PC
Pharmacology Concepts
By Rajesh Choudhary

CVS Disorders Pathophysiology

Pharmacology 2

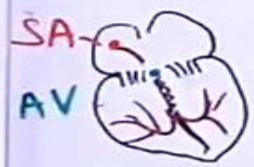
CVS : General Introduction

Cardio → Heart | Vascular - Blood Vessels

HEART - [Contractile muscles
Conductive cells - SA, AV, Fibres

1. **Rythmicity** :- 60-80 Beats/min (HR) 0.8 Sec/beat
Ventricle - Systol = 0.3 sec & Diastol = 0.5 Sec.
Atrium = Systol = 0.1 sec & Diastol = 0.7 Sec

2. **Automataciity** :- Intrinsic property of Card. muscle to generate Impulse by SA-node and Conduct through AV node to whole Heart.



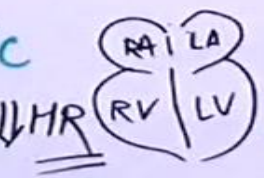
SA node → Atria → AV node → Bundle of His (AVB) (R&L) → Purkinje Fibre ← Muscle

3. **Excitability & contractility** = Respond to stimulys & contract

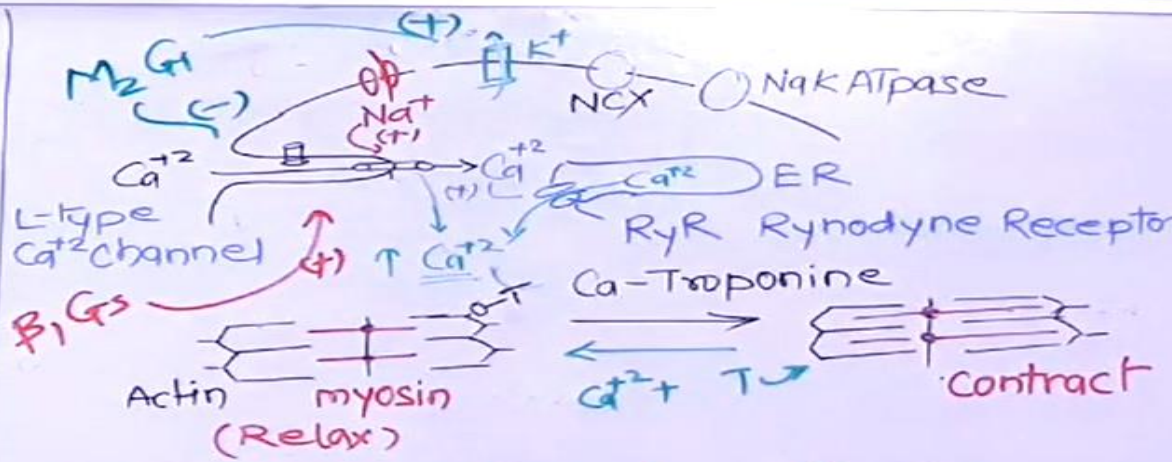
4. **Tonicity** = have some tone, not fully relaxed

NEUROGENIC CONTROL = "Autonomic Neurones"

Parasympathetic
Ach → M_2 (GiPCR)
↓HR

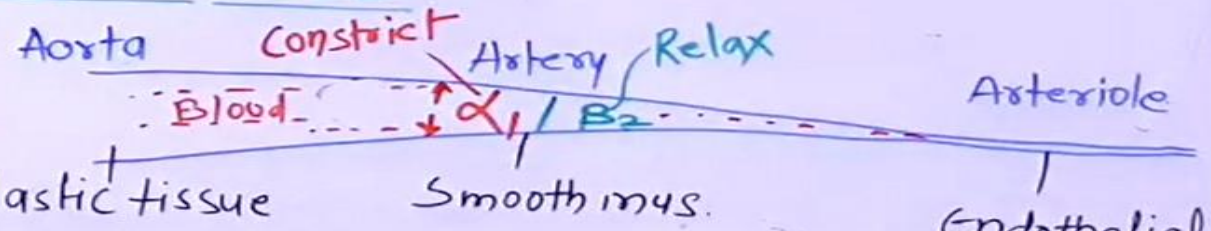


Sympathetic Neur.
N-Ad/Ad
↑HR ... B_1 (GsPCR)



DISORDERS = CHF, Arrythmia

BLOOD VESSELS :-



Sympathetic Neuron only → N-Ad/Ad → α_1 (GqPCR)
→ B_2 (GsPCR)..

