a. Thrombosis following plaque rupture may lead to nonocclusive or occlusive thrombosis depending on exposure to underlying thrombogenic factors, balance between clot formation and lysis and flow patterns within affected vessel.

- b. Possible outcomes include thrombus organization and incorporation leading to plaque progression, thrombotic embolization, and/or luminal obstruction.
- 4. Medial spasm
 - a. Vasospasm may cause luminal narrowing or initiate surface disruption of plaques.

I. Clinicopathologic correlation of plaque types

<u>Clinical State</u>	<u>Microscopic Findings</u>
Asymptomatic	Stable noncritical plaques
Angina Pectoris	
Stable	Stable critical plaques (2-3 vessel)
Variant	Stable critical/noncritical plaques +/- plaque progression
Unstable	Unstable plaque with rupture and acute nonocclusive thrombus
Myocardial Infarction	
Acute MI	Unstable plaque with rupture and acute thrombus; other stable plaques
Chronic Ischemia	Stable critical plaques; old thrombus; evidence of plaque progression
Sudden Death	Unstable plaque with rupture and acute thrombus; other stable plaques; 2-3 vessel disease in 80%

J. Pathology findings in coronary interventions

1. Current techniques include balloon angioplasty, directional or rotational atherectomy, laser angioplasty, stent placement.
2. Resultant arterial injury produces unstable region.
3. Balloon angioplasty causes plaque rupture at junction between plaque and “normal” wall or along thin fibrous cap.
 - a. Tear extends through intima into media (to external elastica).
 - b. Iatrogenic medial and adventitial stretching enlarges lumen.
 - c. Healing mimics atherogenesis; excessive intimal proliferation 40-50% leading to restenosis.
4. Venous grafts for CABG develop concentric intimal proliferation.

K. Pathology of acute myocardial infarction

1. Coronary artery patterns and myocardial supply: (Rt dominant)
 - a. LAD: anterior 2/3 of IVS and anterior LVFW
 - b. Cx: lateral wall of LV including A-L papillary muscle
 - c. RCA: posterior 2/3 of IVS, posterior LV and P-M papillary muscle
2. **Macroscopic changes in AMI**
 - a. 18-24 hrs: pallor
 - b. 1-3 days: pallor +/- hyperemic border
 - c. 3-7 days: hyperemic border with central yellowish softening

- d. 10 days: central depression with vascularized margins
- 3. **Microscopic changes in AMI**
 - a. 12-18 hrs: hypereosinophilic, wavy fibers
 - b. 24 hrs: initial neutrophilic infiltrates; coagulative necrosis
 - c. 2-3 days: maximal leukocyte infiltrates; prominent necrosis
 - d. 3-7 days: macrophages, phagocytosis; initial granulation tissue response
 - e. 10 days: phagocytosis and conspicuous granulation tissue
 - f. 7-10 wks: admixture of immature and mature scar

L. Complications of acute MI

- 1. Extension, expansion and progression
- 2. Septal or free wall perforations
- 3. Papillary muscle infarction/rupture
- 4. Intracoronary/systemic embolism
- 5. Aneurysm/pseudoaneurysm
- 6. Arrhythmia
- 7. Pericarditis
- 8. RV infarction

M. Nonatheromatous CAD

- 1. Congenital anomalies: anomalous origin of coronary artery may lead to sudden death.
 - a. Origin of LAD/LCA from RCA
 - b. Origin of RCA from LAD/LCA
 - c. Origin of orifice from pulmonary trunk may lead to L-to-R shunt and aneurysmal dilatation.
 - d. Segmental LAD stenosis/atresia
- 2. Spontaneous dissection
 - a. May be isolated or part of aortic dissection
 - b. Isolated lesions arise as dissections along medial-adventitial plane; 40% occur in puerperium.
- 3. Arterial bridging
 - a. Occurs in up to 50% of normal hearts
 - b. Also reported in hypertrophic cardiomyopathy
- 4. Coronary aneurysms
 - a. Most are secondary to atherosclerosis.
 - b. Localized saccular aneurysms are associated with **Kawasaki's disease.**

