PHARMACOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 3

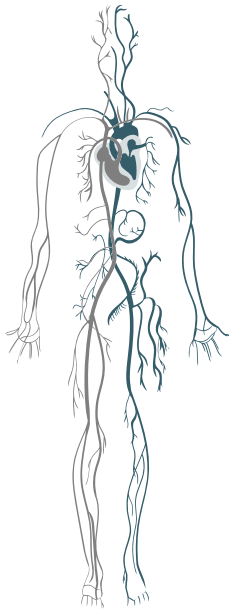
Anti-hypertensives (Pt.2)

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

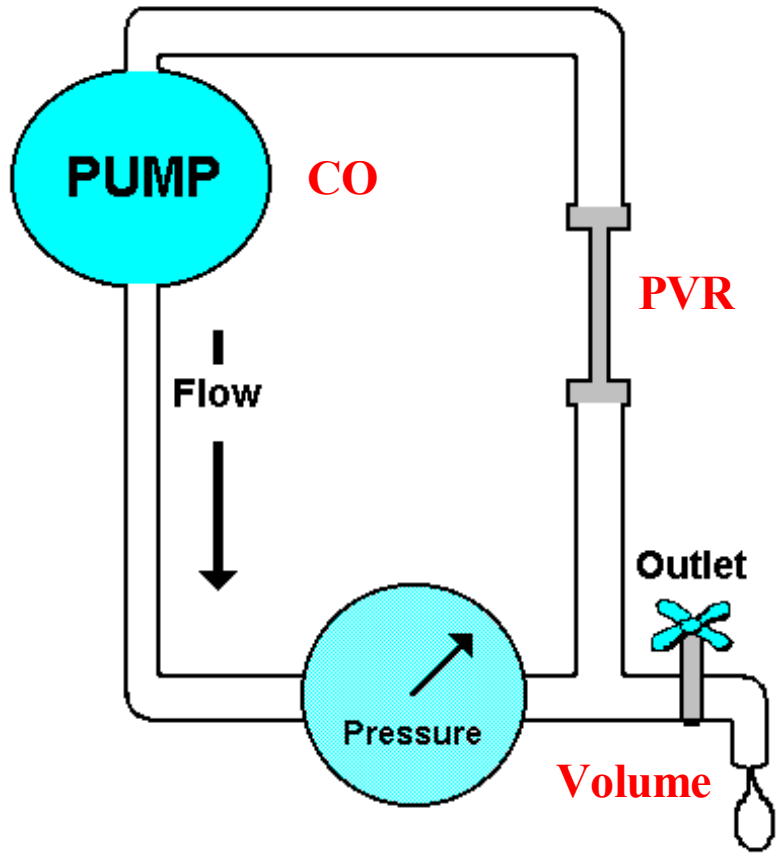
اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

Written by: Roaa Maakoseh
Heba Suliman

Reviewed by: Sarah Mahasneh



Ways of Lowering Blood Pressure



- Reduce plasma volume (diuretics)
- Reduce cardiac output (ß-blockers, Ca^{2+} channel blockers)
- Reduce peripheral vascular resistance (vasodilators)

