

Atherosclerosis: progressive disease of intima affecting large & medium-sized elastic & muscular arteries, characterized by focal lipid-rich intimal lesions called atheromas/atheromatous or atherosclerotic plaques.

Risk Factors:

<u>Modifiable</u>	<u>Non-modifiable</u>	<u>Additional</u>	
● Hyperlipidemia ● Hypertension ● Cigarette smoking ● Diabetes mellitus CH²D	● Genetic abnormalities ● Family history ● Increasing age ● Male gender F-GIM	● Inflammation ● CRP level ● Hyperhomocystinemia ● Metabolic syndrome ● Lipoprotein (A)	● Raised procoagulant levels ● Inadequate physical activity ● Stressful lifestyle ● Obesity ● Alcohol MARCH SOL²L

→ HDL = good cholesterol ; LDL = bad cholesterol

Pathogenesis: proposed theories:

- Insudation hypothesis: focal accumulation of lipid in a vessel wall due to insudation (transport) of plasma lipoproteins across an intact endothelium
- Encrustation hypothesis: small mural thrombi formed at the site of endothelial damage
- Monoclonal hypothesis: single clone (monoclonal) of smooth muscle migrate from the underlying tunica media into intima & then proliferate
- Response-to-injury hypothesis

Response-to-injury hypothesis: atherosclerosis develops as a chronic response of arterial wall to endothelial injury ; Sequence of events :-

① Endothelial injury & dysfunction:

- Causes:-
- Hemodynamic disturbances: development of plaque in regions of disturbed blood flow
 - Risk factors: ● hyperlipidemia ● hypertension ● cigarette smoking ● diabetes
 - Others: homocysteine, infectious agents

- Effect:
- leukocyte adhesion to endothelium
 - increased vascular permeability
 - platelet adhesion & thrombosis
 - Movement of LDLs across endothelium into intima.

② Migration of Monocytes into the intima:

- leukocytes adhere at site of endothelial injury → initiates the atheroma formation
- chemokines allow penetration of endothelial layer by monocytes & lymphocytes
- Monocytes migrate into intima & are transformed into macrophages.

③ Lipid Accumulation in Intima: lipoproteins penetrate endothelium → LDLs accumulate in intima → LDL is oxidised by oxygen free radicals

④ Formation of foam cells & activation of macrophages: macrophages engulf lipoproteins & oxidized LDL to form foam cells → some foam cells undergo apoptosis → release lipids form lipid-rich centre (necrotic core)

- oxidised LDL is cytotoxic to endothelial & smooth muscle cells
- Activated macrophages produce:

- cytokines ⇒ increase leukocyte adhesion
- chemokines ⇒ accumulation of monocytes
- ROS ⇒ ↑ oxidation of LDL
- Growth factors ⇒ stimulate smooth muscle cell proliferation & ECM synthesis.

⑤ Migration of smooth muscle cells into intima: due to growth factors

⑥ Smooth muscle cell proliferation in intima & ECM synthesis: growth factors — PDGF, FGF, TGF α

- smooth muscle cells also engulf oxidized LDL to form foam cells.

⑦ Lipid Accumulation: occurs intracellularly & extracellularly.

Fatty streaks: earliest precursor lesions of atherosclerosis

- found in younger children (> 10 years) & adults.

Gross: multiple, small flat yellow lesions in intima ⇒ may coalesce to form long streaks (~1 cm)

- mildly elevated above intima without affecting blood flow.

Microscopy: presence of lipid-filled foamy macrophages in intima.

Atherosclerotic lesions:

Gross: major vessels involved in atherosclerosis in descending order are:

- Lower abdominal aorta
- Coronary arteries
- Popliteal arteries
- Internal carotid arteries
- Vessels of circle of Willis

→ Colour: white - yellow (reddish-brown if superimposed by a thrombus)

→ Irregular shape with well-defined borders

→ soft yellow core of lipid covered by a white fibrous cap

Microscopy: • Cells: smooth muscle cells, macrophages, T-cells

• ECM: collagen, elastic fibres, proteoglycans

• Lipids: extracellular & intracellular

→ 3 regions: • Superficial fibrous cap: smooth muscle cells + collagen

• Necrotic core: cholesterol (seen as empty needle-shaped cleft-like spaces) + debris from dead cells + foam cells + fibrin $F^{2}DC$

• Shoulder: peripheral region which is more cellular & neovascularization may be seen.

Complications:

• Rupture, ulceration or erosion: plaque protrudes into lumen & disturbs blood flow → turbulent blood flow → damage of endothelium → rupture, ulceration or erosion

• Thrombosis & embolism $DA^{2}RTH$

• Haemorrhage into plaque

• Atheroembolism

• Dystrophic calcification

• Aneurysm formation

Clinical Manifestations:

• Atherosclerotic stenosis: reduction in size of lumen → ischaemia (called critical stenosis)

• Acute plaque change

• Vasospasm

• Thrombosis

$VA^{2}T$

(Achilles tendon xanthoma: pathognomic of familial hypercholesterolemia)

Clinical Consequences of atherosclerosis:

• MI

• Cerebral stroke

• Aortic aneurysms

• PVD (gangrene of legs)

