Objectives

- **Vascular structure and function:**
  - Explain the pathogenesis of atherosclerosis, its risk factors and consequences, including ischaemic heart disease
  - Identify aneurysms and dissections as possible consequences of atherosclerosis and hypertension
  - List some of the more common vasculitides
- **Hypertension:**
  - Discuss the principles of normal blood pressure regulation and the pathogenesis of hypertension and its complications, including hypertensive heart disease
  - Describe the morphology of hypertensive vascular disease, atherosclerosis, hypertensive heart disease and acute myocardial infarction
- **Heart failure:**
  - Illustrate the causes and consequences of heart failure
- **Ischaemic heart disease:**
  - Outline the four clinical manifestations of ischaemic heart disease and their pathogenesis: angina pectoris, myocardial infarction, chronic ischaemic heart disease with heart failure, and sudden cardiac death
- **Valvular heart disease:**
  - Identify and describe some common causes of valvular stenosis and valvular insufficiency, including rheumatic heart disease
  - Describe the pathogenesis and morphologic features of infective endocarditis
- **Cardiomyopathies:**
  - State the different morphological patterns of cardiomyopathies
- **Congenital heart disease:**
  - Discuss the principles of classification for the major congenital heart diseases and their possible complications, including shunt reversal
- **Pericardial disease:**
  - List the types and causes of pericardial effusions and pericarditis

Outline

This chapter is divided roughly into **TWO main sections** – **sections I – VI. Diseases of blood vessels**, and **sections VII – XIII. Diseases of the heart and its structures**. Note that hypertension is divided into hypertensive vascular disease and hypertensive heart disease.

a. **Endothelial cells:** *Normal state vs Endothelial activation*
b. **Smooth muscle cells**
c. **Intimal thickening**

III. Hypertensive Vascular Disease

a. **Hypertension and Malignant Hypertension**

IV. Arteriosclerosis and Atherosclerosis

a. **Arteriosclerosis:** *Atherosclerosis, Arteriolosclerosis, Mönckeburg medial sclerosis, Fibromuscular intimal hyperplasia*
b. **Atherosclerosis**

V. Aneurysms and Dissection

a. **Aneurysm:** *True vs false, Saccular vs fusiform, Abdominal aortic aneurysm, Thoracic aortic aneurysm*
b. **Dissection**

VI. Vasculitis

a. **Non-infectious vasculitis:** *Giant cell arteritis, Polyarteritis nodosa, Granulomatosis with polyangiitis etc.*
b. **Infectious vasculitis**

VII. Heart Failure

a. **Systolic vs Diastolic heart failure**
b. **Cardiac hypertrophy:** *Pressure-overload vs Volume-overload; Physiologic vs Pathologic*
c. **Left-sided vs Right-sided heart failure**

VIII. Hypertensive Heart Disease

a. **Systemic (left-sided) hypertensive heart disease**
b. **Pulmonary (right-sided) hypertensive heart disease (cor pulmonale)**

IX. Ischaemic Heart Disease

a. **Angina pectoris:** *Stable angina, Prinzmetal variant angina, Unstable angina*
b. **Acute myocardial infarction**
c. **Chronic ischaemic heart disease with heart failure**
d. **Sudden cardiac death**

X. Valvular Heart Disease

a. **Valvular stenosis and insufficiency:** *Aortic stenosis, Aortic regurgitation, Mitral stenosis, Mitral regurgitation*
b. **Infective endocarditis**
c. **Non-infective vegetations:** *Non-bacterial thrombotic endocarditis, Libman-Sacks endocarditis*
d. **Prosthetic valves**

XI. Cardiomyopathies

a. **Dilated cardiomyopathy**
b. **Arrhythmogenic right ventricular cardiomyopathy**
c. **Hypertrophy cardiomyopathy**
d. **Restrictive cardiomyopathy**

XII. Congenital Heart Disease

a. **Left-to-right shunt:** *ASD, VSD, PDA*
b. **Right-to-left shunt:** *(PFO), TOF, TGA, TA*
c. **Obstruction:** *Coarctation of aorta, Aortic valvular stenosis, Pulmonary stenosis*

XIII. Pericardial disease

a. **Pleural effusion and haemopericardium**
b. **Pericarditis:** *Acute, Chronic / healed*

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

The first few sections (I - VI) will focus on diseases of blood vessels.

I. VASCULAR STRUCTURE, FUNCTION AND ANOMALIES

All vessels except capillaries generally have 3 layers: endothelium-lined intima, smooth muscle media, supporting connective tissue adventitia

Regional specialization of vasculature

- **Elastic arteries** (aorta, major branches of aorta, pulmonary arteries.): Have substantial elastic tissue to accommodate high pulsatile forces in a high pressure system
- **Muscular arteries and arterioles**: Only have limited elastic fibers (internal and external elastic lamina) but substantial muscular wall to exert control over blood flow and pressure
- **Venous vessels**: Thinner medial layers allow greater capacitance in a low pressure system
- **Capillaries**: Only composed of endothelial cells and few encircling pericytes with no media, facilitating gas and nutrient exchange (low flow rate and large cross-sectional area)
- **Lymphatics**: Thin-walled endothelium-lined channels draining lymph from the interstitium to lymph nodes and eventually back to the blood stream via the thoracic duct, facilitating antigen presentation

Many vascular disorders affect only particular types of vessels and therefore have characteristic anatomic distributions:

- **Atherosclerosis**: Elastic and muscular arteries
- **Hypertension**: Small muscular arteries and arterioles
- **Vasculitis**: Usually only vessels of a certain calibre

Vascular anomalies

- **Developmental / berry aneurysms**: Cerebral vessels; can rupture → intracerebral haemorrhage
- **Arteriovenous fistulas**: Direct connection between arteries and veins, bypassing capillaries. Usually small, mostly developmental defect but can also result from rupture of arterial aneurysm into adjacent vein, penetrating injuries, inflammatory necrosis of adjacent vessels or surgically created (for hemodialysis). Can rupture; large fistulas can allow significant shunting causing high output cardiac failure
- **Fibromuscular dysplasia**: Focal irregular thickening causing stenosis in medium and large muscular arteries e.g. renal artery. Unknown cause. Can cause hypertension in renal arteries, or adjacent aneurysms that rupture
- **Anomalous coronary artery origin**: Developmental anomaly; can be a cause of sudden death

II. GENERAL VASCULAR RESPONSE TO INJURY

Vascular disease is usually due to either: 1. Narrowing (stenosis) or complete obstruction of the vessel lumen or 2. Weakening of the vessel wall, leading to dilation or rupture. The integrated functioning /

dysfunctioning of endothelial cells and smooth muscle cells affects physiologic and pathophysiological responses to hemodynamic and biochemical stimuli

Endothelial cells

- **Normal (basal) state**: Has properties/ constitutive functions critical for vessel homeostasis and circulatory function e.g. maintains the permeability barrier, forms a non-thrombogenic surface, modulates vascular tone, regulates inflammation
- **Endothelial activation**: Induced by various stimuli (e.g. cytokines, bacterial products, hemodynamic stresses) to express adhesion molecules, produce cytokines, chemokines, growth factors, vasoactive molecules, pro/anti-coagulant factors and other biologically active products

Smooth muscle cells

- When stimulated, can proliferate, synthesize collagen, elastin, proteoglycans and secrete growth factors and cytokines
- Also responds by vasoconstriction or vasodilation to stimuli

Stereotypical response to vascular injury: Intimal thickening

- Intimal thickening results when vascular injury associated with loss or dysfunction of endothelial cells stimulates recruitment and proliferation of smooth muscle cells and associated synthesis of extracellular matrix (similar to how fibroblasts fill a wound). The resulting neointima is usually completely covered by endothelial cells
- This response is typical regardless of insult, and can result in luminal stenosis and vessel occlusion
- The neointimal smooth muscle cells are more proliferative, less contractile and have increased biosynthetic capabilities compared to normal medial smooth muscle cells. They are regulated by cytokines, growth factors etc. from other cells like endothelial cells, platelets, macrophages, and can return to a non-proliferative state with time