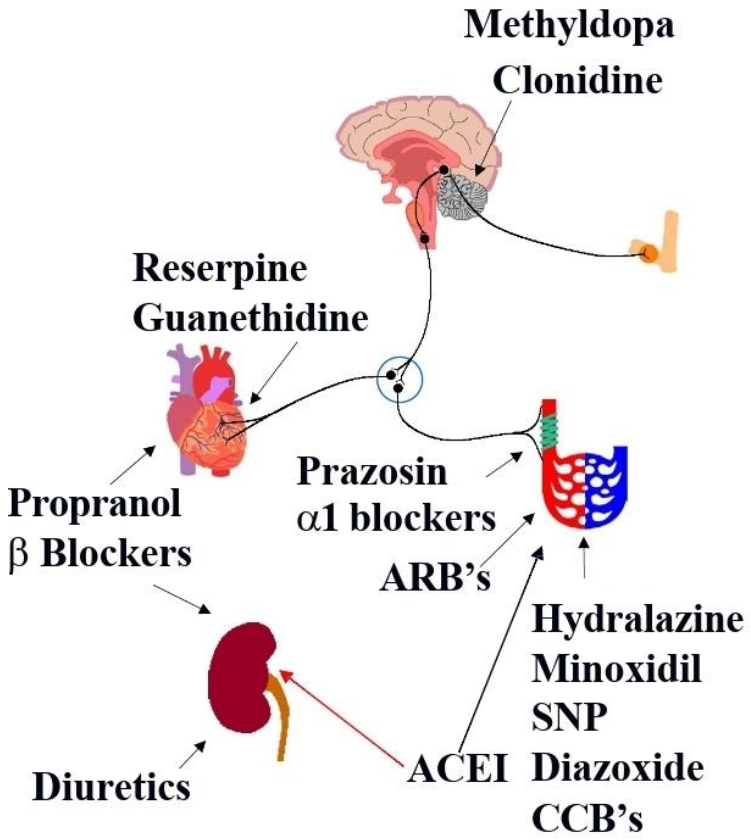
- Blood pressure (BP) depends on two main variables:
  - cardiac output (CO)
  - peripheral vascular resistance (PVR).
- Therefore, to lower BP, we can reduce either CO or PVR.

- The heart functions as a pump that ejects blood into the circulation, determining the cardiac output (CO). When cardiac output decreases, blood pressure also falls, since less blood is being pumped per minute. Agents such as **beta-blockers and calcium channel blockers** lower cardiac output by reducing heart rate and myocardial contractility.

- When blood vessels constrict, peripheral vascular resistance (PVR) increases, leading to a rise in blood pressure. Conversely, the use of **vasodilators** causes the blood vessels to relax and widen, which **reduces PVR** and **lowers blood pressure**.

- Excess salt (sodium) intake increases blood volume, since sodium draws water with it by osmosis, which can contribute to elevated blood pressure (BP). This condition can be managed using **diuretics**, which reduce sodium reabsorption in the kidneys, leading to increased excretion of sodium and water, thereby decreasing blood volume and lowering blood pressure.

Overview: Antihypertensives and sites of action



• B1 receptors are found mainly in the heart, where they increase heart rate and contractility, while β2 receptors are primarily located in the lungs and blood vessels, where they promote smooth muscle relaxation.

Regarding to the previous diagram

· Recall that the sympathetic nervous system (SNS) causes vasoconstriction of blood vessels and increases cardiac contractility and heart rate, both of which contribute to elevated blood pressure.

○ **B-blockers** act directly on the heart by blocking β1-adrenergic receptors, preventing adrenaline (epinephrine) and norepinephrine from activating them.
→ This leads to reduced heart rate, decreased contractility, and consequently lowered cardiac output and blood pressure.