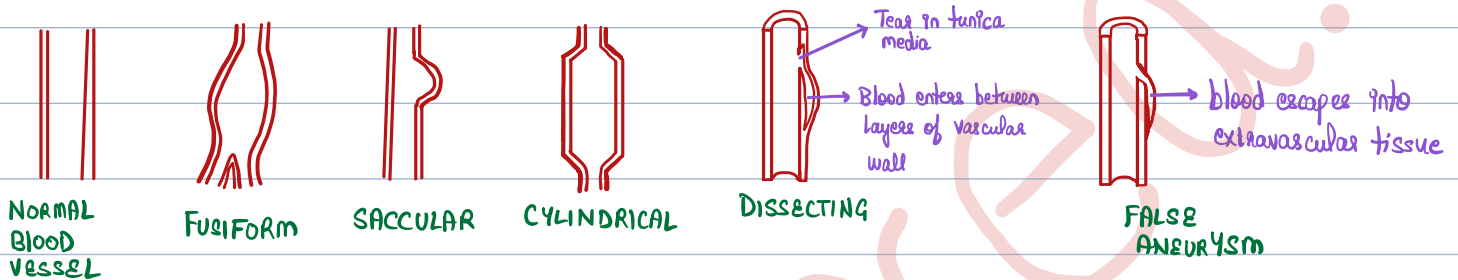
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Aneurysms: Congenital/acquired, localised, abnormal, permanent dilation of a blood vessel or the heart

Classification:

I Depending on gross appearance:

- ① Fusiform aneurysm ② Saccular aneurysm ③ Cylindrical aneurysm
- ④ Arterial dissection / dissecting hematoma: blood enters between the layers of arterial wall
- ⑤ Arteriovenous / racemose aneurysm: direct communication between artery & vein



II Depending on Composition of Wall of aneurysm:

- ① True aneurysm: composed of all three arterial layers (intima, media, externa)
- ② False / pseudo aneurysm: aka pulsating hematoma $\Rightarrow$ freely communicates with extravascular space due to defect in vascular wall
- ③ Arterial dissection: blood enters into arterial wall through intimal defect

III Depending on etiology (causes):

- ① Atherosclerotic aneurysm ③ Dissecting hematoma ⑤ Berry aneurysm
- ② Syphilitic aneurysm ④ Mycotic aneurysm

Pathogenesis: aneurysm develops due to weakening of vessel wall due to loss of balance between connective tissue synthesis & degradation

I Inadequate / Abnormal Synthesis of Connective tissues of Vascular wall: due to TGF- β mutations

$\rightarrow$ TGF- β regulates smooth muscle cell proliferation & synthesis of connective tissue

- Marfan syndrome (defective fibrillin)
- vit. C deficiency
- Ehlers-Danlos syndrome

② Increased degradation of Connective Tissue: due to increased synthesis of Matrix Metalloproteinases (MMPs) which degrade ECM

Predisposing factors:

① Atherosclerosis (aneurysm of abdominal aorta)

③ Trauma

⑤ Congenital defects

② Hypertension (aneurysm of ascending aorta)

④ Vasculitis

⑥ Tertiary syphilis

Vascular Tumors:

- Classification:
- Benign Neoplasms: • Capillary hemangioma • Cavernous hemangioma • Pyogenic granuloma
 - Intermediate-grade Neoplasms: • Kaposi sarcoma • Hemangioendothelioma
 - Malignant neoplasms: • Angiosarcoma • Hemangioepithelioma

Hemangioma: common benign tumor of blood vessels

→ mostly present from birth & increase in size as the child grows

Capillary Hemangioma: skin, subcutaneous tissue, mucous membranes of oral cavity & lips.

Gross: colour ⇒ bright red to blue

→ in level with surface of skin or slightly raised (skin overlying it is usually intact)

Microscopy: • unencapsulated lesion • composed of aggregates of closely-packed, thin-walled vascular channels

→ vascular channels resemble normal capillaries

Cavernous Hemangioma: large, dilated vascular channels

Gross: red-blue, soft spongy masses

→ more frequently involves deep structures like liver, spleen, pancreas.

Microscopy: sharply defined unencapsulated mass

→ large cavernous blood-filled vascular spaces

Heart Failure: (aka CHF)

→ pathophysiologic condition in which heart is unable to eject blood delivered to it by venous system ⇒ causes inadequate perfusion of tissues or increased diastolic filling pressure of left ventricle or both.

Causes: • CHD • HTN • Dilated cardiomyopathy • Congenit heart defects
• Valvular disorders • Anemia • Hyperthyroidism

Types of HF:

I Based on Onset:

• Chronic Heart Failure: gradual development of heart failure

→ systemic arterial pressure: normal → edema

Ex: • Valvular heart disease • Hypertension • Ischemic heart disease Dilated cardiomyopathy

Acute HF: sudden development of HF

Ex: • acute MI • Rupture of a cardiac valve

II Based on Ejection Fraction: (normal ejection fraction = 60 - 80%)

① HF with reduced ejection fraction (HFrEF): [Systolic dysfunction]

→ ejection fraction < 40% due to inadequate myocardial contractile function

→ increased size of left ventricle

② HF with preserved ejection fraction (HFpEF): [Diastolic dysfunction]

→ inability of heart to adequately relax & fill

→ ejection fraction > 50%

→ decreased left ventricular size

[5:38]

Myocardial Infarction (MI): coagulative type of necrosis of cardiac muscle due to prolonged severe ischemia

Risk factors: • whites are affected more than blacks

• Peak age: 40-65 years

• Males > females $\Rightarrow$ during reproductive period; risk is same in men & post-menopausal women

Etiology: ischemic heart disease is caused by imbalance between demand & supply of oxygenated blood to myocardium.