III. HYPERTENSIVE VASCULAR DISEASE

- Hypertension can cause end-organ damage and is one of the major risk factors for atherosclerosis
- Both systolic and diastolic pressure is important in determining risk for cardiovascular disease (above 120 mmHg and 80 mmHg is generally considered hypertensive)
- **Causes**:
    - **Essential (90-95%)**: Idiopathic; multifactorial disorder resulting from interaction of genetic polymorphisms and environmental factors. Prevalence increases with age
    - **Secondary (10%)**: From underlying disease e.g. renal disease (e.g. chronic renal disease, renal artery stenosis causing decreased glomerular flow and resulting renin secretion), adrenal disease (e.g. primary hyperaldesteronism), phaeochromocytoma, endocrine disorders (e.g. acromegaly, exogenous hormones), cardiovascular and neurologic disorders, single gene disorders e.g. Liddle syndrome (affects sodium reabsorption)
- **Pathogenesis:**

- **Normal blood pressure regulation:** Blood pressure = cardiac output x total peripheral resistance
  - **Cardiac output** = stroke volume x heart rate
    - **Stroke volume**: determined mainly by filling pressure, which is regulated through **sodium homeostasis**. Also affected by myocardial contractility
    - **Heart rate**: regulated by α and β adrenergic systems
  - **Peripheral resistance**: regulated predominantly at the arteriole level by **neural** (α and β adrenergic systems) and **humoral** factors (balance of vasoconstrictors e.g. angiotensin II and vasodilators e.g. prostaglandins, nitric oxide). This is moderated by **local** factors e.g. autoregulation, tissue pH and hypoxia in accordance to local metabolic demands
  - **Renin-angiotensin-aldosterone system (RAAS)** and **atrial natriuretic peptide (ANP)** interact to maintain blood pressure homeostasis
    - **Renin** is released in response to low blood pressure in glomerular afferent arterioles, increased circulating catecholamines or low sodium levels in the distal convoluted tubules, triggering the RAAS system
    - **ANP** is released in response to volume expansion and inhibits sodium resorption in the distal renal tubules leading to diuresis; also induces systemic vasodilation
- **Mechanisms of essential hypertension:** Interaction of genetic and environmental factors (dietary sodium intake, stress, smoking, obesity, physical inactivity), likely initiated by insufficient renal sodium excretion in the presence of normal arterial pressure, resulting in body responses to achieve a new steady state of sodium balance at a higher blood pressure

- **Clinical features**: Often asymptomatic until late. **Complications**: Atherosclerosis (leading to ischemic heart disease), hypertensive heart failure, cerebrovascular disease, multi-infarct dementia, aortic dissection, renal failure
- **Malignant hypertension**: Rapidly rising severe high blood pressure (>200/120 mmHg) associated with renal failure, retinal haemorrhage +/- papilledema (from raised intracranial pressure), usually arising in patients with pre-existing hypertension
- **Microscopy**:
  - **Hyaline arteriolosclerosis**: Homogeneous pink hyaline thickening of arteriole wall with luminal narrowing due to plasma protein leakage across injured endothelial cells and increased smooth muscle cell matrix synthesis in response to the chronically elevated blood pressure
  - **Hyperplastic arteriolosclerosis**: Concentric laminated ('onion-skinning') thickening of walls with luminal narrowing in severe hypertension +/- fibrinoid necrosis (necrotizing arteriolitis) due to proliferation of smooth muscle cells with thickened reduplicated basement membrane

IV. ARTERIOSCLEROSIS AND ATHEROSCLEROSIS

Arteriosclerosis: generic term for arterial wall thickening and loss of elasticity, including:

- **Atherosclerosis**: Most frequent pattern with significant clinical effects (see below)
- **Arteriolosclerosis**: Affects small arteries and arterioles (see above section "hypertensive vascular disease"); can cause downstream ischaemia
- **Mönckeburg medial sclerosis**: Calcifications of medial walls of muscular arteries; usually not clinically significant
- **Fibromuscular intimal hyperplasia**: Occurs in muscular arteries larger than arterioles, as a healing response driven by inflammation or mechanical injury e.g. healed arteritis, stenting; can result in stenosis

Atherosclerosis: Degenerative and inflammatory disease affecting large and medium sized arteries causing thickening and loss of elasticity. Accounts for coronary, cerebral and peripheral vascular disease, resulting in extensive morbidity and mortality worldwide

- **Risk factors**: Acquired, inherited, gender and age-associated factors interact synergistically
    - **Constitutional (non-modifiable)**:
        - **Genetic abnormalities**: e.g. familial hypercholesterolemia, hyperhomocysteinemia from homocystinuria
        - **Family history:** Most important independent risk factor, usually polygenic
        - **Increasing age:** Development of atherosclerosis is progressive, usually clinically manifest after middle age
        - **Male gender**: Premenopausal women are relatively protected compared to age-matched men; however, after menopause, the incidence increases and exceeds men at older ages
    - **Modifiable**:
        - **Dyslipidaemia / hypercholesterolemia (high LDL)**: Sufficient to initiate atheroma formation even in absence of other risk factors. High HDL (the complex that mobilizes cholesterol from the peripheries and transports it to the liver for catabolism and biliary excretion) is protective. Contribution from dietary fats now considered minimal, except for protective effect of omega-3 fatty acids and adverse effects of trans-fat. Cholesterol levels can be lowered with statins (inhibitors of HMG-CoA reductase)
        - **Hypertension:** Causes left ventricular hypertrophy and increases risk of ischemic heart disease (IHD) by ~60%
        - **Cigarette smoking:** Prolonged use doubles death rate from IHD
        - **Diabetes:** Induces hypercholesterolemia and markedly increases risk of atherosclerosis. Incidence of myocardial infarction in diabetics is 2x; also increases risk of stroke and peripheral vascular disease

        - **Inflammation:** Present during all stages of atherosclerosis. Several serum markers of inflammation correlate with IHD although not necessarily causally related e.g. C-reactive protein (CRP), an acute phase reactant synthesized by liver
        - **Metabolic syndrome**: Associated with central obesity, insulin resistance, hypertension, dyslipidaemia, hypercoagulability and proinflammatory state
    - **Others**: e.g. lipoprotein a, factors affecting haemostasis, lifestyle stress
- **Pathogenesis**: Current hypothesis is the "response to injury" model i.e. atherosclerosis is a chronic inflammatory and healing response of the arterial wall to endothelial injury
    - **Endothelial injury and dysfunction**: Increased vascular permeability, enhanced leukocyte adhesion and thrombosis, caused by:
        - **Hemodynamic disturbance**: turbulent non-laminar flow e.g. at branch points, ostia
        - **Hypercholesterolemia / dyslipoproteinemia**: directly impairs endothelial cell function by increasing local reactive oxygen species production. Lipoproteins also accumulate within the intima and can become oxidized by free radicals; these modified lipoproteins are toxic to endothelial cells, smooth muscle cells and macrophages and also stimulate release of factors creating a vicious inflammatory cycle
        - **Inflammation**: contributes to both initiation and progression of atherosclerotic lesions. Inflammation is triggered by accumulation of cholesterol crystals and free fatty acids in macrophages, which further release cytokines and chemokines
        - **Others** e.g. toxins from cigarette smoke, homocysteine, infections
    - **Accumulation of lipoproteins**: Mainly LDL in the vessel wall
    - **Monocyte and platelet adhesion to endothelium**: Monocytes migrate into the intima and transform into macrophages and foam cells as they engulf lipids. These early lesions containing lipid-filled macrophages are called "fatty streaks"
    - **Smooth muscle cell recruitment and proliferation, extracellular matrix production and recruitment of T cells**: Stimulated by factors released from activated platelets, macrophages and vascular wall cells, converting a fatty streak into well-developed plaque (fibrofatty atheroma)
    - **Lipid accumulation**: Both extracellularly and within macrophages and smooth muscle cells.
    - **Calcification** of extracellular matrix and necrotic debris occurs late
- **Clinical features / complications**: Atherosclerosis affects large elastic arteries and large and medium-sized muscular arteries. Often asymptomatic unless there are increased metabolic demands or sudden plaque change, resulting in myocardial infarction, cerebral infarction, aortic aneurysm and peripheral vascular disease. These clinical manifestations occur due to the following consequences of atherosclerotic lesions:
    - **Stenosis / obstruction of blood flow**: limits on the extent of compensatory outward remodeling of the vessel media to preserve lumen size results in atherosclerotic plaques eventually narrowing and occluding blood flow. "Critical stenosis": occlusion is sufficiently severe to cause tissue ischemia (usually 70-75% decrease in luminal cross-sectional area) –

the effects depend on balance between arterial supply and metabolic demand e.g. in stable angina (chest pain on exertion); development of collateral circulation for perfusion