Role = Transportation of O_2 / Neutrients / molecules through Blood to all body tissues

Disorder = Peripheral Artery disease
↳ Hypertension
- Coronary A.D. → Myocardial Infarction
Angina

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CARDIO-VASCULAR DISORDERS

HEART :→ MI, CHF, Arrhythmia, Valvular disease

Vessels → Hypertension, Atherosclerosis, Coronary artery disease

- → Genetic
- → Unhealthy Life Style
- → Kidney Problem
- → Neurogenic defect
- → Hyperlipidemia
- → Diabetes
- → Adrenal tumour
- → Hyper Thyroidism
- → Aging
- → Steroids
- → Races

→ (+) Sympathetic
→ (+) RAAS
→ (+) ROS
→ (+) Vascular Damage

(+) HR, (+) TPR
(Vasoconstriction)

BP = CO × TPR
CO = HR × SV

HYPERTENSION

↑ Aortic Pressure
↑ Required force on LV wall
↑ Cardia work load
Weakness
↓ SV
↓ CO

ATHEROSCLEROSIS
↑ Atheroma Deposition
↑ Vas. Endothelial Damage
- Inflammation
- Hyperlipids
- Diabetes
- HTN
- Genetic
- Unhealthy L.S.

Myocardial Ischemia
ANGINA / M. INFRACTION
Ischemia
- Coronary Artery Dis
- Hyperlipids
- Atheroma
- HTN
- Diabetes
- Unhealthy L.S.

Myocyte damage (Weakness)
↓ Contract° force
↓ SV
CHF
↓ CO

Ischemia
- Ischemic Heart Dis. (IHD) - Angina/MI
- Coronary artery Dis (CAD)
- Hypertension
- Cardiomyopathy
- Valvular disease

End Organ Damage
- → Kidney
- → Brain
- → Eye

+ RAAS
↑ HR
ARRHYTHMIA

Odema
Cardiovascular Complecation

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CHF: CONGESTIVE HEART FAILURE

Congestive :- Congestion of Fluid / Volume Overload

Heart failure :- Cardiac Dysfunction

HEART - FAILURE (HF)

$CO_{sup} < CO_{demand}$

* Function of Heart ⇒ Blood Circulation → CO
* In HF ⇒ Heart unable to maintain CO

$CO = SV \times HR = 70 \times 72 \approx 5\ L/min$

* HF = ↓CO = ↓SV (pump) × HR $< 3\ L/min$
  - ↳ Heart unable to pump enough amount of Blood
  - ↳ Due to either Systolic or Diastolic Failure

* **SYSTOLIC FAILURE** - Left Ventricles unable to produce adaquate wall pressure to overcome the *Afterload or Aortic Pressure
* **Afterload** :- load or pressure required on LV wall to eject blood from Heart

Proper Ejectn = Pressure Generated by LV wall > Aortic pressure

* Systolic failure occurs due to → ✓HTN, ↑HD, Cardiomyopathy

Ejection Fraction = Stroke Volume (SV) / End Diastol Volume (EDV)

$= \frac{70\ ml}{110\ ml} = 0.64$, o/oE = 64%

In SHF → ↓SV, $EF = \frac{44}{110} = 0.40$ ⟹ o/oE = 40% (50-70%)

* HF refers when o/o Ejection < 40%

* **Preload** = load/Pressure on LV wall after EDV/ED
  - Preload ↑ due to ↑↑ Venous Return and Venoconstrictn
  - In CHF → ↑Afterload & Preload both are Increased

DIASTOLIC FAILURE :- Reduction on filling or ↓EDV

DHF occurs due to chronic HTN, Cardiomyopath, Congenital Heart Disease, Ventricular Hyperthophy