① Decreased/Impaired Coronary Blood Flow: due to Coronary Artery Occlusion caused by:-

① Coronary Atherosclerosis: narrowing of one or more epicardial coronary arteries (IHD/CAD)

$\rightarrow$ Risk of IHD depends on - extent & severity of pre-existing (fixed) atherosclerotic occlusion
- sudden morphological changes in atheromatous plaque

a) Extent & severity of pre-existing (fixed) atherosclerotic occlusion:

* Number of coronary arteries involved: 1/2/all 3

* Structure of plaque:

$\rightarrow$ Stable plaque: Dense collagenous & thick fibrous cap, minimal inflammation, negligible atheromatous core $\Rightarrow$ less likely to rupture

$\rightarrow$ Unstable plaque: core with many foam cells & abundant extracellular lipid, thin fibrous cap, increased inflammation $\Rightarrow$ likely to rupture.

* Degree of stenosis by atheromatous plaque:

$\rightarrow$ < 70%: asymptomatic

$\rightarrow$ $\geq 75\%$: critical stenosis $\rightarrow$ ischemia precipitated by exercise $\rightarrow$ stable angina

$\rightarrow$ $\geq 90\%$: inadequate coronary blood flow even at rest $\rightarrow$ unstable angina

* Rate of development of occlusion:

$\rightarrow$ Slow progressive occlusion: allows time for development of collateral circulation

$\rightarrow$ Acute blockage: no time for collateral flow $\rightarrow$ infarction

* Factors which influence consequences of coronary atherosclerosis:

- extent of inflammation in atherosclerosis
- thrombus development on disrupted plaque
- Coronary vasoconstriction

b) Sudden morphological changes in atheromatous plaque: aka Acute Plaque Change

→ thrombosis → unstable angina → MI → Sudden cardiac death ⇒ Acute Coronary Syndrome

② Nonatheromatous Causes:

- * Coronary Vasospasm without atherosclerosis
- * Coronary emboli
- * Diminished availability of blood/oxygen
- * Ischemia due to vasculitis/sickle cell disease/amyloid deposition/vascular dissection

② Increased Myocardial Demand: • Myocardial hypertrophy • Tachycardia
• Increased physical activity • Emotional stress

Pathogenesis: sequence of events:

① Acute Plaque Change: sudden change in atheromatous plaque to produce sudden ischemia by:

- * Rupture, fissuring
- * Erosion/ulceration
- * Haemorrhage into central core of plaque

→ Factors triggering acute plaque change: — vulnerable plaque — Platelet reactivity — BP

② Formation of Microthrombi: acute plaque changes expose thrombogenic subendothelial collagen → platelets

adhere to the site → platelet activation & aggregation → formation of microthrombi → partial/complete occlusion of affected coronary artery

③ Vasospasm: inflammatory cells release mediators → vasospasm → further narrowing of lumen

④ Activation of coagulation pathway: → increases the size of thrombus

⑤ Complete occlusion of vessel

⑥ Myocardial necrosis: complete occlusion → ischemic coagulative necrosis of area supplied by particular coronary artery called area at risk

Consequences of Myocardial Ischemia:

I Reversible Injury:

① Biochemical changes: cessation of aerobic glycolysis → decreased production of ATP → accumulation of toxic metabolites (eg: lactic acid)

② Functional disturbances: loss of contractility within 60 seconds → can precipitate acute HF

③ Morphological changes: • mitochondrial swelling • glycogen depletion • myofibrillar relaxation MGM

II Irreversible Injury: develops only after prolonged myocardial ischemia > 20-40 min.

① Biochemical changes: leakage of cytoplasmic proteins into blood due to breakdown of sarcolemmal membrane (LDH, CK, myoglobin, Troponin I & T)

② Functional disturbances: Arrhythmias

③ Morphological changes: Coagulative necrosis is generally completed within 6 hours of onset of ischemia

Dominant vessel: Posterior descending artery ⇒ posterior 1/3 of interventricular septum & inferior/posterior left ventricle.



Collaterals in Heart: the intercoronary anastomoses (collateral circulation) normally remains closed
→ narrowing one artery allows blood to flow from high- to low pressure areas through collateral channels.

Classification of MI:

I Depending on thickness of myocardium involved:

① Transmural infarct: ischemic necrosis of entire thickness of ventricular wall

→ usually associated with chronic coronary atherosclerosis, acute plaque change, superimposed thrombosis.

② Subendocardial (Nontransmural) infarct: ischemic necrosis of inner 1/3 - 1/2 of ventricular wall

③ Multifocal infarcts: develops with occlusion of small vessels.