- **Acute plaque change**: refers to (1) rupture/fissuring, exposing highly thrombogenic plaque constituents often inducing completely occlusive thrombosis; (2) erosion/ulceration, exposing the thrombogenic subendothelial basement membrane inducing usually partially occlusive thrombosis; and (3) haemorrhage into the atheroma, expanding its volume. Triggering events include both intrinsic and extrinsic factors: plaques with thin fibrous caps and active inflammation over a large necrotic core are more likely to rupture (vulnerable plaques vs stable plaques), adrenergic stimulation e.g. awakening, intense emotional stress. Note: not all acute plaque changes causes occlusive thromboses; many are clinically silent and heal with organisation of the overlying thrombi, resulting in growth of the lesion
- **Emboli**: Thrombi or plaque contents from acute plaque change can embolize
- **Aneurysm formation:** from ischemic injury and weakening of the vessel wall (as the plaque compresses the underlying media)

- **Morphology**:
  - **Fatty streaks**: Small flat yellow macules that can coalesce into elongated streaks
    - Consists of lipid-filled foamy macrophages within the intima
    - Do not cause significant flow disturbances and can be seen in virtually all adolescents regardless of risk factors
  - **Atherosclerotic plaques (atheroma):** Raised yellow-tan lesions, usually only involving part of the vessel wall (eccentric on cross-section); may be ulcerated with overlying red-brown thrombosis
    - Consists of a fibrous cap (smooth muscle cells and collagen) and a central necrotic core containing cholesterol and other lipids, debris from dead cells, foam cells, fibrin, thrombi. The junction of the fibrous cap and fatty core ('shoulder') is more cellular: macrophages, T cells, smooth muscle cells, as well as neovascularisation. Older plaques can have less lipid and show calcification
    - Starts off patchy and focally (at turbulent flow areas, lower abdominal aorta and iliac arteries > coronary arteries > popliteal arteries > internal carotid arteries > circle of Willis) but can enlarge over time and become numerous and broadly distributed, due to cell death, remodeling of extracellular matrix, organisation of any thrombus and secondary calcifications
  - **Complicated plaques**: Secondary changes including rupture, ulceration or erosion of the fibrous cap, leading to thrombosis. Intraplaque haemorrhage can also occur which may expand the plaque or induce plaque rupture
  - **Aneurysm**: Due to atherosclerosis-induced pressure/ischemic atrophy of the underlying media (see next section "Aneurysms and dissection")

V. ANEURYSMS AND DISSECTION

Aneurysm: Congenital or acquired localised abnormal dilation of blood vessel or heart

- **Classification:**
  - **True vs false aneurysms**:
    - **True**: Involves all layers (although attenuated) of the vessel / heart wall e.g. atherosclerotic aneurysms
    - **False**: Extravascular hematoma that communicates with the intravascular space through a defect in the vessel wall ('pulsating hematoma') e.g. ventricular rupture from myocardial infarction that is contained by pericardial adhesions
  - **Saccular vs fusiform**:
    - **Saccular**: Spherical outpouchings involving only a portion of the vessel wall
    - **Fusiform**: Diffuse circumferential dilation of a long vascular segment
- **Pathogenesis:** Both congenital and acquired aneurysms occur when the structure or function of the connective tissue within the vascular wall is compromised, resulting in **medial degeneration**. This can be due to:
  - **Poor intrinsic quality of the connective tissue** e.g. defective type III collagen synthesis in Ehler-Danlos syndrome
  - **Abnormal TGF-β signalling** altering vascular wall remodeling e.g. in Marfan syndrome;
  - **Inflammation and associated proteases** altering the balance of collagen degradation and synthesis e.g. in aortitis or atherosclerosis
  - **Weakening of vessel wall through loss of smooth muscle cells or inappropriate synthesis of non-collagenous/nonelastic extracellular matrix**, usually due to ischemia e.g. from atherosclerosis, narrowing of vasa vasorum in the aorta from chronic hypertension or syphilis
- **Risk factors:**
  - **Atherosclerosis** (mainly in abdominal aortic aneurysms) and **hypertension** (mostly ascending aortic aneurysms)
  - **Other factors**: advanced age, smoking, trauma, vasculitis, congenital defects (fibromuscular dysplasia and berry aneurysms), infection (mycotic aneurysms)

Abdominal aortic aneurysm (AAA)

- Involves the abdominal aorta usually between renal arteries and aorta bifurcation and may be accompanied by smaller aneurysms of the iliac arteries
- **Clinical features**: Mostly men >50yo, smokers, with atherosclerosis. Mostly asymptomatic and discovered incidentally as a palpable pulsating abdominal mass. **Complications**: Rupture with massive intrabdominal haemorrhage; obstruction of a branch vessel with downstream tissue injury e.g. mesenteric artery occlusion with gastrointestinal tract ischemia; embolism from atheroma or mural thrombus; impingement of adjacent structures e.g. ureter compression, vertebral erosion. Most aneurysms generally expand at 0.2-0.3 cm/yr but 20% expand more rapidly. Risk of rupture is

directly related to aneurysm size (nil for ≤ 4 cm); those ≥ 5 cm are generally managed aggressively through surgery or endovascular therapies.

- **Morphology**: Saccular or fusiform, with severe complicated atherosclerosis causing destruction and thinning of the underlying aortic media. Aneurysm often contains a bland poorly organised mural thrombus
    - **Inflammatory AAA:** 5-10% of all aneurysms, typically in younger patients. Have abundant lymphoplasmacytic inflammation with many macrophages associated with periaortic scarring; a subset may be a manifestation of IgG4-related disease
    - **Mycotic AAA:** Lesions that have become infected by circulating microorganisms lodging in the wall, further destroying the media with risk of rapid dilation and rupture

Thoracic aortic aneurysm

- Most commonly due to hypertension; other causes: Marfan syndrome, aortitis
- **Clinical features**: Often asymptomatic until dissection or rupture. Less common symptoms include: chest pain (from bone erosion) or myocardial ischemia (coronary artery compression), difficult swallowing (oesophagus compression), voice hoarseness (irritation of recurrent laryngeal nerve), respiratory complications (bronchi compression)

Dissection: Blood separating the laminar planes of the vessel media / medial-adventitial junction to form a blood-filled channel. Occurs when blood enters a defect in the intima; often associated with dilatation. Less likely when there is extensive atherosclerosis or other causes of medial scarring e.g. syphilis, as the fibrosis makes it less likely for blood to dissect through

- **Pathogenesis**:
    - **Hypertension** is the major risk factor, causing medial degeneration with loss of smooth muscle cells and alterations of extracellular matrix. Other causes are inherited or acquired connective tissue disorders. Regardless of aetiology, the actual trigger for the intimal tear and blood entry into the media is not known in most cases; traumatic chest injury can cause intimal tears usually at the ligamentum arteriosum
    - Once there is a tear, blood flow under systemic pressure causes progression of the intramural haematoma
    - Rarely, disruption of penetrating vasa vasorum can also cause an intramural hematoma without an intimal tear
- **Clinical features**: 90% are middle-aged men with hypertension; 10% are in younger patients with syndromic diseases affecting the aorta e.g. Marfan syndrome; iatrogenic (e.g. during catheterization), pregnancy. Morbidity and mortality depends on which part of the aorta is involved: Type A dissections (involving the ascending aorta) are more dangerous and also more common; type B dissections usually begin distal to the subclavian artery. **Classic symptoms**: Sudden onset of excruciating chest pain radiating to the back and moving downwards as the dissection progresses. **Complications**: Rupture through adventitia causing massive haemorrhage or cardiac tamponade. Rarely, the dissection can re-enter the aorta through a second intimal tear, causing a false vascular channel (double barrelled aorta) that can become a chronic dissection. Disruption of the aortic valve

annulus can cause aortic insufficiency; dissections into the other branching vessels can cause vascular obstruction and ischemia e.g. myocardial infarction. **Treatment**: antihypertensive therapy can limit evolving dissections; surgical repair especially for type A dissections

