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PHARMACOTHERAPEUTIC 828801

CARDIOVASCULAR SYSTEM

HYPERTENSION

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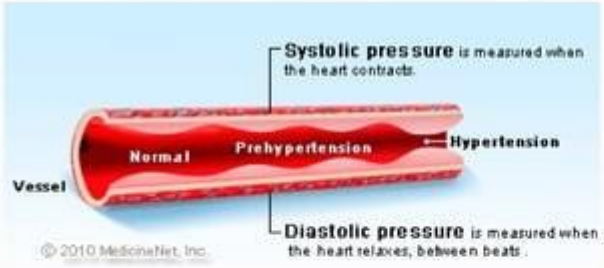
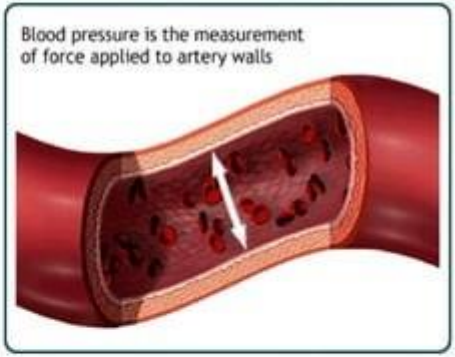
Introduction

- Hypertension is an abnormally high blood pressure especially arterial blood pressure. Blood pressure is the force exerted by the blood against the walls of blood vessels.





- Hypertension is usually indicated by an adult systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg with a consensus across medical guidelines.

- This means the systolic reading (the pressure as the heart pumps blood around the body) is over 140 mmHg (millimeters of mercury) and/or the diastolic reading (as the heart relaxes and refills with blood) is over 90 mmHg.
- According to The "Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure" (JNC-7), the Hypertension can be categorized into following :

Blood Pressure(mmHg)	Systolic (Upper number)		Diastolic (Lower number)
Normal	Less than 120	AND	Lower than 80
Pre-Hypertension	120-139	OR	80-89
Hypertension(Stage1)	140-159	OR	90-99
Hypertension(Stage2)	160 or greater	OR	100 or greater
Hypertension Crisis (Needs Emergency Care)	Greater than 180	OR OR	Greater than 110 End organ damage

Measurement of Blood Pressure

- Regulation of Normal Blood Pressure is carried out by :

Blood Pressure	=	Cardiac Output (CO)	×	Systemic Vascular Resistance

- **Systemic Vascular Resistance** is an index of arteriolar compliance or constriction throughout the body. It is the resistance that left ventricle must overcome to pump blood through the systemic circulation.
- **Cardiac Output** is the amount of blood pumped by the heart per min. The cardiac output is usually expressed in lit/min. A normal adult has a cardiac output of around 5 liters of blood per minute.

- Cardiac output can be calculated by following :

Cardiac Output (CO)	=	Heart Rate (HR)	×	Stroke Volume (SV)

- **Heart rate** is the speed of the heartbeat measured by the number of contractions of the heart per minute (bpm). A normal resting heart rate for adults ranges from 60 to 90 beats in a minute. But ideally it is 72 beat/ min.
- **Stroke volume** (SV) is the volume of blood pumped from the left ventricle per beat. The stroke volumes for each ventricle are generally being approximately 70 ml/ beat in a healthy man.
- Hence, cardiac output = 72 * 70 = 5040 ml/min
- A normal adult has a cardiac output of around 5 liters of blood per minute.

Factors influencing Blood Pressure

- Heart Rate

  ↑ heart rate ⟶ ↑ blood pressure

- Vasoconstriction / Vasodilation

  Vasoconstriction ⟶ ↑ blood pressure

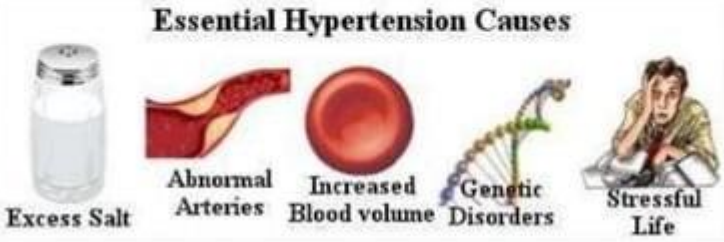
  Vasodilation ⟶ ↓ blood pressure

- Fluid Volume

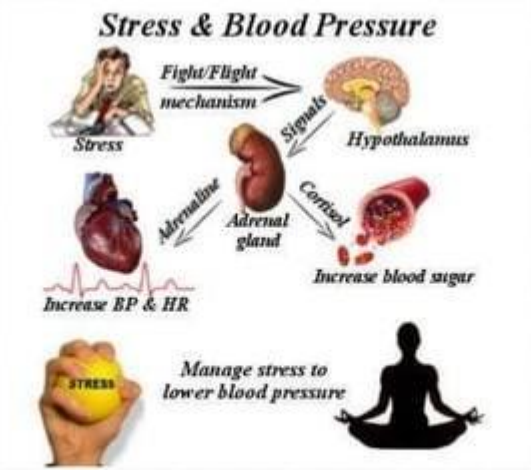
  ↑ fluid volume ⟶ ↑ blood pressure

Etiology

1. Hypertension may transfer due to HEREDITARY TENDENCY. It have passed down through 3 generations by statistically significant application of Mendel's law.
2. FAULTY DIET frequently associated with OVERWEIGHT. The person predisposed toward hypertension on a hereditary basis must frequently acquire faulty dietary habits. The effect of salty food or overuse of salt is also well demonstrated in patients in whom hypertension has developed.