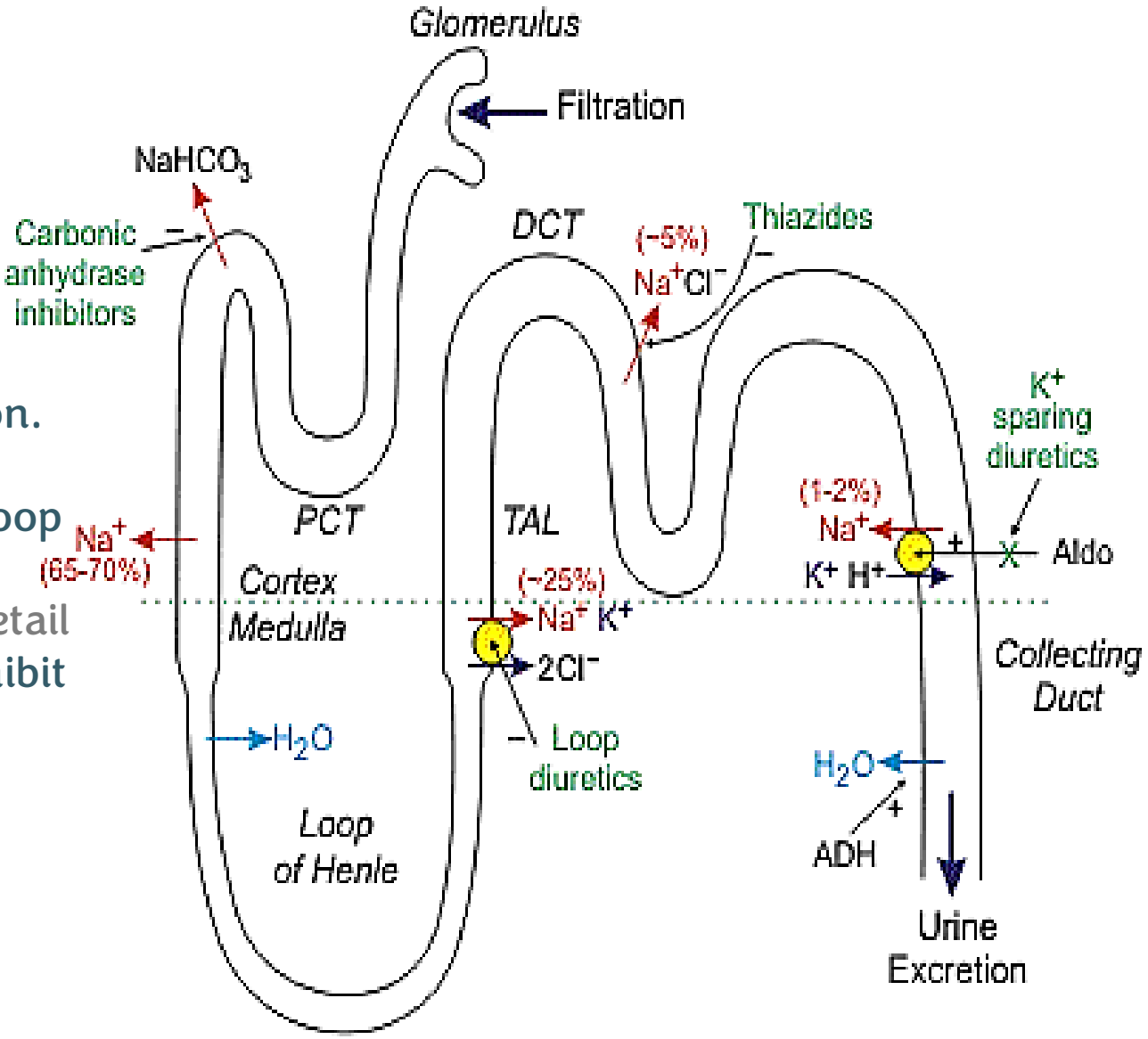
○ **Methyldopa**, **clonidine**, and **reserpine** also act on the sympathetic nervous system, leading to a decrease in its activity. Methyldopa and clonidine are **α2-adrenergic agonists** that reduce sympathetic outflow from the central nervous system.

○ **Reserpine**, on the other hand, inhibits the storage of norepinephrine in nerve terminals, which reduces neurotransmitter release and lowers blood pressure.

○ **Prazosin** is an **α1-adrenergic** receptor blocker.
α1 receptors are located mainly on resistance blood vessels (arterioles and veins), when activated by norepinephrine or adrenaline, these receptors cause vasoconstriction, increasing blood pressure.
By blocking α1 receptors, prazosin induces vasodilation, thereby reducing peripheral vascular resistance and lowering blood pressure.

Diuretics (‘Water Pills’)

· Different diuretics act on specific segments of the kidney tubule to increase sodium and water excretion.
·Examples include:
Carbonic anhydrase inhibitors, Thiazide diuretics, Loop diuretics and potassium-sparing.
We will go through diuretics mechanisms in more detail in UGS, but for now, know that thiazide diuretics inhibit sodium-chloride reabsorption. and loop diuretics blocking the sodium-potassium-chloride (NKCC2) cotransporter.