N. Specimen handling and processing

- Clinical circumstances under which Bx is taken largely determines how specimens are fixed, processed and stained:
 - 1. CMP/myocarditis/specific heart muscle disease:
 - a. Light microscopy: 4-6 pieces in formalin
 - b. EM: 1-2 pieces (optional) in gluteraldehyde
 - 2. Cardiac transplant rejection
 - a. Light microscopy: 5-6 pieces in formalin

- b. IF: 1-2 pieces in Zeus or saline
- 3. Anthracycline cardiotoxicity
 - a. EM: 4-6 (**ALL**) pieces in glut

O. Definition of myocarditis

1. 1986. Dallas Classification System
 - a. "Process characterized by an **inflammatory infiltrate** of the myocardium **with necrosis and/or degeneration of adjacent myocytes** not typical of ischemic damage associated with coronary artery disease."
 - b. Aretz HT, Billingham ME, Edwards WD, et al. *Am J Cardiovasc Pathol.*1987;1:3.
2. Criteria were utilized in NIH sponsored myocarditis trial.
3. Incidence of myocarditis is 3-5% of cases of CHF of less than 2 years duration.

P. Histopathologic features in myocarditis

1. **Myocyte necrosis/damage**
 - a. Criteria are similar to cardiac transplantation.
 - b. Additional leveled sections are helpful.
 - c. Trichrome stain may highlight damage.
2. **Inflammatory infiltrate**
 - a. Intensity: mild, moderate, and severe
 - b. Distribution: focal, confluent, and diffuse
 - c. Composition: purely lymphocytic vs polymorphous
 - d. Neutrophils, eosinophils, giant cells
3. **Fibrosis**
 - a. Distribution: perivascular, interstitial, endocardial
 - b. Extent: mild, moderate, and severe

Q. Classification of myocarditis

1. **First biopsy**
 - Myocarditis with/without fibrosis
 - Borderline myocarditis
 - No myocarditis
2. **Subsequent biopsy(ies)**
 - Ongoing (persistent) myocarditis +/- fibrosis
 - Resolving (healing) myocarditis +/- fibrosis
 - Resolved (healed) myocarditis +/- fibrosis
 - a. Idiopathic (lymphocytic) myocarditis
 - Viral link is suspected but remains unproven.
 - Definitive diagnosis requires mononuclear cell infiltrates in association with myocyte damage.
 - Scattered interstitial lymphocytes may be seen in normal hearts and in dilated CMP.
 - DDx includes collagen vascular disease, drugs, infections such as Lyme's disease.
 - Treatment with immunosuppressive agents remains controversial.
 - b. Giant cell myocarditis
 - Virulent form of myocarditis affecting young adults

- Patients present with acute onset of florid CHF +/- arrhythmias.
 - Reported associations include thymoma, myasthenia, myositis, thyrotoxicosis and collagen vascular diseases.
 - Microscopic findings include diffuse geographic necrosis, mixed inflammation (including eosinophils), multinucleated giant cells and absence of sarcoid-like granulomas.
 - Primary therapy is aggressive immunosuppression followed by transplantation.
 - GCM may recur in 25% of grafts.
- c. Hypersensitivity myocarditis
- More than 20 drugs have been incriminated.
 - Methyldopa, sulfonamides, penicillin account for 75%.
 - Unlike toxic myocarditis **HM is not dose-related.**
 - Histopathologic findings include interstitial infiltrates composed of eosinophils +/- scattered mononuclear cells.
 - Myocyte damage and fibrous are **not conspicuous.**
 - Histiocytic aggregates around degenerating collagen suggests vague granulomatous pattern.
- d. Sarcoidosis
- Majority of patients have systemic involvement.
 - Clinical manifestations include heart block, CHF, arrhythmias, sudden death, and pericarditis.
 - Sites of predilection include: base of IVS and LVFW.
 - RV biopsy is often negative (sampling error).
 - Findings include well-formed, “hard” granulomas, variable interstitial fibrosis.
 - Other patterns include lymphocytic myocarditis, interstitial fibrosis, dilated cardiomyopathy.
- e. Rheumatic myocarditis
- Uncommon cause of myocarditis.
 - Clinical criteria are composed of Major/Minor Jones.
 - Myocardial lesions include: 1. lymphocytic myocarditis; 2. Aschoff’s nodules.
 - Aschoff’s nodules consist of round cellular aggregates within interstitium adjacent to small arteries.
- 1) Aschoff cells are multinucleated histiocytes (diagnostic).
 - 2) Anitschow’s cells and mononuclear cells are nonspecific.