II Depending on the age of infarct: recent (fresh) or old (healed)

III Depending on the anatomic region involved: anterior, posterior, lateral, septal or combinations

IV Depending on ECG changes:

① STEMI: transmural infarct

② NSTEMI: subendocardial infarct

③ Microinfarctions: electrocardiographically silent

	Transmural Infarcts	Subendocardial infarcts
Nature of lesion	Unifocal & solid	Multifocal & patchy
Distribution	Specific coronary artery	Circumferential
Thrombus in coronary artery	Common	Rare
Shock	Causes shock	Results from hypotension or shock
Pericarditis	Common	Absent
Cardiac aneurysm	May develop	Does not develop
ECG changes	STEMI	NSTEMI

Morphology:

Duration	Gross Changes	Light Microscopic Changes
<u>Reversible injury:</u> 0 - 1/2 hours	None	<u>Electron microscopy:</u> relaxation of myofibrils, loss of glycogen, swelling of mitochondria
<u>Irreversible injury:</u> 1/2 - 6 hours	None	Waviness of fibers at border <u>Electron microscopy:</u> mitochondrial amorphous densities
6 - 12 hours	Dark mottling	Early coagulative necrosis

12-24 hours	Dark mottling	Coagulative necrosis, pyknotic nuclei, increased eosinophilia of cytoplasm, contraction band necrosis at margins, beginning of neutrophilic infiltrate
1-3 days	Mottling with yellow-tan center	Coagulative necrosis, loss of nuclei & striations, increased interstitial infiltration of neutrophils
3-7 days	Hyperemic border; central yellow-tan	Disintegration of dead myocardial cells, phagocytosis of dead cells by macrophages at border of infarct
7-10 days	Maximally yellow-tan & soft	Phagocytosis of dead cells, formation of granulation tissue at margins
10-14 days	Red-gray depressed infarct borders	Well-established granulation tissue & collagen deposition
2-8 weeks	Gray-white scar, progressive from border toward the center of infarct	Increased collagen deposition & decreased cellularity
> 2 months	Scarring complete	Dense collagenous scar tissue

Histochemical Stain: Triphenyl tetrazolium chloride (TTC)

- Noninfarcted myocardium: appears brick-red (lactate dehydrogenase activity is preserved)
- Infarcted area: unstained pale (loss of LDH)
- Old infarcts: white & glistening.

Reperfusion: done to rescue ischemic myocardium

- done by dissolving thrombus using thrombolytic drugs or angioplasty / stent placement or CABG
- benefits of reperfusion depend on rapidity of restoration
- reperfusion within 20 min of onset of ischemia may completely prevent necrosis

Gross: reperfused infarct is hemorrhagic $\because$ restoration of blood flow causes leakage of blood from the injured microvasculature

Microscopy:

- Acceleration of acute inflammatory response: rapid appearance & disappearance of neutrophils
- Contraction band necrosis: thick, irregular, transverse, intensely eosinophilic intracellular bands in necrotic myocardial cells

Complications of Reperfusion: Reperfusion injury: caused by ROS, calcium overload & severe inflammatory reaction

Diagnosis of MI: • severe retrosternal chest pain that can radiate to neck, jaw, epigastrium or left arm • Profuse sweating (diaphoresis) • Dyspnea

- Rapid, weak pulse
- About 10-15% cases are asymptomatic $\Rightarrow$ silent MIs.

ECG changes: • T-wave inversion, deep T wave • ST elevation • Q wave elevation

Laboratory findings:

Cardiac Enzyme	Onset	Peak	Total duration	Normal level
most sensitive { Troponin I (TnI) Troponin T (TnT)	2-4 hours	48 hours	7-10 days	$< 0.04 \text{ ng/mL}$
	"	"	"	$< 0.04 \text{ ng/mL}$
CK-MB	2-4 hours	24 hours	72 hours	5-25 IU/L
LDH	24-48 hours	-	7-14 days	110-350 IU/L
Myoglobin	1-3 hours	8-12 hours	24-36 hours	0-85 ng/mL

$\rightarrow$ earliest marker

Stress Testing: exercise tolerance test (ETT) or dobutamine stress test

Coronary Arteriography: done with a view to perform CABG or PCI

Newer modalities: • Computed tomographic Coronary angiography (CTCA)

- Magnetic resonance coronary angiography (MRCA)
- Positron emission tomography

Complications of MI:

- ① Left ventricular failure & cardiogenic shock
- ② Arrhythmias
- ③ Myocardial rupture:
 - rupture of ventricular free wall → hemopericardium & cardiac tamponade
 - rupture of ventricular septum → acute VSD & left-to-right shunt
 - rupture of papillary muscle → acute severe mitral regurgitation
- ④ Dilatation of ventricular chambers
- ⑤ Ventricular aneurysm
- ⑥ Mural thrombus
- ⑦ Pericarditis
- ⑧ Extension of infarct
- ⑨ Infarction of RV
- ⑩ Progressive late HF (chronic IHD)

Sudden Cardiac Death: (SCD) ⇒ unexpected death from cardiac causes in individuals without symptomatic heart disease or within 1 hr of onset of symptoms.