3. The connection between blood pressure and the emotions, especially ANGER and FEAR has long been established.
4. Long-continued increased TENSION eventually produces degenerative changes in the intima and thickening of the walls of arterioles.



Epidemiology

- Overall, approximately 20% of the world's adults are estimated to have hypertension.
- Worldwide, approx. 1 billion people have hypertension, contributing to more than 7.1 million deaths per year.
- The age-specific prevalence was

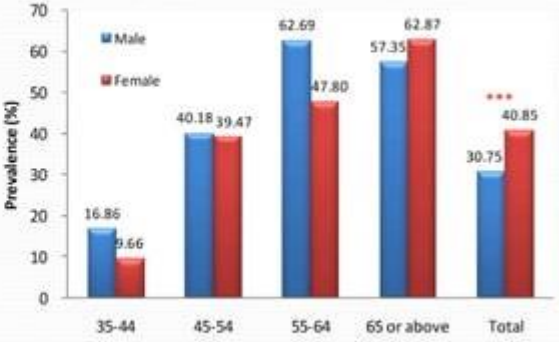
  3.3% in group aged 18-29 yr

  13.2% in group aged 30-39 yr

  22% in group aged 40-49 yr

  37.5% in group aged 50-59 yr

  51% in group aged 60-74 yr



Types

1. **Essential hypertension**

- This type of hypertension is diagnosed after a doctor notices that your blood pressure is high on three or more visits and eliminates all other causes of hypertension.
- Usually people with essential hypertension have no symptoms, but may experience frequent headaches, tiredness, dizziness or nose bleeds.
- Although the cause is unknown, researchers do know that obesity, smoking, alcohol, diet and heredity all play a role in essential hypertension.

2. **Secondary hypertension.**

- The most common cause of secondary hypertension is an abnormality in the arteries supplying blood to the kidneys. Other causes include airway obstruction during sleep, diseases and tumors of the adrenal glands, hormone abnormalities, thyroid disease, and too much salt or alcohol in the diet.
- Drugs can cause secondary hypertension, including over-the-counter medications such as ibuprofen (Motrin, Advil, and others) and pseudoephedrine (Afrin, Sudafed, and others).
- The good news is that if the cause is found, hypertension can often be controlled.

Special type

Malignant hypertension.

- This hypertension type occurs in only about 1 percent of people with hypertension.
- With malignant hypertension, high blood pressure occurs suddenly and drastically. A person might experience numbness in the body as well as vision problems, extreme fatigue, confusion, anxiety, and seizures.
- Malignant hypertension is reversible when the underlying condition is cured. Malignant hypertension is very rare and affects both children and adults.

Isolated systolic hypertension.

- Blood pressure is recorded in two numbers: The upper or first number is the systolic pressure, which is the pressure exerted during the heartbeat; the lower or second number is the diastolic pressure, which is the pressure as the heart is resting between beats.
- This type of hypertension is a result of old age and a poor diet. The arteries become stiff, resulting in a high systolic number with a normal diastolic number. Isolated systolic hypertension does not have an identifiable cause.
- Risk factors include old age, obesity, using tobacco products, and having diabetes.

Resistant hypertension.

- If your doctor has prescribed three different types of antihypertensive medications and your blood pressure is still too high, you may have resistant hypertension.
- Resistant hypertension may occur in 20 to 30 % of high blood pressure cases.
- At least four medications may be necessary to treat resistant hypertension.
- Resistant hypertension may have a genetic component and is more common in people who are older, obese, female, African American, or have an underlying illness, such as diabetes or kidney disease.

Signs & Symptoms

- Severe headache
- Fatigue /confusion /dizziness
- Vision problems
- Chest pain
- Difficulty breathing
- Irregular heartbeat
- Blood in the urine
- Pounding in neck or ears

It is often called Silent Killer because it is frequently asymptomatic until it has become severe.