R. Cardiomyopathy

- Originally defined as heart muscle disorder of unknown etiology
 - Currently classified by dominant pathophysiology or by etiologic/pathogenetic factors.
1. **WHO** classification (1980):
 - a. Dilated (congestive) (90%)
 - b. Hypertrophic (asymmetric/symmetric) (< 10%)
 - c. Restrictive (obliterative) (< 2%)
 2. **WHO** classification (1995):
 - a. Dilated CMP
 - b. Hypertrophic CMP
 - c. Restrictive CMP
 - d. Arrhythmogenic RV CMP
 - e. Unclassified CMP (fibroelastosis, noncompacted myocardium, systolic dysfunction with minimal dilatation)
 - f. Specific CMP (ischemic, valvular, hypertensive, inflammatory, metabolic, muscular dystrophies, drug, systemic diseases, peripartal)

S. Dilated cardiomyopathy

1. Most common type of CMP characterized by progressive failure with 4-chamber dilatation
2. Cardiac failure is manifested as hypertrophy and dilatation secondary to **systolic** “pump” failure.
3. Possible etiologies include:
 - a. Postviral myocarditis (5-10%)
 - b. Postpartum CMP (1/1300-1/15000)
 - c. Alcohol toxicity
 - d. Familial CMP (7-30%)
4. **Macroscopic features**
 - Increased heart weight (up to 1 kg)
 - Dilatation +/- hypertrophy of chambers
 - Mural thrombi in chambers
 - CAD is minimal or absent
5. **Microscopic features**
 - Myocyte hypertrophy and interstitial fibrosis
 - Occasional mononuclear inflammatory cells
 - Active myocarditis is rarely observed.

T. Arrhythmogenic RV dysplasia

- Uncommon, familial form of CMP that affects young adults
- Patients present with normal contractile function and exercise-induced arrhythmias/sudden death.
- RV is markedly dilated, thinned and replaced by fat.
- Microscopy shows fatty replacement, fibrosis +/- scattered mononuclear cells.
- Clinicopathologic correlation is required as fat is common finding in RV myocardium.

U. Hypertrophic cardiomyopathy

1. Asymmetric (90%) and symmetric (10%) forms
2. 50% are familial with defect in myosin heavy chain.
3. Hypercontractile myocardium with impaired relaxation and cardiac filling (diastolic dysfunction)
4. Most patients are asymptomatic; presentations include sudden death, syncope, exertional dyspnea, angina.
5. Surgical myomectomy for IHSS may relieve symptoms.
6. **Macroscopic features**
 - Increased weight with mural hypertrophy
 - IHSS displays IVS thickening with “banana” shape.
 - Left atrium is markedly enlarged; LV chamber is small.
7. **Microscopic features**
 - Endocardial thickening (LV outflow tract plaques)
 - Myocyte hypertrophy and fibrosis
 - Myocyte disarray in deeper portions of IVS
 - Intramyocardial arterial thickening

V. Restrictive cardiomyopathy

- Characterized by restriction of ventricular filling
- Normal systolic function with diminished cardiac output
- Endocardial/subendocardial fibrosis +/- eosinophilia
- Fibrosis along inflow tracts +/- valves
- Mural thrombus overlying fibrosis is common.

W. Specific cardiomyopathies (specific heart muscle disease)

- Divergent causes of cardiac dysfunction; many may be diagnosed by endomyocardial biopsy.
1. **Infiltrative:** amyloidosis, lymphoma
 2. **Inherited metabolic:** carbohydrate/glycoprotein, mineral, sphingolipid, neuromuscular
 3. **Toxins, drugs, poisons:** adriamycin, cobalt, cyclophosphamide.
 4. **Nutritional:** thiamine

X. Amyloidosis

1. Cardiac involvement associated with variety of types
 - a. AL: primary/myeloma-related
 - b. AA: secondary
 - c. ASc: senile/familial (transthyretin)
2. Clinical setting of constrictive vs restrictive disease
3. Deposits may be interstitial, vascular, nodular.