- **Morphology**: In spontaneous dissections, the intimal tear usually occurs in the ascending aorta within 10 cm of the aortic valve, and can extend retrograde towards the heart or distally. The dissecting hematoma usually occurs in the outer third of the media or between media and adventitia. **Medial degeneration** (fragmentation and loss of elastic fibers, mucoid ECM accumulation, attenuation of smooth muscle cells) is often seen at the site of the intimal tear but not necessarily at the area of propagation. The severity of these morphologic changes do not correlate with the presence of dissection

VI. VASCULITIS

- **Vasculitis** = general term for inflammation of the vessel wall; findings depend on the vascular bed affected in addition to constitutional signs and symptoms e.g. fever, malaise
- Most primary vasculitides tend to affect vessels of a particular size or location, with considerable clinical and pathologic overlap
- **Causes**: **Non-infectious** (immune mediated inflammation, physical and chemical injury e.g. radiation) and **infectious** pathogens directly invading vascular walls

Non-infectious vasculitis

Immunologic mechanism	Examples
Immune complex-associated vasculitis Not clear whether the pathogenic antigen-antibody complexes are deposited from circulation or form in-situ; the specific antigen is also often not identified	• SLE-associated vasculitis • Drug hypersensitivity vasculitis • Vasculitis secondary to infections e.g. HBV
Antineutrophil cytoplasmic antibodies (pauci-immune) • Anti-proteinase-3 (PR3-ANCA, aka c-ANCA) • Anti-myeloperoxidase (MPO-ANCA, aka p-ANCA) Titres are associated with disease activity	• Granulomatous with polyangiitis • Microscopic polyangiitis, Churg-Strauss syndrome
Anti-endothelial cell antibodies Possibly induced by defects in immune regulation	• Kawasaki disease
Autoreactive T cells	• Giant cell (temporal) arteritis

Entity	Vessel involvement (calibre)	Characteristic features
Giant cell (temporal) arteritis	Aorta and large to small-sized arteries, principally in the head	• Most common vasculitis among elderly adults (>50 years old) in US and Europe • Classically granulomatous • Ophthalmic artery involvement can lead to sudden and permanent vision loss
Takayasu arteritis	Aorta and large to medium-sized arteries	• Largely similar to Giant cell arteritis but in patients < 50 years old • Classically involves the aortic arch, resulting in weakness of peripheral pulses

Polyarteritis nodosa	Small to medium-sized arteries, typically renal and visceral vessels, sparing lung	• Segmental transmural necrotizing inflammation often with superimposed aneurysms or thrombosis; lesions usually of varying ages • Manifests as ischemia/infarction of various organs (especially renal), usually in young adults
Kawasaki disease (mucocutaneous lymph node syndrome)	Large to medium-sized arteries, especially coronary arteries	• Acute febrile usually self-limited disease of infancy and childhood (usually <4 years old) • Coronary artery involvement can cause aneurysms and subsequent myocardial infarction
Microscopic polyangiitis (leukocytoclastic vasculitis)	Capillaries, small arterioles and venules	• Necrotizing vasculitis with lesions of the same age (unlike polyarteritis nodosa) • Often involves kidneys (glomerulonephritis) and lungs • Most associated with MPO-ANCA
Granulomatosis with polyangiitis (Wegener granulomatosis)	Small to medium-sized vessels, mostly lungs and upper airways	• Classic triad of: 1. Acute necrotizing granulomas of upper respiratory tract, lung or both; 2. Necrotizing or granulomatous vasculitis most prominent in lungs and upper airways but also other sites; 3. Focal necrotizing (often crescentic) glomerulonephritis
Churg-Strauss syndrome (allergic granulomatosis and angiitis)	Small vessels	• Necrotizing vasculitis typically associated with asthma, allergic rhinitis, lung infiltrates, peripheral eosinophilia, extravascular necrotizing granulomas and marked eosinophilic infiltrate
Thromboangiitis obliterans (Buerger disease)	Medium to small-sized arteries esp. tibial and radial arteries	• Almost exclusively in heavy cigarette smokers <35yo • Segmental thrombosing acute and chronic inflammation of arteries with vascular insufficiency

Infectious vasculitis

- Direct invasion of infectious agents e.g. *Aspergillus* or *Mucor* species as part of a localised tissue infection or less commonly from hematogenous spread (from septicemia or emboli from infectious endocarditis)
- The infective vasculitis can cause mycotic aneurysm formation or induce thrombosis and downstream infarction e.g. bacterial meningitis

The following sections (VII – XIII) focus on diseases of the heart.

VII. HEART FAILURE

- Failure of the heart pump to adequately meet the metabolic demands of peripheral tissues, or only at elevated filling pressures i.e. decreased cardiac output and tissue perfusion
- Common progressive condition, often the end stage of many forms of chronic heart conditions, with poor prognosis
- Normal physiological adaptive mechanisms when cardiac workload increases or cardiac function is compromised:
    - Frank Starling mechanism: triggered by increased filling volume
    - Activation of neurohormonal systems e.g. release of norepinephrine, renal-angiotensin-aldosterone system, release of atrial natriuretic peptide
    - Myocardial adaptation: cardiac hypertrophy, ventricular remodeling
- Heart failure results when these adaptive mechanisms are overwhelmed:
    - **Systolic heart failure**: decreased ejection fraction (normal = 45-65%) due to progressive deterioration of myocardial contractile function. Causes include ischaemia, pressure or volume overload from hypertension or valvular disease, or ventricular dilation
    - **Diastolic heart failure (heart failure with preserved ejection fraction)**: inability of the heart chamber to relax / expand and fill sufficiently during diastole. Causes include left ventricular hypertrophy e.g. from hypertension, myocardial fibrosis, cardiac amyloidosis, constrictive pericarditis
- **Cardiac hypertrophy**: Increase in size of myocytes which cumulatively increase the size and weight of the heart; the cell nuclei also enlarge / multiply due to DNA replication
    - Due to sustained increase in mechanical work of the heart due to pressure overload, volume overload or trophic signals (e.g. through activation of β-adrenergic receptors)
    - Pattern of hypertrophy depends on stimulus:
        - **Pressure-overload hypertrophy**: concentric increase in wall thickness as new sarcomeres are assembled in parallel to the long axes of cells e.g. hypertension
        - **Volume-overload hypertrophy**: dilated heart with normal, thinner or thicker wall as new sarcomeres are assembled in series within existing sarcomeres e.g. valvular regurgitation. Heart weight rather than wall thickness is thus a better indicator
    - Physiologic vs pathologic hypertrophy:
        - **Physiologic**: Regular exercise especially aerobic exercise tends to be associated with volume-load hypertrophy accompanied by increases in capillary density, while also decreasing resting heart rate and blood pressure
        - **Pathologic**: Associated with persistent mechanical stressors. Hypertrophied hearts are vulnerable to ischemia as 1. Myocyte hypertrophy is not accompanied by a proportional increase in capillary numbers; 2. Cardiac hypertrophy is associated with increased metabolic demands due to increase in mass, heart rate and contractility. Cardiac hypertrophy is also typically associated with interstitial fibrosis which increases resistance to diastolic filling

  - The degree of anatomic abnormality does not always correlate with the severity of dysfunction; nevertheless, cardiomegaly from disease correlates with excess cardiac morbidity and mortality, and is a independent risk factor for sudden death
- Although left- and right-sided heart failure can occur independently, failure of one side (particularly the left) will usually also affect the other side resulting in global heart failure