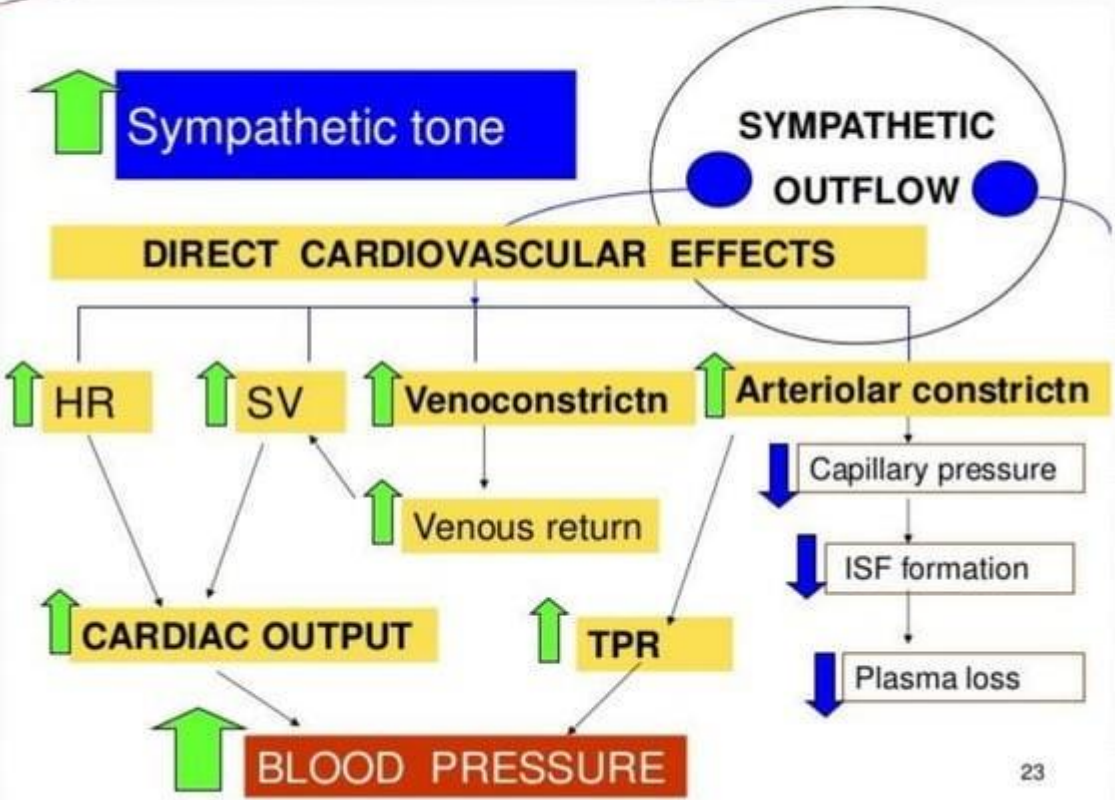
Pathophysiology

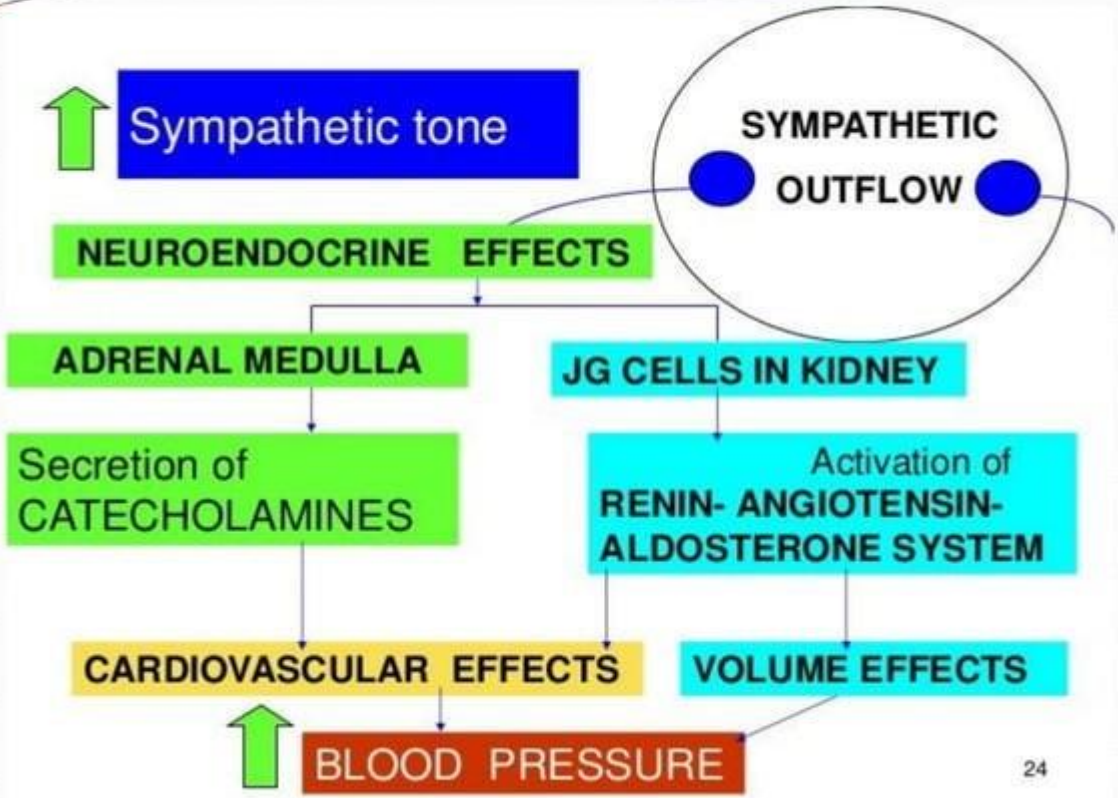
- The pathophysiology behind this disease mainly related to regulation of blood pressure.
- Blood pressure is regulated by following theories :
  1. **Sympathetic Nervous System** (Short-term Regulatory Mechanism / **Nervous Mechanism**)
  2. **Renin Angiotensin Aldosterone System** (Long-term Regulatory Mechanism / **Renal Mechanism**)
  3. **Fluid Volume Regulation**

Sympathetic Nervous System

- Regulation by Sympathetic Nervous System is also called Short-term Regulatory Mechanism which is carried out by 2 types of receptors :
  1. Baro-receptors
  2. Chemoreceptors
- Sympathetic Nervous System act on regulation of blood pressure by the action on Renin.
- Renin is an enzyme released by the kidney to help control the body's sodium-potassium balance, fluid volume and blood pressure.
- Renin release is stimulated by β and decreased by α adrenoceptor stimulation.

- Baro-receptors (Pressure Receptors) in carotid artery & aortic arch respond to changes in blood pressure and influence arteriolar dilation and arteriolar constrict ion.
- When stimulated to constriction, the contractile force strengthens, increasing the heart rate and augmenting peripheral resistance, thus increasing cardiac output and hence blood pressure.