DHF = ↓↓EDV → ↓SV → ↓CO
= ✓EF

$0.64 = \frac{SV}{70}$

$SV = 0.64 \times 70 \approx 45\ ml$

$CO = 45 \times 72 = 3.2\ L/min$

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PATHOPHYSIOLOGY OF CHF

PATHOGENESIS:- ↓ ATP Production

① HTN → ↑ Aortic Pressure (Afterload) → Harder to Pump (↑ Req. Pressure) → Hypertrophy → ↑ O_2/Engery Demand → weaker Contraction → ↓FC* → ↓SV → ↓CO → CHF

Systolic Failure

② IHD → ↓ O_2 Supply → Myocardial Damage → Cardiomyopathy → ↓LV Space → ↓EDV → ↓SV → ↓CO → CHF

Diastolic Failure

③ ↑ Venous Return → ↑ Filling → ↑ EDV → Dialated Cardiomyopathy → Weak contraction → ↓FC* → ↓SV → ↓CO → CHF

Systolic H.F.

PATHOPHYSIOLOGY

CHF (Weak Heart) ↓CO

(+) Sympathetic System (CO = SV x HR) → Nor-Ad/Ad → HR↑, ↑FC, α_1 Vasoconstriction → ↑Afterload → ↑↑CHF

(+) RAAS → ① Edema ② ↑Afterload ③ CVS Remodelling → ↑↑CHF

(+) Hypertrophy → ↓FC → ↑EDV → Dialated Cardiomyopathy → Hypertrophy

HR↑ → Tachycardia → O_2 demand → ↑Weakness → ↑↑CHF

① ↓CO/SV/FC
② Tachycardia
③ Edema
④ Shortness of breathing
⑤ weakness in exercise

HYPERTENSION (HTN)

HTN:- Consistant Elevation of BP/Arterial Pressure Above the normal (120/80 mmHg)

Class of HTN, According to BP:-

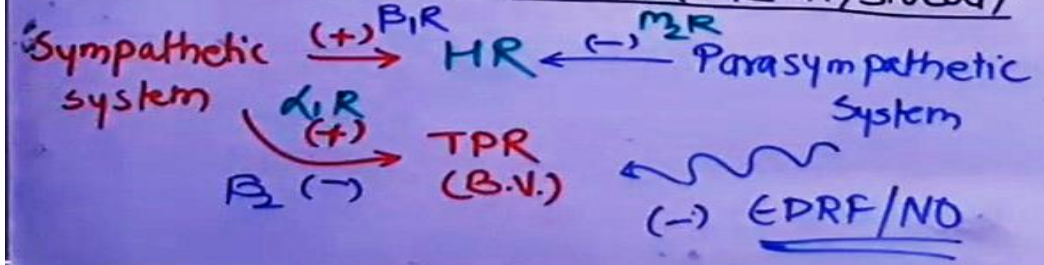
JNC - Joint National Committee

	SBP	DBP
1. Normal -	90-119	60-79
2. Pre HTN -	120-139	80-89
3. Stage I (Mild)	140-159	90-99
4. II, (Moderate)	160-179	100-109
5. III, (Sever)	>180	>109
6. Isolated Systolic HTN =	≥140	<90

$BP = CO \times TPR$ | $CO = HR \times SV$

$PP = SBP - DBP$ | $MAP = DBP \times \frac{1}{3} PP$

AUTONOMIC CONTROL IN NORMAL PHYSIOLOGY



HTN (DISEASE) = ↑↑ BP, ↑↑ TPR, ↑ HR

↑ ∈ ↑ TARGETS

CLASSIFICATION BASED ON OCCURANCE

I. P°/ESSENTIAL/IDIOPATHIC HTN =

↳ 90% Cases are P°HTN

↳ Etiology is unclear & unclear Pathophysiology

↳ Possible Pathophysiology → "Genetically"

- ↳ Volume Overload
- ↳ Salt/Water Retaintion ← Abnormal kidney Funct° & RAS
- ↳ Over Sympathetic Stimulation
- ↳ Abnormal Diet/Life Style

II. SECONDARY HTN: → Only 10% Cases.

* Due to - "Renal Artery Stenosis" → ⊕RAS → Hyper Aldosteronism & Pheochromocytoma