Infective Endocarditis (IE): infection (usually bacterial) of endocardium of heart valves or mural endocardium $\Rightarrow$ results in formation of vegetations contain microbial colonies

Sites of Microbial Colonization:

- Heart valves
- Mural endocardium
- Congenital defect
- Prosthetic devices
- Aorta
- aneurysmal sacs

Lesions: Vegetations: composed fibrin, platelets, scanty inflammatory cells, microbial colonies

Classification:

	Acute IE	Subacute IE
Onset	Rapid evolution	Slow evolution
Condition of valve	Involves normal cardiac valve	Involves previously damaged (scarred/deformed) valves
Virulence	Implicated organism is of high virulence (Eg: S. aureus)	Implicated organism is of low virulence (Eg: viridans Streptococci)
Lesions	More valve destruction	Less destruction
Course	Causes substantial morbidity & mortality	Most patients recover after antibiotic therapy
Frequency	Less common (10-20%)	More common (50-60%)

Causative Organisms:

Staphylococcus aureus: IE in IV drug abusers

Streptococcus viridans: IE in previously damaged or abnormal valves

Coagulase-negative Staphylococci (Eg: *S. epidermidis*): prosthetic valve IE

HACEK group

Enterococci

Culture-negative endocarditis: 10-15% of cases.

Predisposing factors: ① Conditions with bacteraemia

② Underlying heart disease: • Congenital heart disease • Mitral valve prolapse • Bicuspid aortic valve
• Chronic rheumatic heart disease • Degenerative calcific valvular diseases
• Prosthetic valves • Indwelling vascular catheters

③ Impaired host defense mechanism: • Diabetes mellitus • Malignancies • Cytotoxic therapy • Neutropenia

Pathogenesis:

① Endocardial damage & denudation: micro-abrasions → turbulent blood flow → endocardial damage & denudation

② Formation of sterile thrombus: damaged endothelium → focal deposition of platelets & fibrin → platelet aggregation → formation of sterile thrombotic vegetations (NBTE)

③ Proliferation of microorganisms within vegetations: microbes are deposited on NBTE → further deposition of platelets & fibrin → microorganisms proliferate within vegetations → vegetations enlarge

④ Formation of emboli: vegetations may get detached to form infective emboli → metastasis to distant sites

Gross: - aortic & mitral valve (most commonly affected)

- tricuspid valve is involved in IV drug abusers

Vegetations: friable, bulky, potentially destructive

→ single or multiple; vary in size

→ Common sites: • atrial side of atrioventricular valves
• ventricular side of semilunar valves
• point of closure of leaflets or cusps

Valvular changes: edema & inflammation; leaflet may perforate causing regurgitation

Microscopy:

→ Vegetations: composed of platelets, fibrin, cell debris, inflammatory cells, masses of bacteria

• vegetations of subacute IE show granulation tissue at their bases

Complications of IE:

Cardiac complications:

- Ring abscess
- Perforation & rupture
- Myocardial abscess
- Suppurative pericarditis
- Valvular dysfunction

M RSV

Extracardiac Complications:

① Embolic complications (due to septic emboli):

- Septic emboli from left side of heart → enter systemic circulation → septic infarcts, mycotic aneurysms, splinter/subungual hemorrhages, Janeway lesions
- Septic emboli from right side of heart → enter pulmonary circulation → pulmonary abscess

② Immunological phenomena:

- Focal segmental glomerulonephritis
- Osler nodes
- Roth spots

Clinical features:

- fever, chills, weakness, lassitude
- murmur may be heard

Diagnostic criteria: Modified Duke Criteria

→ Definitive IE: 2 major or 1 major + 3 minor or 5 minor

→ Possible IE: 1 major + 1 minor or 3 minor.

Major Criteria:

① Positive Blood Culture:

- typical IE organism isolated from 2 separate blood cultures

- persistently positive blood culture for atypical IE organisms in at least 2 positive blood samples drawn ≥ 12 hours apart

- single positive blood culture for *Coxiella burnetii* or phase I IgG titer $> 1:800$.

② Evidence of endocardial involvement:

- positive ECG: • vegetation • abscess • new partial dehiscence of prosthetic valve
- new valvular regurgitation

Minor Criteria:

- ① Fever: $\geq 38^{\circ}\text{C}$ (100.4°F)
- ② Predisposing factors

③ Vascular phenomena: arterial petechiae, septic pulmonary infarcts, intracranial hemorrhage, Janeway lesion

④ Immunological phenomena: Focal segmental glomerulonephritis, Osler nodes, Roth spots

⑤ Microbiologic phenomena: positive blood culture but not meeting major criteria

Rheumatic Fever & RHD: acute, post-streptococcal, immune-mediated, multisystem inflammatory disease

→ occurs a few weeks after group A streptococcal pharyngitis.