Not required, Know the general idea

History

- Diuretics discovered in the 1930s and used to treat antibacterial infections
- Patients noticed that the drugs made them urinate frequently
- In 1950s, William Schwartz and Karl Beyer implemented and refined their usage to treat patients with hypertension

Diuretics:
General Properties

- Reduce morbidity and mortality in patients with hypertension
- Often first-line antihypertensive therapy either alone or in combination
  (Depending on the patient's clinical status, they are often given in combination therapy).
- Provide adequate treatment of BP control in patients with mild or moderate primary hypertension
- Most efficacious in "low renin" or volume-expanded forms of hypertension
- Very effective for treatment of hypertension in African Americans

· As we know, renin plays a key role in the renin-angiotensin-aldosterone system (RAAS), catalyzing the conversion of angiotensinogen to angiotensin I, which is then converted to angiotensin II. Angiotensin II stimulates sodium and water reabsorption, thereby increasing blood volume and blood pressure. In low-renin hypertension, renin secretion is suppressed due to preexisting volume expansion, making these patients more responsive to diuretic therapy. This pattern is commonly observed in African American individuals, who tend to have salt-sensitive hypertension.

Initially work by increasing urine output, which reduces plasma and intravascular volume. This leads to a temporary drop in blood pressure, and patients may notice increased urination soon after starting therapy. However, the body activates compensatory mechanisms, which partially restore plasma volume and increase peripheral vascular resistance (PVR).

- The long-term blood pressure-lowering effect, usually observed after about 2 weeks, is **primarily** due to a **reduction in peripheral vascular resistance**. This may involve decreased sodium content in the vascular smooth muscle and **reduced vascular contractility**. Overall, diuretics typically lower blood pressure by approximately **10–15** mmHg.

- Another class of diuretics, known as **loop diuretics**, produce a much stronger diuretic effect (i.e., a greater increase in urine output). Although they are highly effective in relieving fluid overload, their long-term blood pressure-lowering effect is comparable to that of other diuretics.

Diuretics: Drawbacks

- Can adversely affect serum lipids and can reduce insulin sensitivity (watch out for diabetic patients!)
  - The effect on diabetes may occur in the long-term use of diuretics (i.e. years of treatment)
- Requires 2 weeks to become fully effective
  - PVR may increase at first

(This does not mean that diuretics are contraindicated in diabetic patients, but they may interfere with glucose control)

Diuretics and Kidney Disease

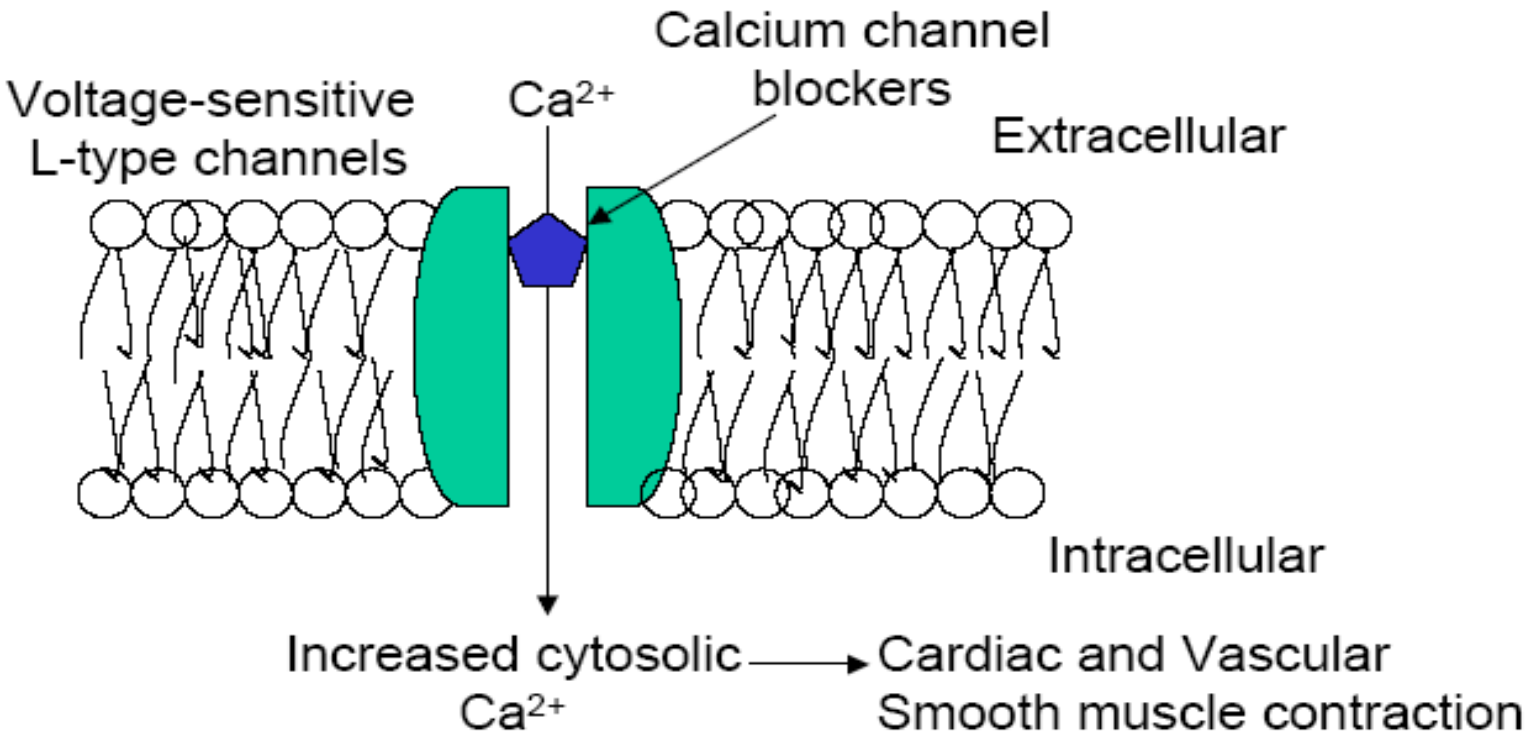
Efficacy of diuretics may be compromised during kidney failure