Treatment = Angioplasty, α_1 blocker, ACEIs/ARBs

III MALIGNANT HTN: →

= Sudden dramatic ↑ in BP > 140 mmHg

= Emergency of Treatment Required ⇒ Vasodilators

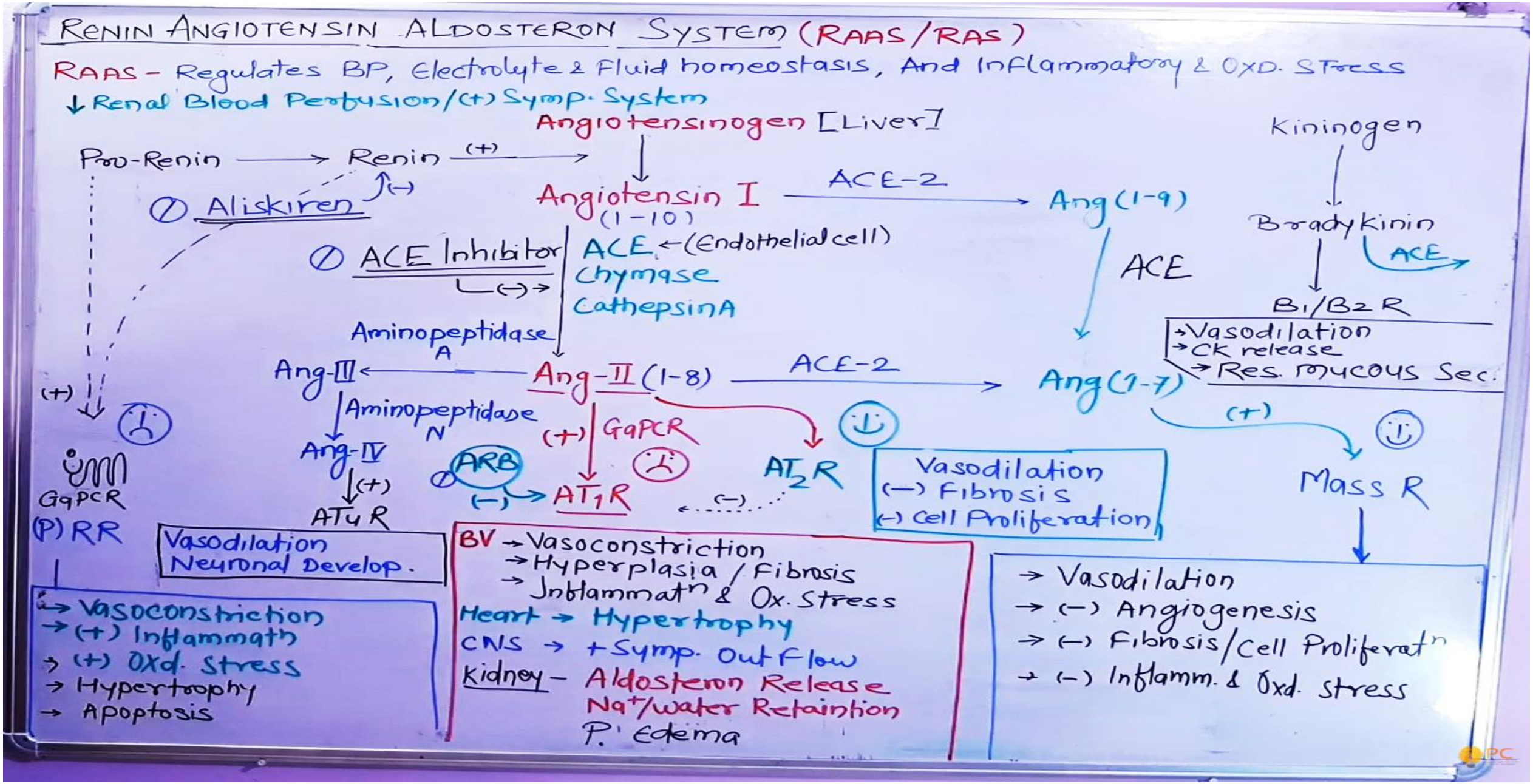
MANIFESTATION OF HTN ⇒

Vascular hypertrophy, Coronary Artery Diseases, Heart failure, Arrythmia, Renal failure, Edema, Retinal Damage, etc