→ Age: 5-15 years

Major Phases:

① Acute rheumatic fever

② Chronic rheumatic heart disease

Morphology of Acute Rheumatic Fever:

① Cardiac lesions:

① Aschoff Body: spheroidal / fusiform lesion

→ found in perivascular interstitial region of heart (in any one of the 3 layers of heart)

→ Formation of Aschoff Bodies consists of 3 phases:

i) Early/exudative phase: perivascular focus of swollen eosinophilic collagen surrounded by lymphocytes, plasma cells & macrophages

ii) Intermediate/granulomatous phase: granulomatous lesion with central fibrinoid focus

→ Anitschkow cells: plump activated macrophages with abundant cytoplasm, round to oval nuclei with central, wavy ribbon of chromatin

- These nuclei resemble a caterpillar when cut longitudinally ∴ aka caterpillar cells.

- nuclei have owl-eye appearance on cross-section

→ few Anitschkow cells become multinucleated to form Aschoff giant cells

iii) Late/healed/final phase: Aschoff body is replaced by a nodule of scar tissue.

② Valvular Endocarditis: valve leaflets become inflamed & edematous

- left-sided (mitral & aortic) valves are more injured than right-sided valves (tricuspid, pulmonary)
- focal loss of endothelium & fibrin deposits along lines of closure of valve leaflets or along tendinous cords
- small warty vegetations called verrucae overlying the deposits

③ Mural Endocarditis: lesion $\Rightarrow$ Marcellum plaques:

- subendocardial lesions → irregular, wrinkled, map-like thickenings
- usually seen in posterior wall of left atrium, just above posterior leaflet of mitral valve
- they show multiple Aschoff bodies

④ Pericarditis: irregular deposits of fibrin on both visceral & parietal surfaces of pericardium

- resembles the surfaces of two slices of buttered bread $\therefore$ called bread-&-butter pericarditis

⑤ Myocarditis: myocardium shows lymphocytes & Aschoff bodies

⑥ Changes in Mitral Valve:

i) Thickening of valve leaflet: due to inflammation & fibrosis

ii) Fusion of commissures: fish-mouth or buttonhole appearance

iii) Shortening, thickening & fusion of chordae tendinae

iv) Consequences of mitral stenosis: — left ventricular dilatation favouring mural thrombi

— dislodging of thrombi to form emboli

— CVC in lungs

— pulmonary hypertension

II Extracardiac Lesions:

① Migratory polyarthritis: large, swollen, tender joints which migrates from one joint to another

② Subcutaneous nodules: painless nodules attached to tendons/ligaments

③ Erythema marginatum: non-itchy reddish rashes with bathing suit pattern of distribution

→ they appear & disappear before the examiner's eye.

④ Sydenham's chorea / Saint Vitus' dance: involuntary, jerky, purposeless, rapid movements

Pathogenesis: Latent period = 2-6 weeks

- Antibody-mediated Type II Hs Rx: Antibodies produced against streptococcal M-antigen cross-react with self-antigens in myocardial cell & glycoproteins of valves $\Rightarrow$ Molecular mimicry.
- T-cell mediated Type IV Hs Rx: streptococcal antigens activate CD4+ T-cells which cross-react with self-proteins in the heart $\rightarrow$ cytokine production $\rightarrow$ activation of macrophages

Complications:

- infective endocarditis
- Mural thrombi
- Thromboemboli
- Congestive Heart failure
- Adhesive pericarditis
- Arrhythmias

Diagnostic Criteria: Revised Jones Criteria:

Major Criteria

- i) Carditis
- ii) Migrating polyarthritides of large joints
- iii) Sydenham's chorea
- iv) Erythema marginatum
- v) Subcutaneous nodules

Minor Criteria

- i) Fever
- ii) Polyarthralgia
- iii) Elevated ESR / leukocyte count / acute-phase reactants
- iv) ECG: prolonged PR interval

$\rightarrow$ Diagnosis: 2 major or 1 major + 2 minor.

Ventricular Septal Defect (VSD): incomplete closure of ventricular septum

→ causes free blood flow from left-to-right ventricles.

Classification:

- Membranous VSD: involves membranous region of interventricular septum
- Infundibular VSD: within muscular part of interventricular septum

Clinical features: manifest from birth

→ cause left-to-right shunt → right ventricular hypertrophy & pulmonary hypertension → pressure in right ventricle reaches systemic level → reversal of shunt (right-to-left) → unoxygenated blood enters systemic circulation → cyanosis ⇒ late cyanotic congenital heart disease / Eisenmenger syndrome

Tetralogy of Fallot (TOF)

Main features:

- ① Ventricular Septal defect
- ② Subpulmonic stenosis / pulmonary valvular stenosis
- ③ Aorta overriding the VSD
- ④ Right ventricular hypertrophy

Morphology: Heart is enlarged & boot-shaped (due to marked right ventricular hypertrophy)

Clinical features: cyanosis

[CM] Cardiomyopathies: heart muscle disease

Dilated CM
DCM

Hypertrophic CM /
Hypertrophic Obstructive CM
HOCM

Restrictive CM
RCM

Dilated CM (DCM):

→ most common type of CM

Causes: - idiopathic

- alcohol ⇒ most common cause of DCM

- Cobalt

- Cardiotoxic drugs: Adriamycin, Doxorubicin

- Myocarditis

- Haemochromatosis → causes both DCM & Restrictive CM (mainly)

- Post Partum

Genetic causes: Mutation of sarcolemmal proteins

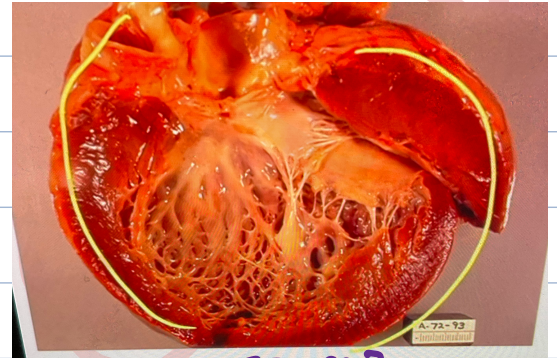
- Titin gene mutation.