- Diuretics act to modulate electrolyte balance via effects on transporters/channels within the kidney
- Thus, the efficacy of diuretics to modulate transporter/channel function within a damaged kidney will likely be diminished
- May not effectively resolve hypertension under these conditions

· In patients with chronic kidney disease (CKD), kidney function may be reduced to approximately 30% of normal, which is typically estimated using serum creatinine levels, if serum creatinine is **elevated**, it indicates that the kidneys are not excreting it efficiently, suggesting impaired kidney function.
 - In patients with severely reduced kidney function (~15% of normal), diuretics may be used not only to lower blood pressure, but also to manage fluid overload in heart failure or edema, relieving pressure on the heart and peripheral tissues.
 · Because kidney function is severely impaired, diuretics are less effective compared to patients with normal kidney function. In such cases, **loop diuretics** are often preferred due to their stronger diuretic effect and ability to work even when renal function is limited.
 · **Some diuretics, can cause hyperuricemia. Therefore, we should monitor patients with a history of gout, as these drugs may trigger or worsen gout attacks.**

Calcium Channel Blockers ‘CCBs’

Calcium Channel Blockers



- **Calcium channel blockers Block Ca^{2+} in cardiac/smooth muscle, which reduces their contraction and relaxes BVs.**
- **Dilate peripheral arterioles.**
- **Reduce peripheral vascular resistance.**

There are two main families of calcium channel blockers **(CCBs)**:

· **Dihydropyridines**: These agents primarily act on **vascular** smooth muscle, leading to a decrease in peripheral vascular resistance.

· **Non-dihydropyridines**: These agents primarily affect the **cardiac** muscle and **conduction** system, resulting in a lower cardiac output.

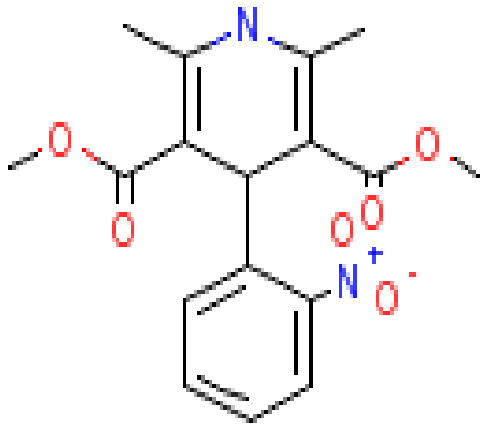
☆ Both families are used to decrease blood pressure, so a predictable side effect for both is hypotension (low blood pressure). *[page 22, first side effect]*

Calcium Channel Blockers (Dihydropyridine Class)

Amlodipine (Norvasc) and Nifedipine (Adalat) *Trade names are not required*

Both are prototype drugs.