Type	Causes	Clinical features and morphologic effects
Left-sided heart failure	• Ischaemic heart disease • Hypertension • Aortic and mitral valvular diseases • Primary myocardial diseases	1. **Passive congestion in pulmonary circulation** (earliest) - Cough and dyspnoea initially only with exertion but later also when lying flat (orthopnoea), at night (paroxysmal nocturnal dyspnoea) and at rest - Pulmonary congestion and oedema with haemosiderin-laden macrophages ('heart failure cells') - Pleural effusion results from transudation of fluid due to elevated pleural capillary and lymphatic pressure 2. **Blood stasis in left heart chambers** - Usually left ventricular hypertrophy and dilation (except for heart failure due to mitral stenosis and restrictive cardiomyopathies) - Secondary left atrial dilation usually follows with mitral regurgitation, blood stasis especially in the atrial appendage and risk of thrombus formation, atrial fibrillation that further reduces ventricular filling and ventricular stroke volume 3. **Organ dysfunction from inadequate peripheral perfusion** - **Kidneys**: Decreased renal perfusion activates the RAAS as a compensatory mechanism, leading to salt and water retention and expansion of interstitial and intravascular fluid volumes (which further worsen pulmonary oedema). Severe renal hypoperfusion results in pre-renal azotaemia - **Brain**: Hypoxic encephalopathy with altered mental status
Right-sided heart failure	• Usually due to left-sided heart failure • Rarely, due to leftward bulging of the interventricular septum • Isolated right heart failure is due to pulmonary parenchymal and vascular diseases causing pulmonary hypertension ('cor pulmonale')	1. **Blood stasis in right heart chambers** - Hypertrophy and dilation of right atrium and ventricle 2. **Engorgement of portal venous system** - **Liver**: Congestive hepatomegaly due to passive congestion around the central veins +/- centrilobular necrosis and fibrosis ('cardiac cirrhosis') - **Spleen**: Congestive splenomegaly due to portal venous hypertension, resulting in platelet sequestration - **Bowel**: Chronic congestion and oedema of the bowel wall can interfere with nutrient and/or drug absorption 3. **Engorgement of systemic venous system** - **Pleural, pericardial and peritoneal** effusions (ascites) - **Peripheral** oedema (especially in dependent portions e.g. foot/ankle/pretibial/presacral); if severe, can be generalised (anasarca) - **Kidneys**: Renal congestion leads to renal ischaemia and its consequences, worsening fluid retention - **Brain**: Venous congestion and hypoxia can manifest as altered mental status

- **Treatment**: correct underlying cause, reduce volume overload (salt restriction, diuretics), increase myocardial contractility (positive inotropes), reduce afterload (adrenergic blockade, ACE inhibitors), cardiac resynchronisation therapy, mechanical ventricular assist devices

VIII. HYPERTENSIVE HEART DISEASE

- Due to increased demands on the heart by hypertension causing pressure overload and ventricular hypertrophy

Systemic (left-sided) hypertensive heart disease

- Defined as: 1. Left ventricular hypertrophy (usually concentric) in the absence of other cardiovascular pathology; 2. Clinical history or pathologic evidence of hypertension in other organs (e.g. kidney)
- **Clinical presentation**: Asymptomatic if compensated (only seen on ECG); may present with symptoms related to atrial fibrillation due to left atrial enlargement, development of ischaemic heart disease (due to hypertension potentiating coronary artery disease and increased risk of ischaemia due to hypertrophic muscle), progressive congestive heart failure or sudden cardiac death, or direct effects of hypertension on other organs (renal damage, stroke)
- **Gross**: Left ventricular wall concentric thickening (hypertrophy) due to pressure overload. Over time, the increased thickness and increased interstitial connective tissue in the left ventricular wall causes stiffness that impairs diastolic filling, leading to left atrial enlargement
- **Microscopy**: Increase in transverse diameter of myocytes, followed later by cellular and nuclear enlargement accompanied by perivascular and interstitial fibrosis

Pulmonary (right-sided) hypertensive heart disease (cor pulmonale)

- Characterised by right ventricular hypertrophy, dilation and potentially right-sided heart failure due to right ventricular pressure overload (see '*right-sided heart failure*' section above)

Gross: If acute, marked dilation of right ventricle without hypertrophy; if chronic, there is right ventricular thickening. Can lead to compression of the left ventricle or tricuspid valve thickening and regurgitation

IX. ISCHAEMIC HEART DISEASE (IHD)

- Myocardial ischaemia = **imbalance** between myocardial supply (perfusion) and cardiac metabolic demands
- Single largest cause of mortality worldwide
- **Causes**: Most often due to reduced blood flow from atherosclerosis in the coronary arteries (**coronary artery disease**); others include coronary emboli, myocardial vasculitis, vascular spasm; also influenced by conditions that reduce oxygen availability in blood e.g. anaemia

- **Pathogenesis**: IHD is usually due to either chronic progressive atherosclerosis or variable superimposed acute plaque change, thrombosis and vasospasm
    - **Chronic vascular occlusion**: >90% of patients with IHD have atherosclerosis in one or more of coronary arteries and/or its branches. >70% occlusion (critical stenosis) results in exertional angina; >90% occlusion causes inadequate perfusion even at rest. However, slowly developing obstruction can induce formation of collateral vessels to perfuse at-risk myocardium
    - **Acute plaque change**: Manifests as acute coronary syndromes (unstable angina, acute myocardial infarction, sudden death) due to unpredictable and sudden conversion of a stable atherosclerotic plaque to an unstable life-threatening atherothrombotic lesion through rupture, erosion, ulceration or deep haemorrhage, which occludes the artery
- Four common **clinical presentations**: **Angina pectoris, acute myocardial infarction, chronic ischaemic heart disease with heart failure,** and **sudden death:**

(1) <u>Angina pectoris</u>: episodes of chest discomfort caused by transient myocardial ischaemia insufficient to cause infarction; usually recurrent

- **Stable angina**: most common form, usually due to fixed stenoses. Does not occur at rest but is induced by activities that increase cardiac demand e.g. exercise, stress, and relieved by rest and vasodilators
- **Prinzmetal variant angina**: uncommon form caused by coronary artery spasm
- **Unstable angina**: increasingly frequent, prolonged (>20 min) or severe angina precipitated by lower levels of exertion or even at rest, usually from acute plaque change. Portends risk of acute myocardial infarction

(2) <u>Acute myocardial infarction (AMI)</u> ('heart attack'): myocardial necrosis from prolonged ischaemia

- Usually due to atherosclerosis; frequency thus increases with increasing atherosclerotic risk factors. Frequency also increases with age; for middle age, M>F but for postmenopausal women, ischaemic heart disease risk rises
- **Pathogenesis**: Coronary arterial occlusion: 90% from acute plaque change with superimposed thrombus formation → early thrombolysis / angioplasty can thus limit extent of myocardial necrosis; 10% from other factors e.g. vasospasm, emboli e.g. from left atrium in atrial fibrillation (these often cause multifocal microinfarcts)
- Area at risk = anatomic region supplied by that artery e.g. Left anterior descending branch (LAD) of the left coronary artery (LCA) supplies most of the apex of the heart, anterior wall of left ventricle, anterior 2/3 of ventricular septum
- **Outcome:** depends on location, severity, rate of development and duration of blood flow deprivation; size and metabolic/oxygen needs of the area at risk; extent of vascular collaterals; presence of coronary artery spasm and other factors e.g. blood oxygenation, cardiac rhythm, heart rate

Seconds	< 2mins	10 mins	20-40 min	> 1hr
Onset of ATP deletion	Loss of contractility	ATP ↓ to 50%	ATP ↓ to 10% Irreversible cell injury	Microvascular injury

Progression of ischemic necrosis		
Subendocardial zone (<2hrs) *Most susceptible as it is furthest from epicardial vessels and subject to relatively high intramural pressures that impeded blood flow*	**Wavefront of ischemia moves through other regions** *Due to progressive tissue oedema and myocardial-derived reactive oxygen species and inflammatory mediators*	**Completed infarct (3-6hrs)** *Transmural, involves nearly the entire area at risk*

- Non-transmural (subendocardial) infarcts can therefore occur when the coronary thrombus from acute plaque change lyses (spontaneously or therapeutically) before transmural necrosis occurs. They can also result from prolonged severe reduction in systemic hypotension e.g. shock on top of chronic otherwise non-critical coronary stenoses; these tend to be circumferential in distribution
- **Clinical features**: Crushing prolonged chest pain (>30 mins) with breathlessness, diaphoresis, nausea and vomiting; 25% are asymptomatic. **ECG**: ST elevation in transmural infarcts; non-ST elevation infarcts in subendocardial infarcts. **Lab findings**: elevation of cardiac-specific troponins in the blood (Trop T, Trop I), usually within 2-4 hr and peaking at 24-48h after an acute infarct. Serial elevations useful to distinguish from "troponin leak" from other conditions e.g. renal failure. **Consequences and complications**: Mortality for out-of-hospital AMI much worse than in-hospital death rates. ~75% of patients experience complications after AMI, depending on the infarct size, location, transmural vs subendocardial infarct:
    - **Contractile dysfunction** (cardiogenic shock if severe)
    - **Papillary muscle dysfunction** (causing postinfarct mitral regurgitation)
    - **Right ventricular infarction** (by RCA occlusions) causing right heart failure
    - **Myocardial rupture** (~1-5%, fatal), most commonly left ventricular free wall rupture resulting in haemopericardium and cardiac tamponade; ventricular septum rupture creating a VSD with left-to-right shunting; papillary muscle rupture with mitral regurgitation. Usually occurs 3-7 days after infaction, when lysis of necrotic myocardium is greatest
    - **Arrhythmias**: the infarct causes myocardial irritability and conduction disturbances that can cause sudden death (greatest risk in 1st hr post-AMI)
    - **Pericarditis**: fibrinohaemorrhagic, in transmural AMIs (usually 2-3 days after AMI, gradually resolves). Dressler syndrome = intense pericarditis weeks after due to formation of antibodies against damaged myocardium
    - **Chamber dilation**: because of the weakened necrotic muscle
    - **Mural thrombus**: due to combination of stasis (decreased contractility), chamber dilation and endocardial damage (forming a thrombogenic surface); risk of thromboembolism
    - **Ventricular aneurysm**: Late complication, due to a large transmural anteroseptal infarct that heals with formation of thin scar tissue (risk of mural thrombi, arrhythmias and heart failure but does not rupture because it is fibrous)
    - **Progressive heart failure (chronic ischaemic heart disease)**