[largest known protein in human body]

Grossly: → dilation of all 4 chambers of heart



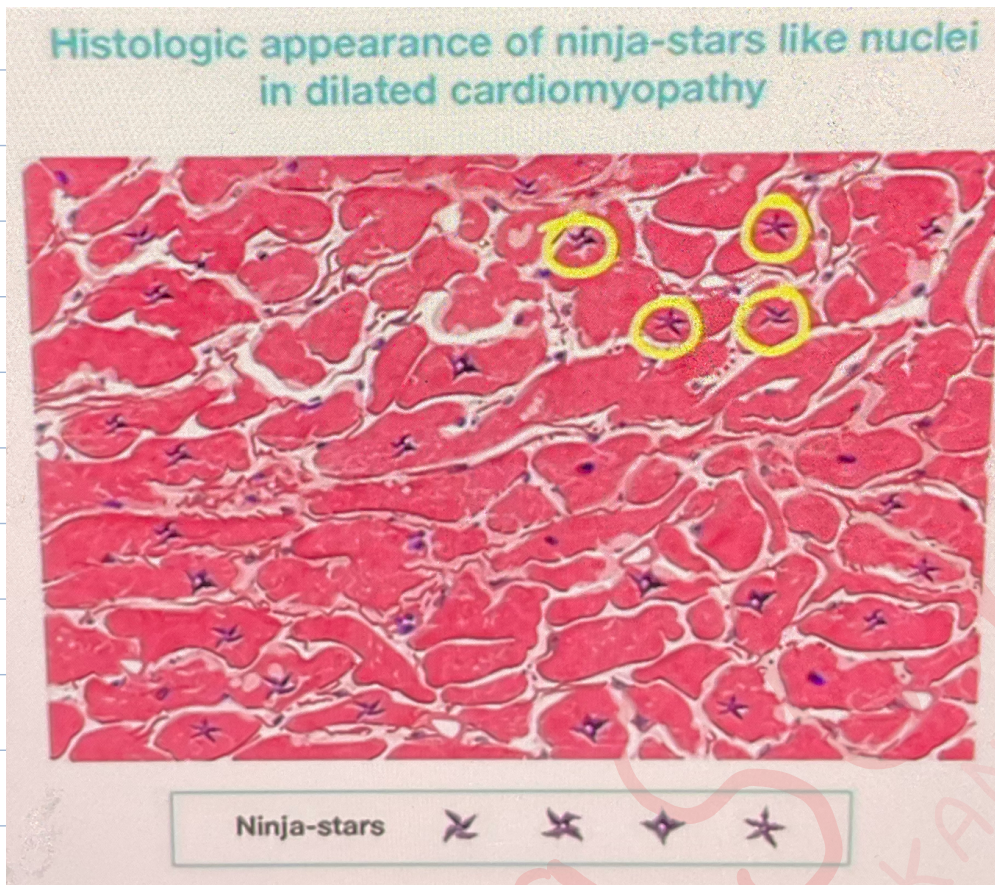
flabby hypocontracting heart



[DCM]

H & E: → Hypertrophied muscle fibres

→ if the Dcm is due to titin gene mutation: ninja star nuclei are seen.



→ Heart begins to look like Takutsubo (Japanese octopus trap)

TAKUTSUBO CARDIOMYOPATHY: type of Dcm.