- Block Calcium in vascular smooth muscle (vasodilate)
- Decrease PVR
- No effect on AV node conduction
- Useful in angina



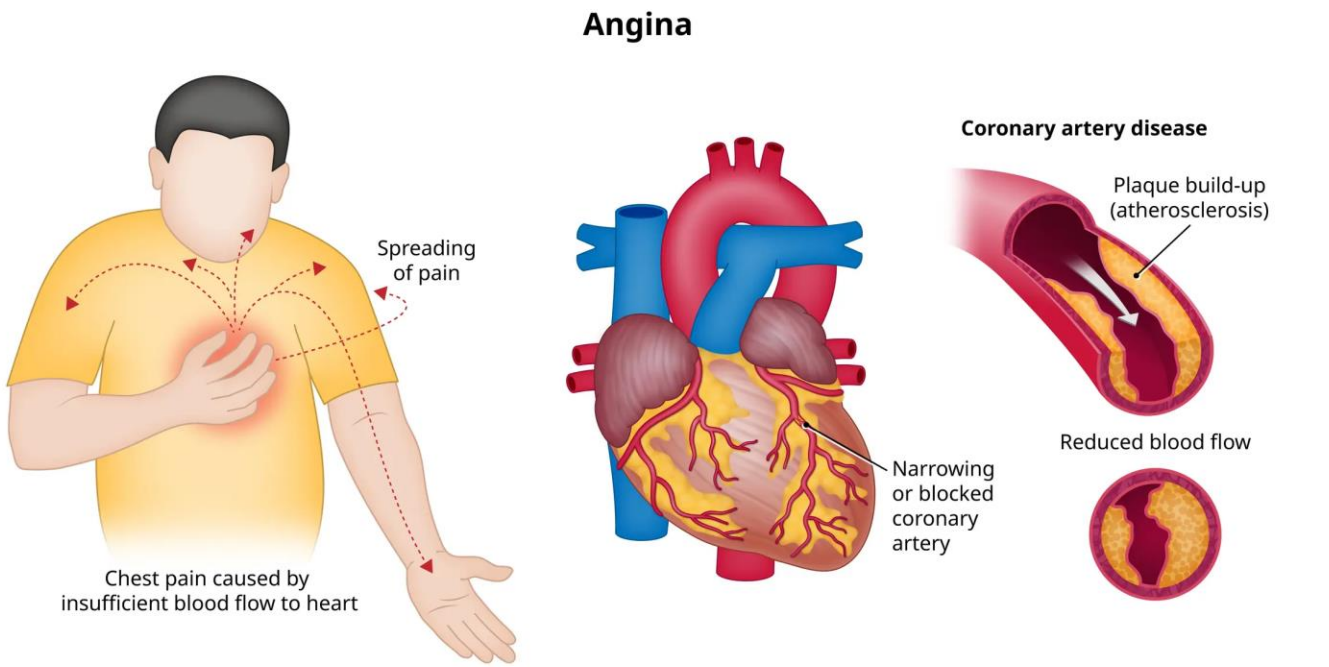
Almodipine
(do not memorize)

Many new drugs have been discovered, differing in their pharmacokinetics, half-lifes, and efficacies. We only need the general concepts, adverse effects, and contraindications.