Renin Angiotensin Aldosteron System (RAAS/RAS)

RAAS - Regulates BP, Electrolyte & Fluid homeostasis, And Inflammatory & Oxd. Stress

↓ Renal Blood Perfusion / (+) Symp. System



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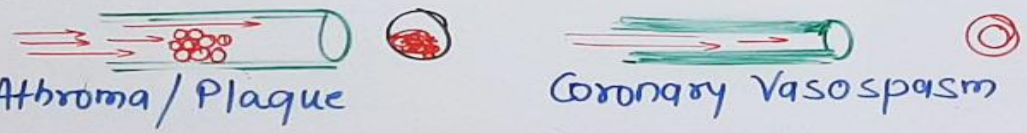
ANGINA PECTORIS

"Angina Pectoris (Chest pain) is caused by Myocardial Ischemia that lead to the imbalance b/w Myocardial O_2 demand & O_2 Supply

In Normal – O_2 demand = O_2 Supply
In Angina – O_2 demand >> O_2 Supply

"Ischemia" → ↓↓ Blood Supply ⇒ Hypoxia → ↓↓ O_2 Supply

#



Alternate Vessel → "Collateral Vessels"
↳ Developed in old-Age = ↓ Chance of Heart Attack

Symptoms:- chest pain, Pressure & burning Sensat", shortness of breath, Fatigue, Dizziness

TYPES OF ANGINA PECTORIS :–

(A) Classical / External / Stable Angina ⇒

↳ Pain occurs due to ↑ Work load on Heart caused by "Excercise", Emotion, Stress, & Cold
↳ "Predictable" & Symptoms may remain Stable for no. of years.
"Atherosclerosis" - is the main reseon
Treatments:- Antiplatelates, Thrombolytics

(B) Unstable Angina –

↳ Attack during Rest condition "Pre-Infract"
↳ Extensive Coronary Artery blockade due to either "Atheroma" and/or "Vasospasm"
↳ Treatment ⇒ Vasodilators & Antiplatelates

(C) Prinz Metal / Variant / Vasospastic Angina

↳ "Unpredictable" & Attack during "Rest & Sleep"
↳ Coronary Vasospasm due to Stress, Cold, Bad life Style, Smoking
↳ Associated with CAD but may result from chronic over Sympathetic Activity

(D) Silent Angina :– "Ischemia without Symptoms"

Diagnosis – Holter monitoring & Exc. stress testing

Rational Treatment :–

Non-Pharm. Therapy → Life Style monitoring

Pharmacotherapy →
↳ ↑ Coronary Flow → Vasodilators – Nitrates, CCB
↳ ↓ Atheroma → Antiplatelates, Thrombolytics
↳ ↓ Cardiac Workload → β-blockers

Surgery – Coronary Angioplasty
Coronary artery Bypass Grafting

Myocardial Infarction

MI :- Irriversible myocardial damages, death or injury that caused by "Chronic Ischemia" and leads to "Heart Attack"

Reseon :- Oclusion of coronary Vesseles due to lipid deposition-"Atherosclerosis" & Chronic Vasospasm.

Coronary Artery :

(A) Left CA :→

↳ Left Anterior Descending :- Anterior L.V. wall

↳ Circumflex Branches :- L.A. & Posterior & lateral Wall of L.V.

B) Right C.A. → Right Atrium & Ventricle

* 50% Cases → Left Anterior Descending artery

Types of MI :-

① Transmular → thickness of V. wall

② Subendocardial → ⅓ - ½ inner wall

Manifestation :-

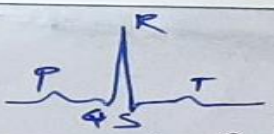
↳ Chest pain & Discomfort

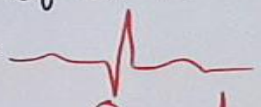
↳ Irriversible Cell injury after 20-30 min of Ischemia

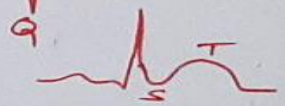
↳ Release myoc. Creatine phosphokinase (CPK)