→ a.k.a BROKEN HEART SYNDROME



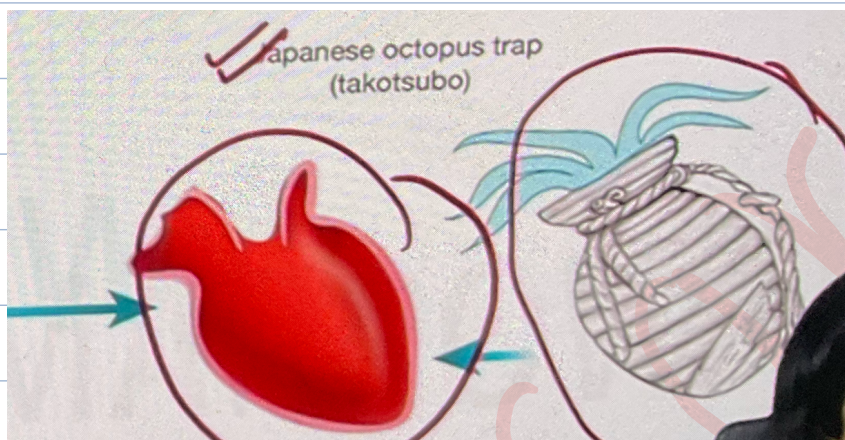
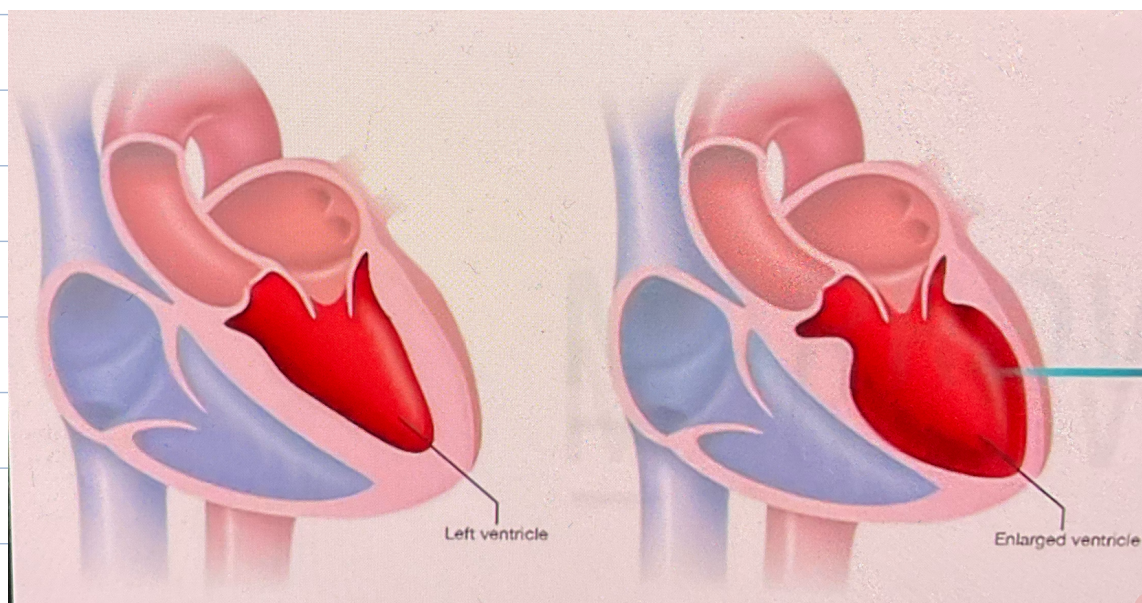
caused due to intense emotional stress



excessive release of catecholamines



Selective ballooning of the left ventricle



ARRYTHMOGENIC RIGHT VENTRICULAR CM:

- autosomal dominant disorder
- Selective right ventricular hypertrophy
- due to mutation of PLAKOGLOBIN or Desmosomes.

Naxos Syndrome: arrhythmogenic RV CM

- wooly hair
- hyperkeratosis of palms & soles
- Due to PLAKOGLOBIN mutation.

HOCM: most common cause of Sudden cardiac death in young athletes.

Causes: - mutation in Sarcoplasmic Proteins:

- myosin binding Protein C
- β -myosin heavy chain

Geose: Selective hypertrophy of interventricular septum
(asymmetric)

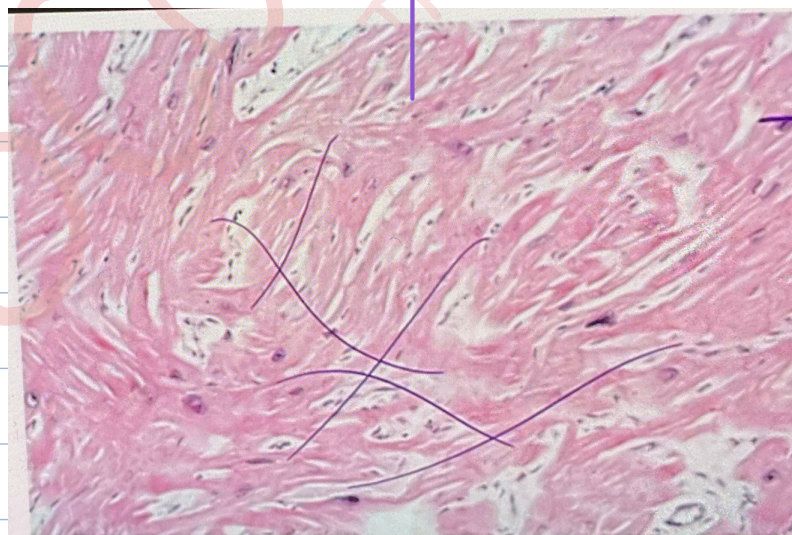
Banana split configuration

H & E: - Hypertrophied muscle fibres

- myofibre disarray

HELTHER SKELTER

ARRANGEMENT OF
MUSCLE FIBRES.



RCM:

- Causes:
- idiopathic
 - Sarcoidosis
 - Metastatic cancer
 - Amyloidosis $\Rightarrow$ most common cause of RCM
 $\rightarrow$ deposition of ATTR (transthyretin)
 - Radiation
 - Haemachromatosis
 - Loeffler's Endomyocarditis

Endocardial Fibroelastosis:

- $\rightarrow$ usually seen in children < 2 years of age
- $\rightarrow$ mostly caused by mumps infection.