- **Ventricular remodelling**: Compensatory hypertrophy and dilation of the non-infarcted segments of the ventricle; initially adaptive but can be maladaptive due to increased oxygen demand exacerbating ischemia and decrease cardiac output

- **Morphology:**

Time	Gross changes	Microscopic changes
Reversible		
0-30 min	None	None
Irreversible injury		
30min-4h	Usually none; variable fibre waviness at border	
4-12h	Occasional dark mottling	Early coagulative necrosis, oedema, haemorrhage
12-24h	Dark mottling	Ongoing coagulative necrosis, nuclear pyknosis, myocyte hypereosinophilia, marginal contraction band necrosis, early neutrophilic infiltrate
1-3 days	Mottling with yellow-tan infarct centre	Coagulative necrosis with loss of nuclei and striations; brisk neutrophils
3-7 days	Hyperaemic border with central yellow-tan softening	Beginning disintegration of dead myofibers, dying neutrophils, early phagocytosis of dead cells by macrophages at infarct border
7-10 days	Maximally yellow-tan and soft, with depressed red margins	Well-developed phagocytosis, granulation tissue at margins
10-14 days	Red-grey depressed infarct borders	Well-established granulation tissue and collagen deposition
2-8 wks	Gray-white scar from periphery to centre	Increased collagen and decreased cellularity
>2 mths	Mature scar	Dense collagenous scar

- **Restoration of tissue perfusion**: Therapeutic goal aims to salvage maximal amount of ischaemic myocardium e.g. via thrombolysis, angioplasty, coronary arterial bypass graft. However, **reperfusion injury** can occur and modify overall infarct size; the return of function of salvaged myocardium may thus be delayed for hours or days (post-ischaemic ventricular dysfunction or stunning)
    - Reperfusion injury occurs through mitochondrial dysfunction, myocyte hypercontracture, production of free radicals, leukocyte aggregation that occludes microvasculature and releases proteases/elastases, and platelet and complement activation that contribute to microvascular injury
    - **Morphology**: Infarcts are typically haemorrhagic because of the vascular injury and leakiness. Microscopically, irreversibly damaged myocytes develop contraction band necrosis

(3) <u>Chronic IHD with heart failure</u>: ischaemic cardiomyopathy

- Progressive congestive heart failure due to ischaemic myocardial damage and/or inadequate compensatory responses; usually post-infarction or in severe coronary artery disease
- ~50% of heart transplant recipients
- **Morphology**: Cardiomegaly with left ventricular hypertrophy and dilation, usually accompanied with coronary artery atherosclerosis. May have scars (healed infarcts) and mural thrombi.

Microscopically, can have myocardial hypertrophy, diffuse subendocardial myocyte vacuolisation and interstitial fibrosis

(4) <u>Sudden cardiac death (SCD)</u>

- Unexpected death from cardiac causes, either without symptoms or within 1-24h of symptom onset
- **Pathogenesis**: Fatal ventricular arrhythmia (e.g. asystole, ventricular fibrillation)
    - **Arrhythmia** = abnormalities in myocardial conduction that can be initiated anywhere in the conduction system
        - **Causes**: Commonly due to ischaemic injury, either through direct damage or via heart chamber dilation that alters conduction system firing; others include inflammation (myocarditis, sarcoidosis), myocyte hypertrophy, infiltrative disease (amyloidosis), heritable conditions (primary electrical disorders e.g. channelopathies)
        - **Clinical presentation**: Asymptomatic, palpitations, syncope (due to decreased cardiac output from sustained arrhythmia) or sudden cardiac death
- **Causes:** Majority of sudden cardiac deaths are due to coronary artery disease (either from fixed critical stenoses (80-90%) or acute plaque change, causing regional myocardial ischaemia and irritability that induces arrhythmia) and can be the first presentation of IHD. Other causes: cardiac conduction abnormalities (see '*Causes of arrhythmia'* above), dilated or hypertrophic cardiomyopathy, congenital coronary arterial abnormalities, myocarditis, mitral valve prolapse, pulmonary hypertension etc.

X. VALVULAR HEART DISEASE

Valvular disease can be congenital or acquired, and usually manifests clinically as valvular dysfunction in the form of stenosis or insufficiency, or even both.

<u>Valvular stenosis and insufficiency</u>

- **Valvular stenosis** = failure of valve to open completely, obstructing forward flow
    - Acquired stenosis is almost always a chronic process due to a primary leaflet abnormality
- **Valvular insufficiency** (regurgitation, incompetence) = failure of valve to close completely, allowing regurgitation / backflow of blood
    - Can be due to intrinsic disease of the valve leaflets or disruption of its supporting structures
    - Can be abrupt (e.g. chordal rupture) or chronic (e.g. scarring and retraction)
- Stenosis and insufficiency can co-exist and affect one or more valves
- **Causes**: Congenital or acquired; structurally abnormal valves are at higher risk

Valvular abnormality	Causes
Aortic stenosis	**Calcific valvular degeneration** • Usually due to age-related "wear and tear" due to repetitive mechanical stress of anatomically normal valve or congenitally bicuspid aortic valve (the latter will usually present earlier as they incur greater mechanical stress)

	• **Consequence**: Left ventricular hypertrophy due to the obstruction • **Presentation**: Onset of symptoms e.g. angina, congestive heart failure, syncope indicates cardiac decompensation and poor outcomes • **Gross**: Mounded calcified masses on the outflow surfaces of the cusps preventing cuspal opening. No commissural fusion seen **Postinflammatory scarring from rheumatic heart disease** (see "mitral stenosis")
Aortic regurgitation	**Dilation of ascending aorta**, often secondary to hypertension and/or aging
Mitral stenosis	**Rheumatic heart disease** • Rheumatic fever = acute immunologically mediated multisystem inflammatory disease classically occurring 2-3 weeks after Group A streptococcal pharyngitis (rarely skin). Due to host immune responses to streptococcal antigens that cross-react with host proteins. Diagnosed by Jones clinical criteria • Acute rheumatic carditis occurs as a manifestation of acute RF, and can progress to chronic RHD years later • Characterised by deforming fibrotic valvular disease (MV>>>AV) • **Acute RF**: Inflammation and **Aschoff bodies** – composed of T cells, occasional plasma cells, plump macrophages called Anitschkow cells – in all 3 layers of the heart (pancarditis). Valvular vegetations (verrucae) can be present • **Chronic RHD**: Leaflet thickening, commissural fusion and shortening, thickening and fusion of the tendinous cords; resulting in "fish-mouth" stenoses. Aschoff bodies rare. **Complications: l**eft atrial dilation +/- mural thrombi, pulmonary congestion and eventual right ventricular hypertrophy; also arrhythmias (e.g. atrial fibrillation), infective endocarditis, thromboembolic complications
Mitral regurgitation	**Mitral valve prolapse (MVP)** (myxomatous degeneration) • One or both mitral valve leaflets are "floppy" and protrude into the left atrium during systole • **Pathogenesis**: unknown in most cases; can be a/w heritable connective tissue disorders e.g. Marfan syndrome. Myxomatous change may also be secondary consequence of regurgitation of other causes e.g. ischaemia • **Clinical features**: Usually asymptomatic; rarely non-exertional chest pain and dyspnoea • **Complications**: (1) infective endocarditis; (2) mitral insufficiency; (3) stroke or systemic infarcts due to embolism of leaflet thrombi; (4) arrhythmias • **Gross**: "ballooning / hooding" of enlarged, redundant, thickened and rubbery mitral valve leaflets, a/w elongated thinned tendinous cords. Secondary changes e.g. fibrous thickening at areas of increased friction due to the floppy mitral valves can be seen like edges of valve leaflets, mural endocardium; leaflet thrombi; focal calcifications at leaflet base • **Microscopy**: Myxomatous degeneration of the spongiosa layer **Mitral annular calcification** • Usually doesn't affect valve function; rarely can lead to regurgitation by affecting physiologic contraction of the valve ring; stenosis; arrhythmias • More frequent with age and with MVP **Left ventricular dilation** due to ischemic or non-ischemic heart failure