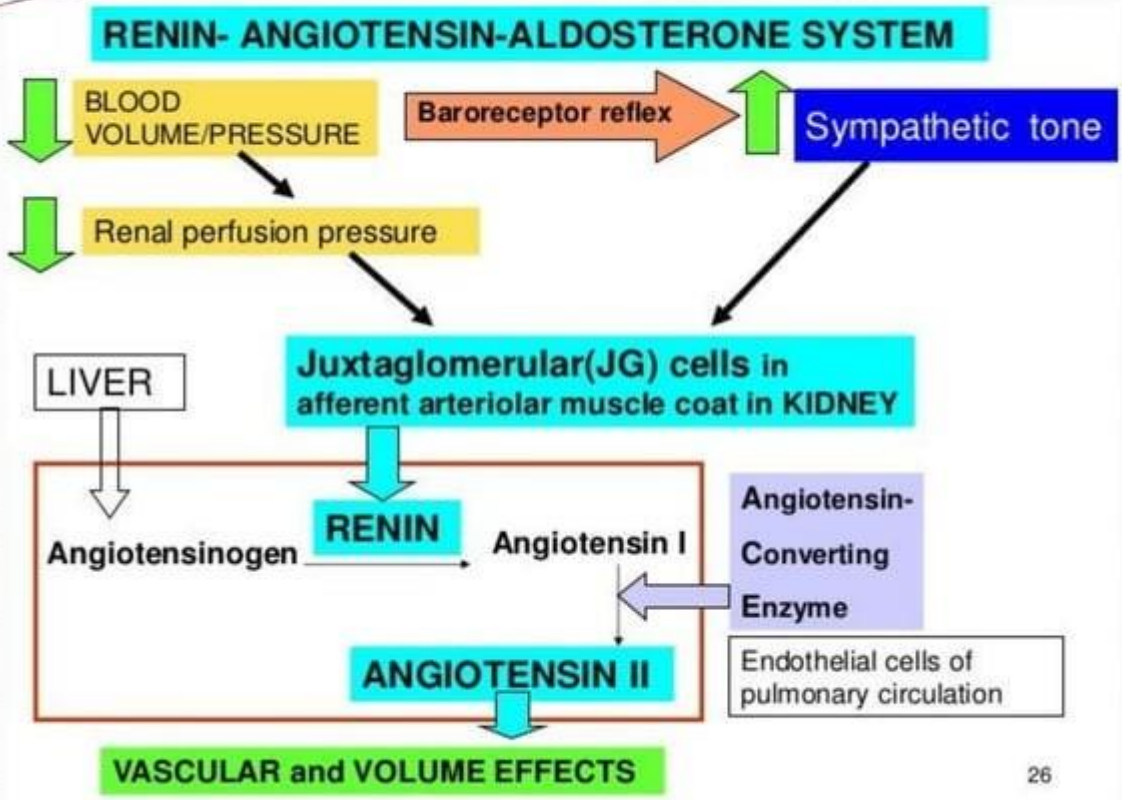

Sympathetic tone
SYMPATHETIC
OUTFLOW
DIRECT CARDIOVASCULAR EFFECTS
HR
SV
Venoconstrictn
Arteriolar constrictn
Capillary pressure
Venous return
ISF formation
CARDIAC OUTPUT
TPR
Plasma loss
BLOOD PRESSURE