Y. Hemochromatosis

- Iron is not normally found in heart.
- Primary and secondary forms mimic dilated CMP; occasionally present as restrictive CMP.
- Classic perinuclear deposition
- Epicardial portions of myocardium are preferentially involved.

Z. Fabry's disease

- X-linked recessive form of shingolipidosis due to deficiency of alpha-galactosidase A
- Presents in adulthood angiokeratomas, renal insufficiency, cardiac failure
- Mimics dilated or hypertrophic CMP
- Biopsy shows diffuse myocyte vacuolization.
- EM shows intralysosomal electron dense lamellae with concentric or packed arrangement (Zebra bodies).

AA. Anthracycline cardiotoxicity

- Common chemotherapeutic agent with risk of toxicity in range of 550 mg/m²
- Considerable individual patient variation in threshold
- ALL tissue (5-6 pieces) should be gluteraldehyde-fixed to obtain at least 10 Epon blocks for grading.
- Grading is based on percentage of myocytes showing myofibrillar loss and/or sarcotubular distension.
- Grades range from 0-3.0 with associated clinical recommendations.

BB. Tumors and tumor-like lesions

- Primary tumors are rare; metastases are common (20-40x).
- Majority are benign (myxomas).
- Variety of schemes: benign/malignant; location; age

CC. Myxomas

- Most common primary tumor; histogenesis remains unclear.
- Majority (75%) occur in **left atrium**.
- Present as exophytic, polypoid, smooth or sessile masses with gelatinous +/- hemorrhagic portions
- Distinction from thrombus based on myxoid stroma containing stellate or globular "myxoma" cells
- May cause AV valve obstruction by "ball-valve" effect or embolize
- Majority are sporadic; some are associated with Carney's syndrome.

DD. Tumors of childhood

1. Rhabdomyoma

- Most common primary tumor of children
- Present with valve orifice or chamber obstruction
- Circumscribed, 1-5 cm, tan-brown
- Composed of "spider" cells with vacuolated cytoplasm with stranding

2. Cardiac fibroma

- LV tumors that may cause obstruction or arrhythmia
- Resemble uterine leiomyoma macroscopically
- Microscopic appearance is similar to extra-abdominal desmoids.

EE. Malignant cardiac tumors

- Sarcoma, lymphoma and malignant mesothelioma
- 1. **Angiosarcoma**
 - Predilection for **right atrium** and **pericardium**
 - Hematogenous spread to **lung** and **liver**
 - Resemble soft tissue lesions with vascular spaces lined by pleomorphic cells.
- 2. **Malignant Lymphoma**
 - Defined as absence of lymphoma outside the pericardial sac or dominant lesion in heart
 - Right atrium is most common site (RA>RV)
 - B-cell lymphoma (large cell or small noncleaved types)

FF. Tumor-like lesions

1. **Papillary fibroelastoma**
 - Incidental findings on valves; 2-5 mm
 - “Sea anemones”; atrial side of AV valves and ventricular side of aortic or pulmonic valves
 - Connective tissue covered by endothelial cells
2. **Cardiac MICE**
 - Monocyte/macrophage incidental excrescence
 - Incidental finding within atria or ventricles
3. **AV nodal tumor**
 - Not mesothelioma; endodermal origin
 - May cause heart block or sudden death

GG. Pathology of cardiac valves

1. Patterns and etiologies of valve disease have changed over the last 50 years.
2. Causes of valve disease
 - Aortic stenosis: degenerative, bicuspid, post-rheumatic (PR). insufficiency: aortic root dilatation, endocarditis, PR
 - Mitral stenosis: post-rheumatic insufficiency: prolapse, IHD and papillary muscle dysfunction
 - Pulmonic and tricuspid: pulmonary hypertension, carcinoid syndrome, drug-related

HH. Bicuspid aortic valve

- Remains second most common valve defect; most common cause of isolated AS in adults.
- In calcific state nodules found within valve fibrosa and protrude into sinus; +/- ulceration and thrombosis
- Complications include endocarditis, aortic dissection.