↳ ECG :- Inversion of T-Wave, elevatⁿ of ST & pronoused Q-wave

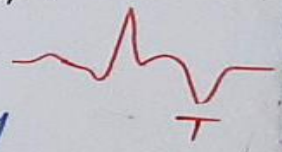
↳ Inflammatory & Oxd. stress







Complication :- Thromboembolism, Cardiogenic Shock, Pericarditis, CHF



Compansatory mech. Activatⁿ :- CA release, (+) RAAS, V. Hypertrophy

Therapy :-

A) Anti-Atherosclerotic drugs
↳ Anti-Platelet drugs

(B) Coguants / clot-disolving Agents - Streptokinase

(C) Tissue Plasmogen Activators - ↑ blood Flow

(D) Anti-hyperlipidemic drugs - "Statins"

ATHEROSCLEROSIS

Atherosclerosis is a condition where arteries become narrowed & hardened due to excessive build up of Plaques called Atheromas (made up of Lipids, Calcium, & others) around the artery walls.

Underlying pathogenesis of coronary, cerebral, & peripheral vascular diseases.

ETIOLOGY :- # Genetic (Familial hypercholesterolemia)

Age & Gender → >60Y & Postmenopausal women

Obesity, # Hyperlipidemia → ↑ LDL/HDL

Hypertension ⟷ Inflammatory mediators

Diabetes → Inflam., Aging, ROS, Insulin Resistance

Smoking & Tobacco → ROS

Chronic inflammation

SYMPTOMS – Initialy asymptomatic, later consequences and severity may showed symptoms

↳ Chest pain (Angina), ↳ Shortness of breath

↳ Fatigue ↳ Muscular weakness

↳ Confusion (Brain stroke) ↳ Palpitation

Consequences/complications –

Ischemic heart dis (IHD) - Myocardial infarct^{n} (Heart-attack)

Cerebral Infarction – Brain stroke

Peripheral vas. Dis - Gangrene of legs

A. stenosis – Critical stenosis → Ischemia

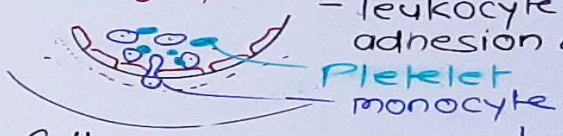
Aneurysm & Rupture

Occlusion by thrombu

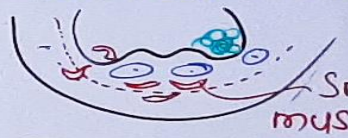
PATHOGENESIS – "Virchow" proposed Lipid theory –

↳ "Response to injury hypothesis"

1. Chronic endothelial injury — Inflamm. Response to injury → 2. Endothelial dysfunction → ↑ permiability, – leukocyte & monocyte adhesion & Emigration

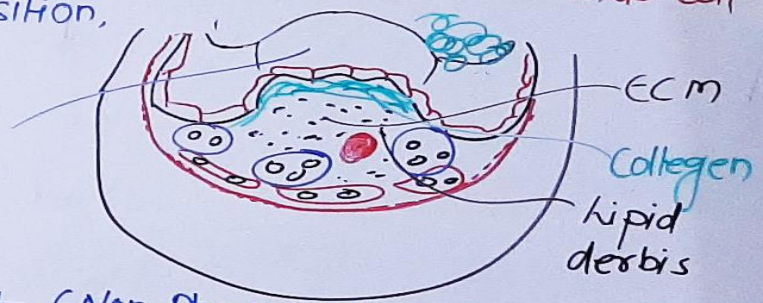


3. Macrophage Activat^{n} & Smooth mus. recruitmen'



4. Macrophage & Smooth mus. Cell engulf Lipid

5. Smooth mus. proliferation, Collegen and ECM deposition, Extracellular Lipids



Fibrofatty atheroma

Treatment :–

Life Style managment – (Non-Pharmacotherapy)

Pharmacotherapy

Anticoagulants (Warfarin)

Antiplatelets (Aspirin)

Anti hyperlipidemics (Statins, Fibrates)

Thrombolytic agent (Streptokinase)

Other → Beta-blockers, ACEIs/ARBs, α-linolenic acid, Beta-sitosterol, Green tea, black tea, etc.