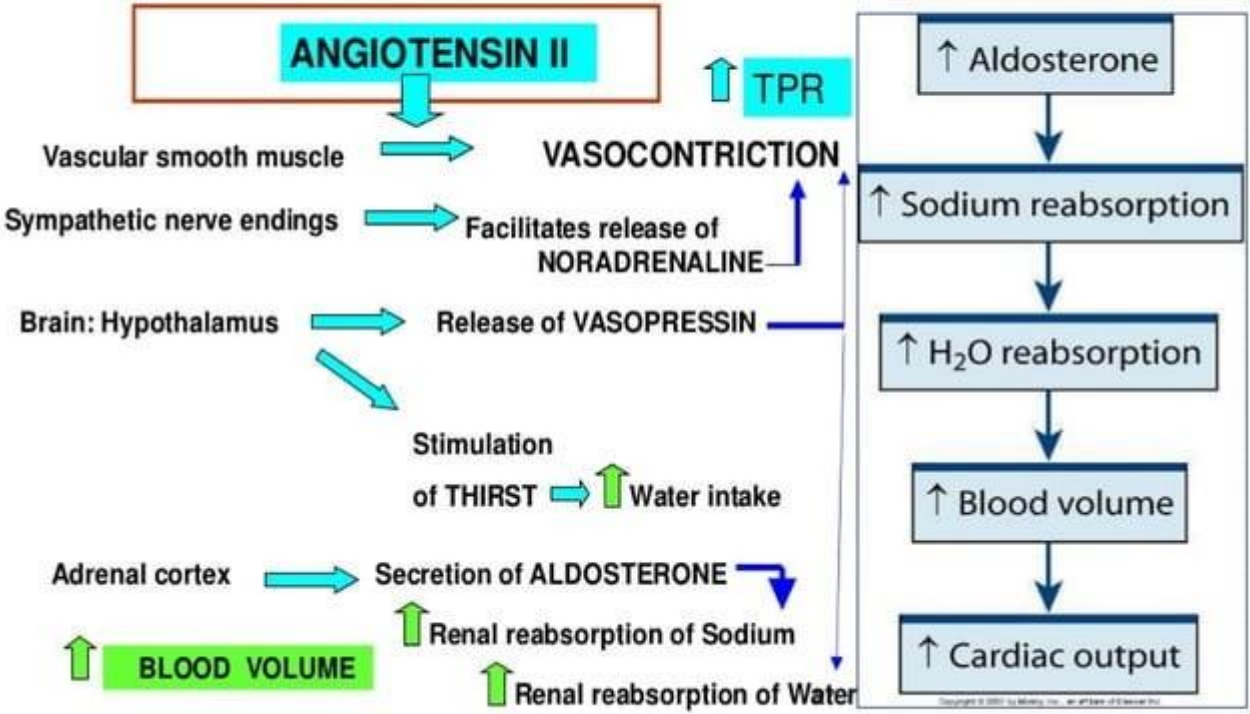

Sympathetic tone
SYMPATHETIC
OUTFLOW
NEUROENDOCRINE EFFECTS
ADRENAL MEDULLA
JG CELLS IN KIDNEY
Secretion of
CATECHOLAMINES
Activation of
RENIN- ANGIOTENSIN-
ALDOSTERONE SYSTEM
CARDIOVASCULAR EFFECTS
VOLUME EFFECTS
BLOOD PRESSURE

Renin – Angiotensin System

- When the kidneys release the enzyme renin in response to certain conditions (*high blood potassium, low blood sodium, decreased blood volume*), it is the first step in what is called the *renin-angiotensin-aldosterone cycle*.
- This cycle includes the conversion of angiotensinogen to inactive peptide *angiotensin I*, which in turn is converted to active octapeptide *angiotensin II* in the lung by presence of *Angiotensin Converting Enzyme*.
- Angiotensin II is a *powerful blood vessel constrictor* and its action stimulates the release of aldosterone from an area of the adrenal glands called the adrenal cortex.
- The main source of renin is the juxtaglomerular apparatus of the kidney.

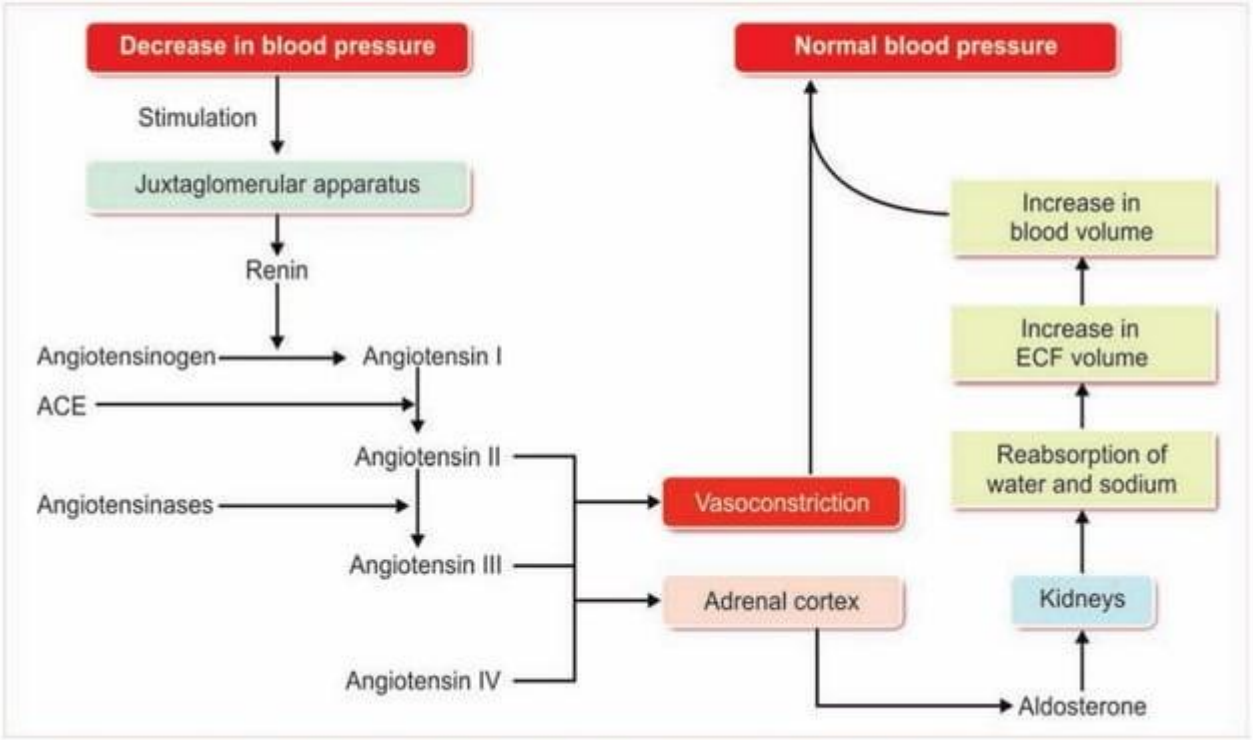
- This juxtaglomerular apparatus senses the renal perfusion pressure and the sodium concentration in the distal tubular fluid.
- Together, *angiotensin and aldosterone increase the blood pressure and the blood sodium to re-establish the body's sodium-potassium and fluid volume balance*.