II. Rheumatic valve disease

1. May affect all 4 valves (MV>AV>TV>PV).
2. Acute RF is characterized by febrile illness associated with rash, transitory arthritis, pancarditis, and/or chorea 2-4 weeks following Gp A Strept pharyngitis.
 - Aschoff nodules may be found throughout heart.
 - Nodules may persist up to 20 yrs following illness.

- Valve lesions include vegetations along lines of closure of leaflets.

JJ. Chronic rheumatic valve disease

1. Latent period of 20-30 yrs before symptoms appear
2. Not all cases have documented acute incident; < 10% of cases of ARF progress to chronic state.
3. Macroscopic hallmarks: commissural fusion, cusp fibrosis with retraction and calcification, chordal thickening and shortening
4. Histologic feature is dense fibrosis that obliterates valve architecture with loss of definition of fibrosa and spongiosa.
 - In MV vascularization of cusps and aggregates of lymphocytes

KK. Mitral valve prolapse

- Most common valve defect and most common indication for MVR for mitral insufficiency
- Variety of terms for lesion but hallmark is replacement of valve fibrosa by acid mucopolysaccharide.
- Posterior cusp and chordae are prone with leaflet scalloping and chordal fusion.
- Complications include endocarditis, chordal rupture, sudden death, arrhythmias, annular calcification.

LL. Infectious endocarditis

1. Patients with underlying congenital or acquired defects are at risk (regurgitant valves > stenotic valves).
2. Clinical presentation is variable but includes new onset murmur and bacteremia +/- embolic lesions.
3. AV and MV are most common sites of involvement (TV in IV drug users).
4. Complications include septic embolism, sudden death, ring abscess, pyogenic myocarditis, incompetent valves.
5. Some pathogens have specific associations:
 - a. *S. aureus* Community acquired, IV drug use
 - b. *S. epidermidis* Prosthetic valves
 - c. *Str. viridans* SBE
 - d. **Enterococci** Normal/damaged valves
 - e. *Str. bovis* Colonic carcinoma
 - f. **Pneumococcus** Alcoholics
 - g. **Gram negative** IV drug users, DM, immunocompromised
 - h. **Fungal** IV drug users, immunocompromised

MM. Marantic endocarditis

- Nonbacterial thrombotic endocarditis (NBTE)
- Postmortem findings in pts with terminal malignancies, autoimmune disorders, etc
- Occasionally large enough to require surgical intervention
- AV: attach to central nodulus Arantii of cusp

- MV: symmetric placement along closure lines
- Composed of platelets, fibrin and rare inflammatory cells

NN. Nonrheumatic valve lesions

1. Libman-Sacks lesions of SLE
 - Flat vegetations covering both cusp surfaces of MV, with extension along atrial and ventricular endocardium
 - Fibrinoid necrosis, inflammation and hematoxyphil bodies in underlying tissues
 - Other autoimmune disorders such as rheumatoid arthritis (thickening vs rheumatoid granulomata), Reiter's syndrome and ankylosing spondylitis may develop lesions.

OO. Prosthetic valves

1. Mechanical: ball and cage, tilting disc, disc and cage, hinged bileaflet
2. Tissue
 - a. Natural: human homograft or porcine AV
 - b. Constructed: pericardial or fascia lata valve

PP. Complications of prosthetic valves

1. **Tissue valves**
 - Calcific degeneration, tears, endocarditis
2. **Mechanical valves**
 - Fractures of struts, thrombosis, pannus overgrowth, ring leakage/abscess

QQ. Carcinoid valve disease

- 50% of pts with metastatic carcinoid tumor develop PV and TV problems.
- PV and TV: thickened, shrunken, white, opaque leaflets and chordae
- Sections display myofibroblastic proliferation along both sides of valve.
- Etiology unclear but direct effect of serotonin on endocardium
- Identical lesions in ergotamine and fenfluramine-phentermine valve lesions
- Fen-Phen affects both sides; variable degrees of regurgitation