• **Dihydropyridines** are beneficial in the management of **Angina Pectoris**, a condition in which patients experience chest pain during exertion, felt in the center of the chest behind the sternum, because the heart is not receiving sufficient blood to function, leading to an imbalance between supply and demand. (Oxygen demand)

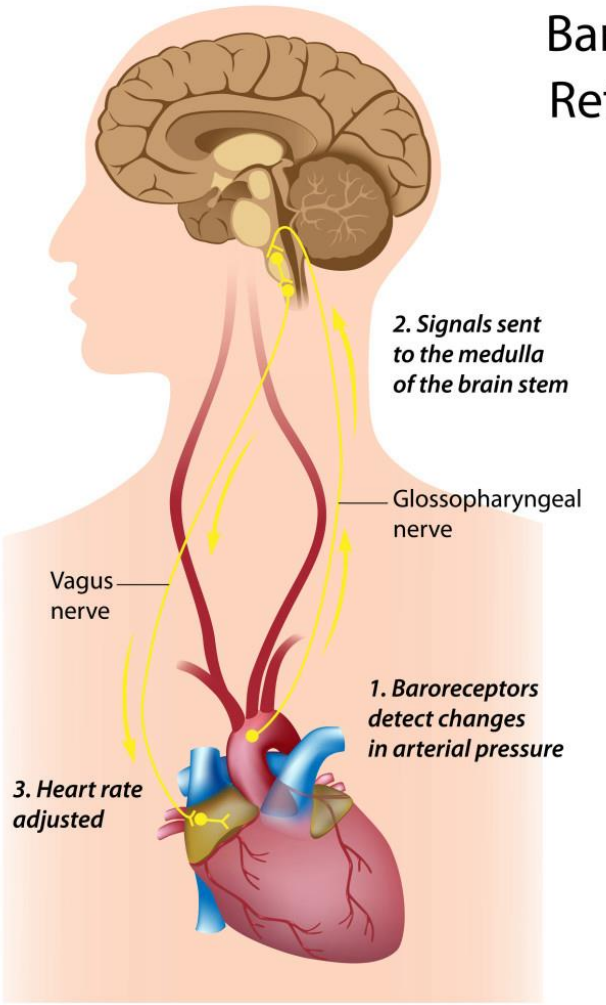
• One of the causes of this condition is the **narrowing of the coronary arteries**, for example, due to **atherosclerosis**. Therefore, one of the treatment approaches is **vasodilation**.

• In this context, **dihydropyridines** can **dilate the coronary arteries** and also act on **other resistance vessels** that determine blood pressure, resulting in a **decrease in BP**.



Extra picture

- The body naturally resists change through **compensatory mechanisms**.
- So, when **peripheral vascular resistance** decreases, the body attempts to restore it –and consequently raise blood pressure– by activating **sympathetic stimulation**, leading to **reflex tachycardia**.This increases both **heart contractility** and **heart rate**.
- As a **reflex (compensatory) mechanism** to the reduction in peripheral vascular resistance, and as a **side effect** of any **vasodilator**, the **baroreceptors** located in the **carotid sinuses and aortic arch** reduce **parasympathetic activity** (which normally decreases heart rate) and enhance **sympathetic stimulation**, resulting in increased **heart rate and contractility**.
- Therefore, these drugs may be **dangerous for patients with heart diseases**, especially those with a **history of cardiac fibrillation or arrhythmia**. Although these drugs dilate the blood vessels, they may cause **tachycardia**, which could be risky for such patients.
- Hence, ***it is always important to consider the patient's comorbidities before using them.***



Extra picture

Calcium Channel Blockers (Nondihyropyridines)

They **reduce the intracellular calcium concentration** in cardiac cells, resulting in **decreased myocardial contractility** and **reduced cardiac output**.

Verapamil (Isoptin)

- Direct negative inotropic and chronotropic action (cardiodepressive)
- May cause heart failure in patients with borderline cardiac reserve (Do not use in patients with LV dysfunction)

- negative inotropic effect, meaning it weakens the force of heart muscle contraction.
- negative chronotropic effect, meaning it slows the heart rate (decreases beats per minute).

⚠ High-Risk Combination

Verapamil should not be given with Beta Blockers.