RENIN- ANGIOTENSIN-ALDOSTERONE SYSTEM
BLOOD VOLUME/PRESSURE
Baroreceptor reflex
Sympathetic tone
Renal perfusion pressure
LIVER
Juxtaglomerular(JG) cells in afferent arteriolar muscle coat in KIDNEY
Angiotensinogen
RENIN
Angiotensin I
Angiotensin-Converting Enzyme
Endothelial cells of pulmonary circulation
ANGIOTENSIN II
VASCULAR and VOLUME EFFECTS


ANGIOTENSIN II
↑ TPR
Vascular smooth muscle
VASOCONTRICTION
Sympathetic nerve endings
Facilitates release of NORADRENALINE
Brain: Hypothalamus
Release of VASOPRESSIN
Stimulation of THIRST
Water intake
Adrenal cortex
Secretion of ALDOSTERONE
Renal reabsorption of Sodium
BLOOD VOLUME
Renal reabsorption of Water
↑ Aldosterone
↑ Sodium reabsorption
↑ H_2O reabsorption
↑ Blood volume
↑ Cardiac output

Fluid Volume Regulation

- Sodium and water retention are associated with an increase in blood pressure. It is postulated that sodium, via the sodium–calcium exchange mechanism, causes an increase in intracellular calcium in vascular smooth muscle resulting in increased vascular tone.
- The primary cause of sodium and water retention may be an abnormal relationship between pressure and sodium excretion resulting from reduced renal blood flow, reduced nephron mass, and increased angiotensin or mineralocorticoids.


Decrease in blood pressure
Stimulation
Juxtaglomerular apparatus
Renin
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Angiotensinases
Angiotensin III
Angiotensin IV
Vasoconstriction
Adrenal cortex
Aldosterone
Kidneys
Reabsorption of water and sodium
Increase in ECF volume
Increase in blood volume
Normal blood pressure

Diagnosis

- **Manometer** : Mercury, anaeroid or electronic devices is used in measurement of blood pressure. It should be calibrated frequently and routinely against standards (typically every 6 months) to assure accuracy.
- **Electrocardiogram** : A test that measures the electrical activity, rate, and rhythm of your heartbeat via electrodes attached to your arms, legs, and chest. The results are recorded on graph paper.
- **Echocardiogram** : This is a test that uses ultrasound waves to provide pictures of the heart's valves and chambers so the pumping action of the heart can be studied and measurement of the chambers and wall thickness of the heart can be made.

Complication Of Hypertension

End organ damage

Heart Attack
Myocardial Infarction
Cardiomyopathy
Heart Failure

Neurological
Stroke
Dementia

Renal Failure

Retinopathy
Visual Loss

Blood Vessel Damage
Artherosclerosis
Aneurysm

Headache
Confusion
Convulsion

Complication

- **Heart attack or stroke :** High blood pressure can cause hardening and thickening of the arteries (atherosclerosis), which can lead to a heart attack, stroke or other complications.
- **Heart failure :** To pump blood against the higher pressure in your vessels, your heart muscle thickens. Eventually, the thickened muscle may have a hard time pumping enough blood to meet your body's needs, which can lead to heart failure.
- **Aneurysm :** Increased blood pressure can cause your blood vessels to weaken and bulge, forming an aneurysm. If an aneurysm ruptures, it can be life-threatening.
- **Renal Failure :** Weakened and narrowed blood vessels in the kidneys can prevent these organs from functioning normally.

- **Retinopathy :** Thickened, narrowed or torn blood vessels in the eyes can result in vision loss.
- **Metabolic syndrome.** This syndrome is a cluster of disorders of the body's metabolism, including increased waist circumference; high triglycerides; low high-density lipoprotein (HDL) cholesterol, the "good" cholesterol; high blood pressure; and high insulin levels. These conditions make the person more likely to develop diabetes, heart disease and stroke.
- **Trouble with memory or understanding.** Uncontrolled high blood pressure may also affect the ability to think, remember and learn. Trouble with memory or understanding concepts is more common in people with high blood pressure.

Management

Non-Clinical Management

Non-pharmacological management plays an important role in the management of hypertension and in improving overall cardiovascular health.

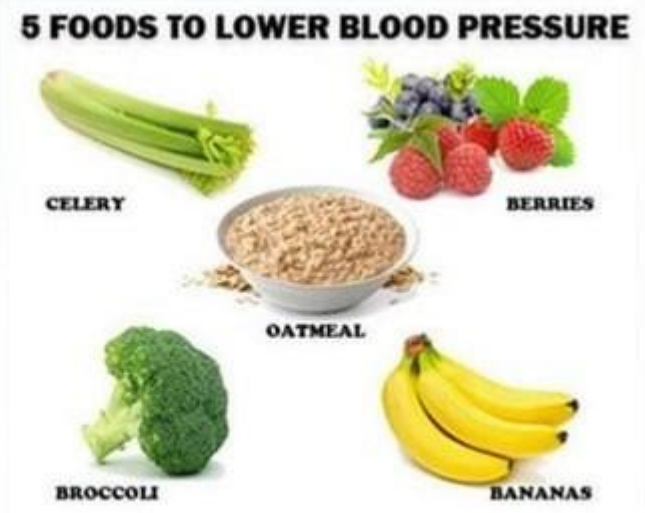
1. Lifestyle Modification

- Weight reduction : Weight-reducing diets in overweight hypertensive persons can result in modest weight loss in the range of 3-9% of body weight and are associated with blood pressure reduction of about 3-6 mmHg. It is advisable for overweight hypertensive patients to lose at least 5% of their weight.
- Quit smoking : Tobacco abuse in any form is found to increase blood pressure acutely.