- **Clinical features**: Can be detected as a heart murmur due to the abnormal flow. **Consequences**: Depends on valve involvement, severity of impairment, tempo of disease onset and compensatory mechanisms (pressure overload in stenosis and volume overload hypertrophy in valvular insufficiency) e.g. chronic processes like rheumatic mitral stenosis develops slowly and can be well-tolerated for long periods. Conditions that increase demand on the heart can cause valvular disease to decompensate e.g. pregnancy

Infective endocarditis (IE)

- Microbial infection of the cardiac valves (including prostheses) or endocardium, forming vegetations composed of thrombotic debris and organisms causing tissue destruction
- **Acute IE**: Infection of previously normal heart valve by highly virulent organisms with rapid destruction e.g. *Staphylococcus aureus* in intravenous drug abusers; difficult to treat with antibiotics alone and may require surgery
- **Subacute IE**: Infection of deformed heart valves by less virulent organisms with less destruction over a longer period of time e.g. *Streptococcus viridans* (oral commensal); usually can be treated with antibiotics alone
- **Pathogenesis**:
    - Abnormal valves are at higher risk e.g. rheumatic heart disease with valvular scarring, MVP, degenerative calcific valvular stenosis etc.
    - Various bacteria (usually oral cavity or skin flora) can be the case; 10% of cases are culture-negative (no identifiable organism). When these bacteria enter the bloodstream (bacteraemia/fungaemia) e.g. from obvious infection, dental or surgical procedure, contaminated needle by intravenous drug users or trivial breaks in skin/mucosal barriers, they can infect the cardiac valves
- **Clinical features:** Acute endocarditis presents with rapid onset of fever, chills, lethargy. Diagnosis made via modified Duke criteria. **Complications**: Erosion into myocardium to form abscesses and arrhythmias; systemic embolization causing septic infarcts or mycotic aneurysms; sepsis; glomerulonephritis (from glomerular antigen-antibody complex deposition)
- **Morphology**: Cardiac valve vegetations = friable bulky potentially destructive lesions containing fibrin, inflammatory cells, and organisms, usually involving the aortic and mitral valves. Vegetations can be multiple and involve more than one valve. Over time, they develop granulation tissue, fibrosis, calcifications and chronic inflammation

Non-infective vegetations

- **Nonbacterial thrombotic endocarditis**: small sterile thrombi on cardiac leaflets often in debilitated patients with hypercoagulable states e.g. cancer, sepsis
- **Endocarditis of systemic lupus erythematosus (Libman-Sacks endocarditis)**: due to immune complex deposition

Prosthetic valves

Complication	Type of prosthetic valve at risk
Thromboembolism • Due to nonlaminar blood flow • Thrombotic occlusion of the prosthesis or emboli released from thrombi formed on the valve • Requires long term anti-coagulation (with risk of haemorrhage)	Mechanical valve
Structural failure • Calcification and/or tearing causes valvular incompetence eventually	Bioprostheses
Infective endocarditis • Vegetations usually at the prosthesis-tissue interface; can cause formation of ring abscess and paravalvular regurgitant blood leak	Both mechanical and bioprostheses
Other complications e.g. paravalvular leak (due to inadequate healing), **obstruction** (due to fibrous overgrowth during healing), **intravascular hemolysis** (from high shear forces)	Both mechanical and bioprostheses

XI. CARDIOMYOPATHIES

- Cardiac dysfunction; can be **primary** (often genetic but can be acquired) or **secondary** (due to other cardiac pathologies that eventually result in cardiac failure e.g. ischaemic heart disease, valvular heart disease, hypertensive heart disease, congenital heart disease). The term "cardiomyopathy" is now generally used to refer to the former group
- Primary or secondary cardiomyopathy can also refer to the **pattern of involvement**: primary cardiomyopathies involve predominantly the heart, while secondary cardiomyopathies have myocardial involvement as a component of a systemic disorder e.g. haemochromatosis
- Cardiomyopathy can also be classified according to their **morphologic patterns**:

Morphologic pattern	Causes	Features
Dilated *Most common ~90%*	• Genetic (mostly cytoskeleton proteins gene mutations) • Alcohol / toxins, peripartum, myocarditis, haemochromatosis, supraphysiologic stress • Idiopathic	• Impaired contractility (systolic dysfunction: EF<40%), with cardiac dilation and often concomitant hypertrophy • **Clinical presentation**: slowly progressive signs and symptoms of congestive heart failure • **Morphology**: Enlarged heavy flabby heart with four chamber dilation +/- mural thrombi; histology is non-specific (interstitial and endocardial fibrosis)
Arrhythmogenic right ventricular cardiomyopathy	• Genetic (autosomal dominant)	• R-sided heart failure and rhythm disturbances that can cause sudden cardiac death • **Morphology**: thinned R ventricular wall with massive fatty infiltration and focal fibrosis
Hypertrophic	• Genetic (autosomal dominant with variable penetrance; due to mutations in any one of several genes encoding sarcomeric proteins)	• Impaired compliance (diastolic dysfunction: EF>40%) due to myocardial hypertrophy also reducing chamber size; 1/3 of cases also have intermittent ventricular outflow obstruction • **Clinical presentation**: Exertional dyspnoea; arrhythmias and sudden cardiac death

		• **Morphology**: Heavy thick-walled hypercontracting heart, usually with asymmetric septal hypertrophy, without ventricular dilation. Histology: myofiber disarray of massively hypertrophic myocytes
Restrictive *Least common*	• Amyloidosis, sarcoidosis • Idiopathic	• Impaired compliance (diastolic dysfunction: EF>40%) • Cardiac amyloidosis can be part of systemic amyloidosis or restricted to the heart (senile cardiac amyloidosis) • **Morphology**: Commonly bi-atrial dilation due to restricted ventricular filling and pressure overloads; ventricles usually normal size and thickness. Histology may reveal a specific cause e.g. amyloid

XII. CONGENITAL HEART DISEASE

- Abnormalities of the heart or great vessels present at birth that are caused by errors that occur during cardiac morphogenesis (mostly during gestational weeks 3-8). Overall incidence ~1%
- Severe defects are incompatible with life and are common among stillbirths; defects more limited in extent can be compatible with live birth and produce clinical impact usually only after birth during the transition from foetal to perinatal circulation (although some may manifest only years later)
    - Septal defects ('holes in heart'): atrial or ventricular
    - Stenotic lesions: at the valves or entire cardiac chamber (e.g. hypoplastic left heart)
    - Outflow tract abnormalities: involving the great vessels, or anomalous coronary arteries
- **Pathogenesis**: Precise cause is unknown in ~90% of cases; likely due to interactions of environmental factors with multiple genes
    - **Genetic factors**: chromosomal abnormalities (e.g. trisomies 13, 15, 18, 21, monosomy X/Turner syndrome, del chr22q11.2/DiGeorge syndrome); single gene mutations
    - **Environmental exposure**: Infections (congenital rubella), teratogens, gestational diabetes
    - **Nutritional factors**: folate supplementation during early pregnancy reduces risk
- Most structural abnormalities in congenital heart disease can be organised into the major functional abnormalities that they cause: **Left-to-right shunt**, **Right-to-left shunt**, **Obstruction**; these present clinically as **acyanotic** vs **cyanotic** disease. Shunts are abnormal connections that allow blood flow down pressure gradients. The altered haemodynamics usually cause cardiac dilation or hypertrophy but may also cause hypoplasia (decrease in volume or mass before birth) or atrophy (after birth)