RR. Cardiac transplantation

1. Early (0-3 wks)
 - Hyperacute rejection
 - Primary graft failure
 - Ischemic/reperfusion injury
2. Intermediate (1 mo-1 yr)
 - Acute cellular rejection
 - Infectious myocarditis
 - EBV-related PTLD
 - Acute vascular rejection

3. Late (> 1 yr)
 - Graft vascular disease
 - Graft hypertrophy and fibrosis
 - Denervation/reinnervation
 - Constrictive pericarditis
 - Recurrence of primary disease

SS. Hyperacute rejection

- Uncommon form of graft failure caused by precirculating antibodies (ABO or HLA)
- As circulation is reestablished the heart rapidly dilates, turns plum-red and fibrillates.
- Microscopy shows diffuse interstitial hemorrhage +/- fibrin thrombi within microvasculature.

TT. Acute cellular rejection

- Significant cause of allograft loss in the first post-transplant year
- Most patients have at least 1 episode of rejection.
- Cardinal histologic features are interstitial and/or perivascular mononuclear infiltrates in the presence or absence of myocyte damage.

1. ISHT grading scheme:

Grade 0	No rejection
Grade 1A	Focal mild
Grade 1B	Diffuse mild
Grade 2	Focal moderate
Grade 3A	Multifocal moderate
Grade 3B	Diffuse moderate
Grade 4	Severe

UU. Mimics of acute rejection

- Quilty effect
- Infectious (CMV/Toxo) myocarditis
- Biopsy site changes
- Ischemic/reperfusion injury

VV. Acute vascular rejection

- Uncommon form of rejection characterized by marked graft dysfunction in absence of cellular infiltrates
- Perivascular and interstitial edema with vessels showing reactive endothelial cells
- IF is required: immunoglobulin, complement, and fibrinogen.
- Associated with poorer short- and long-term graft survival

WW. Graft vascular disease

- Fibrointimal proliferative lesions involving the coronary arteries, aorta and vaso vasorum
- Diffuse, concentric proliferation without calcification or atheromatous material
- Internal elastic membrane is intact.

XX. Sudden cardiac death

1. Coronary artery lesions
 - Atherosclerosis
 - Coronary artery dissection
 - Anomalous coronary artery origin
 - Coronary artery vasculitis
 - Hypoplastic coronary artery
 - Intramyocardial arterial dysplasia
2. Myocardial disease
 - Hypertrophic cardiomyopathy
 - Infiltrative disorders (amyloidosis, sarcoidosis, myocarditis)
 - Arrhythmogenic right ventricular dysplasia
3. Valvular disease
 - Mitral valve prolapse
 - LV outflow obstruction
 - Infective endocarditis
4. Conduction system lesions
 - **SA node**: small vessel disease, hemorrhage, and fibrosis
 - **AV node**: fibrosis, calcification, AV node tumor
 - **His bundle**: discontinuity
 - Accessory/re-entrant pathways

YY. Pericarditis

- Pericarditis: inflammation of the linings of the visceral and/or parietal linings of the heart
1. **Variety of classifications exist**
 - a. **Temporal**: acute, subacute, and chronic
 - b. **Morphologic features**: serous, serofibrinous, fibrinopurulent, purulent, hemorrhagic
 - c. **Etiologies**: infectious (viral, TB, fungal, pyogenic bacterial), immune-mediated (SLE, rheumatic, post-MI), miscellaneous (neoplastic, traumatic, post-radiation)

ZZ. Chronic pericarditis

1. Constrictive pericarditis
 - a. Dense fibrotic or fibrocalcific scar tissue within the pericardium that results in reduced compliance of the pericardial layers
 - b. Lesion may develop slowly over many years or subacutely over weeks/months.
 - c. Severe restriction results in limited diastolic expansion, attenuated diastolic filling, dyspnea, reduced exercise tolerance, abdominal distension, palpitations and syncope.
 - d. Scar tissue may be .5-1.0 cm thick.
 - e. Cardiac hypertrophy and dilatation do **not** develop because of encasement by scar.