- Avoidance of alcohol intake : Moderation of alcohol consumption is advised. Alcohol consumption elevates BP acutely. Meta analyses have shown that, interventions to reduce alcohol consumption caused a small but significant reduction (3.3/2 mmHg) in both systolic and diastolic blood respectively.
- Physical exercise : Aerobic physical exercise for 20–30 minutes per day for at least 5 days per week improves blood pressure and reduces cardiovascular morbidity.

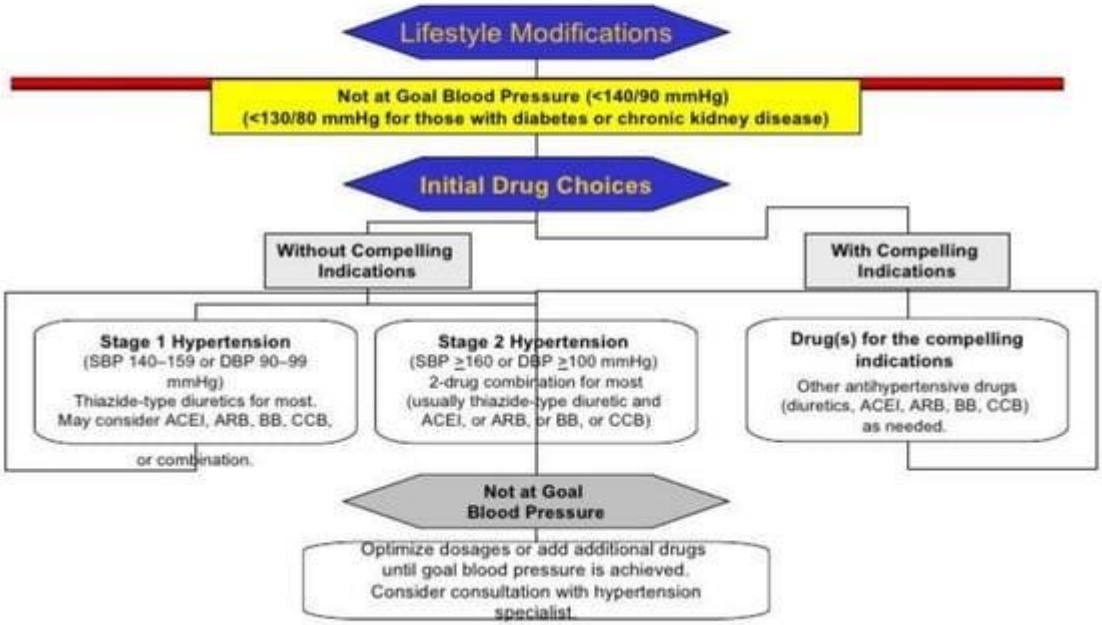
2. Dietary Modification

- A diet rich in fruits, vegetables and low fat dairy products with reduced saturated and total fat can substantially lower BP due to high potassium content. More recently, diet high in L-Arginine has been shown to be able to reduce BP by 5.4/2.3 mmHg.



- Low sodium diet : High salt intake is associated with significantly increased risk of stroke and total cardiovascular disease. Typical Indian food provides 4–5 gm of sodium per day. Pickles, salted vegetables and canned fish are rich in sodium and should be avoided. Intake of 2-3 gm of sodium or less is recommended as per dietary approaches to stop hypertension. Evidence from published systematic review and meta analyses showed that restricting sodium intake in people with elevated blood pressure in the short term leads to reductions in blood pressure of up to 10.5 mmHg systolic and 2 mmHg diastolic.