Diltiazem (Cardizem)

- Decreases AV conduction and heart rate
- Weaker negative inotrope then verapamil

Calcium Channel Blockers: Side Effects

- Hypotension ☆
- Cardiac depression (Diltiazam, verapamil)
- Tachycardia (Nifedipine)
- Headache
- Flushing More blood flow to the skin due to vasodilation.
- Edema (Nifedipine) Plasma leakage from vasodilated blood vessels.
- Constipation A decrease in calcium levels causes less contraction in gastrointestinal smooth muscles.

· Headache is a complex clinical manifestation with multiple etiologies, including systemic issues like arterial hypertension.

Moreover, cerebral vasodilation is a key pain mechanism. This dilation causes the mechanical compression of nerve endings located on the arterial walls, which directly generates the painful sensation.

Calcium Channel Blockers: Drug Interactions

- Use of either verapamil or diltiazem (nondihydropyridines) in combination with β-blocker could cause marked bradycardia and cardiac conduction blockade
- Verapamil and diltiazem may add to the inhibitory effects of digoxin on AV conduction
- Amlodipine: combination with ACE inhibitor reduced CV events in hypertensive patients (ASCOT trial study)

Which can lead to problems such as cardiac arrhythmia.

Beta blockers decrease heart rate and force of contraction by blocking the effects of adrenaline and noradrenaline.

Calcium Channel Blockers: Drug Interactions

- Use of either verapamil or diltiazem (nondihydropyridines) in combination with β-blocker could cause marked bradycardia and cardiac conduction blockade
- Verapamil and diltiazem may add to the inhibitory effects of digoxin on AV conduction
- Amlodipine: combination with ACE inhibitor reduced CV events in hypertensive patients (ASCOT trial study) (Favorable drug combination).
  - Cardiovascular (CV) events are defined as myocardial infarction (MI) or stroke.

Digoxin: is a glycoside that treats Heart Failure by inhibiting the Na^+/K^+ ATPase pump, which causes internal Na to rise and thus slows the Na^+/Ca^{2+} exchanger to accumulate Ca^{2+} and strengthen the contraction. This stronger effect, combined with slowing the heart rate, effectively **reduces the overall workload on the heart muscle.**

CCB Indications

- Useful in low renin hypertension
  - Low renin hypertension is usually more common in certain ethnic groups (ex; African American) and also in elderly patients

- Useful in controlling BP and cardiovascular events in patients with isolated systolic hypertension, particularly the elderly

⚠ But be careful about comorbidities in elderly patients, such as heart failure or cardiac arrhythmias.

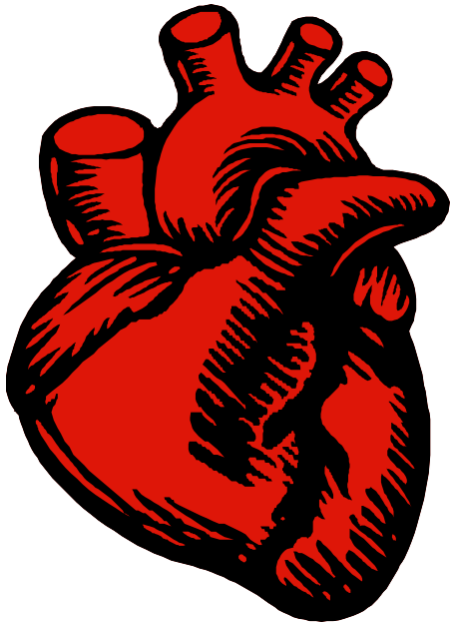
Beta-Adrenergic Receptor Blockers
β-Adrenoceptor Antagonists
‘β Blockers’

Useful not only in treating high blood pressure, but also in treating comorbidities, such as ischemic heart disease, heart failure, and cardiac arrhythmias.

β1 adrenergic receptor

Cardiac effects:

- **Increase cardiac output**
  - **Increase heart rate**
  - **Increase heart contractility**



History

- Raymond Ahlquist (MCG) in 1948 was searching for a drug to relieve menstrual cramps and coincidently found epinephrine stimulated heart rate through a distinct set of receptors (β) in the heart

- By 1964 , a research chemist, Sir James Black, having read these published observations developed β- blockers

PHARMACOLOGY QUIZ LECTURE 3

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	10	(SVR)	(PVR)
V1 → V2			