AAA. Congenital heart disease

1. Most common type of congenital defects (3-8/1000)
2. Variety of environmental (infections, maternal, drugs) and genetic (chromosomal, single gene) factors
3. Variety of classifications
 - a. Cyanotic vs noncyanotic
 - b. Left-to-right shunts vs R-L shunts

BBB. Noncyanotic heart disease

1. **Left-to-right shunts**

a. **Atrial septal defect**

- Communication between RA and LA (secundum type)
- Lesions range from PFO to deficiency of fossa floor to perforations/fenestrations of floor.
- Shunt may lead to increased PVR and hypertension.
- R-to-L shunt and paradoxical embolism

b. **Ventricular septal defect (25%)**

- 1) Defined as opening in ventricular septum separating LV and RV
- 2) Majority of VSD are **perimembranous** (75%) and **muscular** (20%).
- 3) Size, location and response of pulmonary arterioles determine pathophysiologic sequelae.
 - a) Small defect (< 0.5 cm/m²): minimal effect
 - b) Medium defect (.5-1.0 cm/m²): elevated PAP and RV pressures with moderate l-to-r shunt
 - c) Large defect (>1.0 cm/m²): equalization of systolic pressures in RV, PA, LV and aorta
- 4) Small VSD may spontaneously close (25% by 1.5 yr, 60-75% by 10 yr).

c. **Atrioventricular septal defect**

- **Definition:** endocardial cushion defect resulting in defect in lower portion of atrial septum and upper part of ventricular septum
- Absence of V septum results in common AV junction and common AV valve.
- Physiology may mimic secundum type ASD.
- Association with Trisomy 21

2. **Obstructive defects**

a. **Coarctation of aorta**

- **Definition:** narrowing of aorta usually distal to ductus
- Lesions range from waist lesion to tubular narrowing along segment of aorta.
- Associated defects: fibroelastosis, PDA, VSD, bicuspid aortic valve, subaortic obstruction, TGA, etc
- Complications include endocarditis, CHF, aortic rupture.

- b. **Pathophysiology:** systolic and diastolic BP is elevated in arms; (BP arms > BP legs).
 - 1) Increased BP is due to mechanical obstruction and humoral factors.

CCC. Cyanotic heart disease

1. Tetralogy of Fallot
 - a. 4 classic abnormalities
 - 1) Large VSD
 - 2) Aortic origin from both ventricles above VSD (overriding aorta)
 - 3) RV outflow tract obstruction (stenosis/atresia)
 - 4) RV hypertrophy
 - b. High PAP leads to shunt.
 - c. Complications include polycythemia, cerebral thrombosis and endocarditis.
 - d. Surgical repair has led to 1, 5 and 20 yr survival rates of > 90%, > 90% and > 85%.
2. **Transposition of great arteries (TGA)**
 - a. 2 types:
 - 1) Complete TGA
 - 2) Congenitally corrected TGA
 - b. May be associated with additional defects
3. **Complete transposition of great arteries**
 - a. **Anatomic sequence**
 - 1) Right: morphologic RA – morphologic RV – aorta
 - 2) Left: morphologic LA – morphologic LV – pulmonary artery
 - a) **Concordant atrioventricular connection but discordant ventriculoarterial connection.**
 - b. **Pathophysiology:** VSD, PDA or ASD are necessary for survival.
 - 1) Physiologic derangements depend on type and severity of associated defects.
 - c. **Clinical manifestations:** cyanotic heart disease that presents in first few hours or days if intact septum or small VSD
 - 1) Large VSD has less cyanosis but CHF, dyspnea.
 - 2) Without treatment 50% die in 1st mo; 90% in 1st yr.

DDD. Congenitally corrected TGA

1. **Anatomic sequence**
 - a. Right: morphologic RA – morphologic LV – pulmonary artery
 - b. Left: morphologic LA – morphologic RV – aorta
 - c. Discordant atrioventricular and ventriculoarterial connections
2. **Pathophysiology:** VSD is usually present; other defects may include TV and PV stenosis or atresia.
 - If PV stenosis and VSD are present the hemodynamics are similar to tetralogy of Fallot.