Left-to-right shunt: Most common congenital heart disease

- Functional disturbances (from asymptomatic to heart failure) depend on their size and location
- Causes **increased pulmonary blood flow** not initially associated with cyanosis (left side has oxygenated blood); however, chronic elevation of volume and pressure in the normally low pressure and low resistance pulmonary circulation eventually results in pulmonary arterial changes to increase vascular resistance, right ventricular hypertrophy and eventually, **shunt reversal** (right-to-left) as pulmonary vascular resistance approaches systemic levels (Eisenmenger syndrome)

- Early shunt repair is important as once irreversible pulmonary hypertension occurs, combined heart-lung transplantation will usually be necessary for survival

Type	Features

Atrial septal defects (ASD)	• Abnormal fixed opening in atrial septum caused by incomplete tissue formation
	  ○ Secundum ASDs (90%): can be multiple; not usually a/w other anomalies
	  ○ Primum ASDs (5%): often a/w AV valve abnormalities or VSD
	  ○ Sinus venosus defects (5%): can be a/w anomalous pulmonary venous return to the right atrium
	• Less likely to close spontaneously vs VSD → more frequently diagnosed in adults
	• Increases right ventricular and pulmonary outflow volumes but are generally well-tolerated → Usually asymptomatic until adulthood

Ventricular septal defects (VSD)
Most common CHD
	• Incomplete closure of ventricular septum
	  ○ Membranous VSD (90%)
	  ○ Infundibular VSD or within muscular septum (10%)
	• If clinically evident in children, usually a/w other anomalies (e.g. TOF); if first detected in adults, usually isolated defect
	• Increases both pulmonary blood flow and pressure → functional consequences depends on size of defect and any associated right-sided malformations

Patent ductus arteriosus (PDA)	• Delayed closure of the ductus arteriosus (a structure that allows blood flow from pulmonary artery directly to aorta in intrauterine life that is usually closed soon after birth and eventually forms the ligamentum arteriosum) • 90% are isolated defects; some are a/w other defects e.g. VSDs that increase pulmonary vascular pressures thus delaying closure of the PDA • Increases both pulmonary blood flow and pressure → functional consequences depend on its diameter and cardiovascular status of the individual. Isolated defects should be closed as early as possible, while preservation of ductal patency may be important if there are other anomalies obstructing pulmonary or systemic outflow

Right-to-left shunt

- Bypass of pulmonary circulation results in hypoxemia and **cyanosis** as poorly oxygenated venous blood directly enters the systemic arterial supply
- **Complication**: Emboli from peripheral veins can bypass the lungs and directly enter the systemic circulation (paradoxical embolism)

Type	Features
Patent foramen ovale (PFO)	• Postnatal failure to close a foramen that is part of normal development (~20% of people) → the unsealed flap of septum secundum is like a one-way valve that can open if right-sided pressure becomes transiently or permanently elevated
Tetralogy of Fallot (TOF)	• 4 cardinal features (tetralogy): three result embryologically from anterosuperior displacement of the infundibular septum (**VSD, right ventricular outflow tract obstruction (subpulmonic +/- pulmonary valve stenosis), aorta that overrides the VSD and both ventricular chambers**); the 4th (**right ventricular hypertrophy**) is subsequent to the pressure overload (causing a "boot-shaped" heart) • Some cases may have other accompanying anomalies e.g. right aortic arch • Functional consequences depend on the severity of the subpulmonic stenosis → if mild, resembles isolated VSD (L-R shunt with no cyanosis - pink teratology); if severe, causes R-L shunting with cyanosis (classic TOF) which worsens as the child ages and heart increases in size without expansion of the pulmonic orifice

	• The subpulmonic stenosis protects the pulmonary vasculature from pressure overload; right ventricular failure is also rare → complete surgical repair possible
Transposition of great arteries (TGA)	• Causes ventriculoarterial discordance (ventricle outflow goes to wrong vessel) e.g. aorta arises from RV and pulmonary artery from LV, as a result of abnormal formation of the spiraling truncal and aortopulmonary septae (dextro-TGA: no atrioventricular discordance vs levo-TGA aka "congenitally corrected") • Dextro-TGA results in separation of the systemic and pulmonary circulations → incompatible with postnatal life unless a shunt exists for adequate mixing of blood e.g. VSD • Even with a shunt, RV hypertrophy develops as it supports the systemic circulation and the LV becomes atrophic; most die within months without surgical intervention (e.g. arterial switch operation)
Tricuspid atresia	• Complete occlusion of tricuspid valve orifice due to unequal division of the AV canal during embryogenesis, usually a/w RV hypoplasia • Circulation is maintained through R-L shunting via a ASD/PFO and L-R shunting via a VSD into the pulmonary artery arising from the hypoplastic RV • Patients cyanotic with high mortality

Obstruction

- Abnormal narrowing of chambers, valves or blood vessels; **atresia** = complete obstruction

Type	Features

Coarctation of aorta	• Narrowing / constriction of aorta; 50% a/w other anomalies
	  ○ "Infantile" preductal form: Tubular hypoplasia of aortic arch proximal to the ductus arteriosus, which is often patent and supplies blood (unoxygenated) to the distal aorta → results in RV hypertrophy
	  ○ "Adult" postductal form: Ridgelike infolding of aorta opposite the ligamentum arteriosum, distal to the arch vessels → dilation of aortic arch and LV hypertrophy due to this narrowing; often also has dilated collateral channels to perfuse the peripheries
	• M:F = 2:1; also females with Turner syndrome
	• Functional manifestations depend on severity of narrowing and patency of ductus arteriosus: if no PDA and not severe narrowing, can be asymptomatic till adulthood, typically with upper limb hypertension and weak pulses in the lower

Aortic valvular stenosis	• Obstruction can be valvular, subvalvular or supravalvular • Congenital aortic valve stenosis is isolated in 80% of cases; can be part of hypoplastic left heart syndrome
Pulmonary stenosis	• Relatively frequent; obstruction at pulmonary valve • Can be isolated or a/w other anomalies (e.g. TOF, TGA) • Typically causes RV hypertrophy unless there is pulmonary valve atresia

XIII. PERICARDIAL DISEASE

Pleural effusion and haemopericardium

- Normally, pericardial sac contains <50 ml of thin clear straw-coloured fluid
- Pericardial effusion = increased serous fluid; haemopericardium = blood; purulent pericarditis = pus

- If fluid accumulation is rapid without time for the pericardium to accommodate the increase e.g. haemopericardium from ruptured AMI, cardiac tamponade results (restricted cardiac filling)

Pericarditis

- **Causes**: Infectious (viruses, bacteria, fungi, parasites); immunologically mediated (e.g. rheumatic fever, post-myocardial infarction (Dressler syndrome), drug hypersensitivity); miscellaneous (e.g. uraemia, tumours, radiation)
- **Acute pericarditis**:
    - **Serous pericarditis**: Usually by non-infectious inflammatory diseases e.g. rheumatic fever, tumours, uraemia
    - **Fibrinous / serofibrinous pericarditis**: Most frequent. Usually due to AMI, post-myocardial infarction (Dressler syndrome), uraemia, rheumatic fever, trauma / surgery
    - **Purulent / suppurative pericarditis**: Active infection caused by microbial invasion of the pericardial space from direct extension of neighbouring infections e.g. lobar pneumonia; haematogenous spread; lymphatic spread; or direct introduction during cardiotomy. Grossly, reddened granular serosal surfaces are coated with exudate; usually does not resolve completely but heals by scarring, with subsequent constrictive pericarditis
    - **Haemorrhagic pericarditis**: Usually due to malignant tumour spread; also infections and post-surgery
- **Chronic / healed pericarditis:** organisation of pericardial inflammation can produce small fibrous plaques or thin delicate adhesions that usually do not affect cardiac function
    - **Adhesive mediastinopericarditis**: usually post-surgery, infections or radiation. Results in obliteration of pericardial sac and adherence of parietal layer to surrounding tissues, affecting systolic contraction and increased cardiac workload
    - **Constrictive pericarditis**: may or may not follow previous pericarditis. Results in dense fibrous or fibrocalcific pericardial sac that limits diastolic filling and cardiac output (mimics restrictive cardiomyopathy), as well as limits cardiac hypertrophy and dilation