3. **Natural history:** depends on associated defects.
 - Arrhythmias such as heart block are common.
 - Long-term survival is possible.

EEE. Cyanotic heart disease

1. Truncus arteriosus
 - a. Definition: common arterial trunk; single artery exits heart through a common valve above a VSD to supply the systemic, pulmonary and coronary arteries.
 - b. **Anatomic classification:** 4 types based on degree of development of normal outflow arteries
 - c. **Pathophysiology:**
 - In most cases of TA there is increased pulmonary blood flow since contents of RV and LV are expelled into common conduit.
 - Cyanosis depends on size of pulmonary arteries.

FFF. Total anomalous pulmonary venous connections

- Pulmonary veins enter RA, SVC or coronary sinus.
- Some form of ASD must be present for survival.

GGG. Diseases of the aorta

1. Aneurysms
 - a. Dissecting aortic aneurysms
 - May be associated with Marfan's or other fibrillin gene abnormality, hypertension, bicuspid AV
 - Classifications: DeBakey – Types I-III; Stanford A&B.
 - Intimal tear is usually found with antegrade/retrograde dissection along outer 2/3 of media.
 - Complications include hemorrhage, coronary artery occlusion.
 - b. Atherosclerotic aortic aneurysms
 - Majority are located below renal arteries; suprarenal AA should raise possibility of **infected (mycotic) aneurysm**.
 - Lesions > 5 cm are associated with increased risk of rupture.
 - Predicted growth rate is 0.2-0.5 cm/year.
 - Classification includes diffuse/saccular.
 - Distinction from false (pseudo) aneurysm based on presence of wall components

HHH. Inflammatory diseases of vessels

1. Infective
 - Syphilis, TB, bacterial, fungal
2. Noninfective
 - a. **Large arteries/aorta:** Takayasu's, giant cell, rheumatoid, ankylosing spondylitis

- b. **Medium arteries:** PAN, Kawasaki's, Wegener's, Churg-Strauss, rheumatoid, SLE, dermatomyositis
- c. **Small arteries:** serum sickness, H-S purpura, cryoglobulinemia, drug-induced angiitis

III. Syphilitic vascular disease

- Form of tertiary involvement affecting < 15% of untreated patients.
- Predilection for ascending aorta resulting in AV annular dilatation and AR, +/- coronary ostial narrowing
- Inflammation of vaso vasorum leads to intimal proliferation with obliteration, medial destruction (ischemic).
- Medial changes cause "tree barking" appearance.

JJJ. Takayasu's aortitis

- Pulseless form of vasculitis with predilection for young Asian women
- Patchy distribution leading to narrowed, rigid segments of aorta +/- pulmonary and great vessels
- Intense medial destruction, fibrointimal proliferation, thrombus formation
- Occasional giant cells but absence of fibrinoid necrosis

KKK. Giant cell aortitis/arteritis

1. Characterized by fragmented elastic fibers, prominent giant cell response and diffuse mural mononuclear cells
2. Temporal arteritis in elderly is classic form.
 - a. False negatives due to small biopsy samples (< 3-5 cm), patchy distribution of lesions and treatment before Bx
3. Giant cells are **not** required for temporal arteritis; mononuclear cell inflammation with destruction of internal elastica.

LLL. Polyarteritis nodosa

- Classic form is characterized by fever, weight loss, myalgia, hypertension, organ-specific symptoms.
- Classic features are focal fibrinoid necrosis with PMNs of muscular arteries and arterioles in early stages.
- Lesions progress to granulation tissue and then scar.
- Aneurysms occur at branching points of vessels.

MMM. Microscopic polyarteritis/angiitis

- pANCA positive form of PAN with involvement of small and medium arteries of kidneys, lungs, skin
- Immune complexes are absent.

NNN. Wegener's granulomatosis

- Necrotizing granulomatous form of vasculitis
- Classic form involves kidney, upper and lower respiratory tracts.
- Veins and arteries are affected with additional sites of involvement including brain, skin, heart.

Pathology Review Course

- > 90% are cANCA positive.
- Treatment including steroids and Cytoxan is effective.