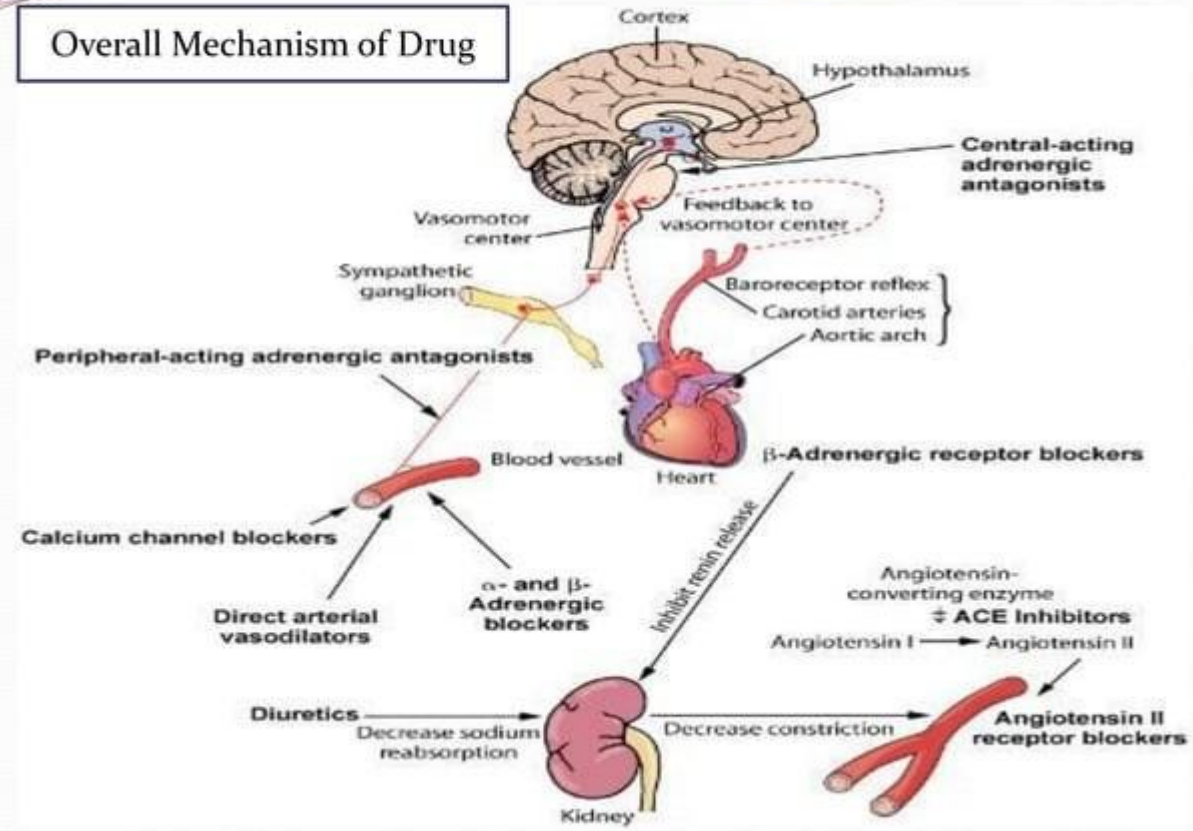
Algorithm for Treatment of Hypertension



Clinical Treatment

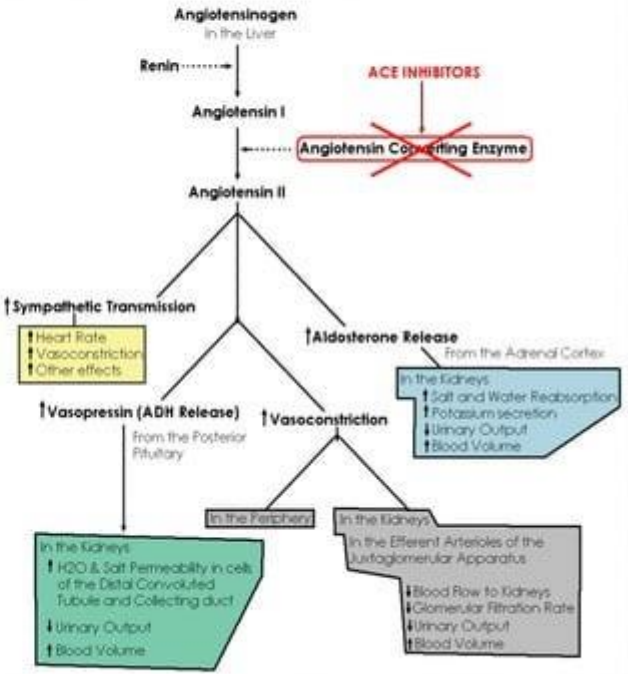
- There are following class of drugs useful for the treatment of Hypertension :
  1. Angiotensin Converting Enzyme (ACE) Inhibitors
  2. Angiotensin Receptor Blockers
  3. Diuretics
  4. Calcium Channel Blockers
  5. β blockers
  6. α blockers
  7. Centrally acting agents
  8. Direct Vasodilators

Overall Mechanism of Drug



Angiotensin Converting Enzyme (ACE) Inhibitors

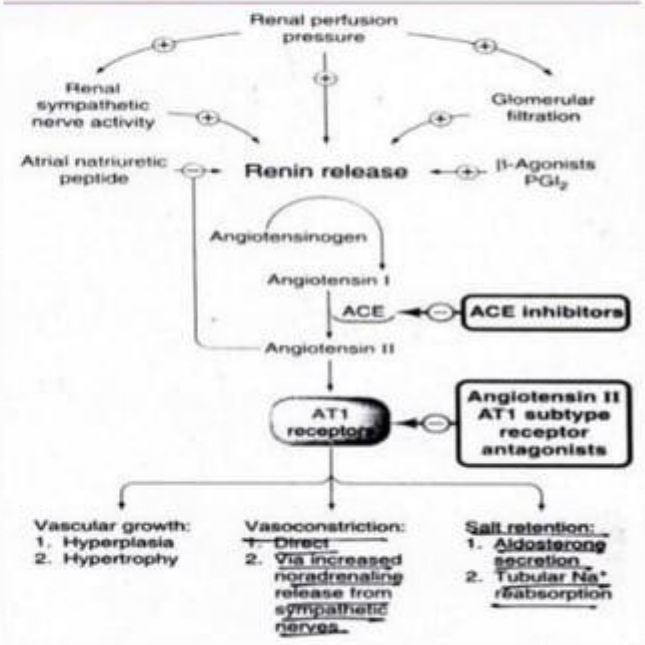
- These agents reduce blood pressure by blocking the renin-angiotensin system. They do this by preventing conversion of angiotensin I to the blood pressure raising hormone angiotensin II. They also increase availability of the vasodilator bradykinin by blocking its breakdown.



- Use : These drugs have established clinical outcome benefits in patients with heart failure, post–myocardial infarction, left ventricular systolic dysfunction, and diabetic and non-diabetic chronic kidney disease.
- Side Effects : They are well tolerated. Their main side effect is cough. Angioedema is an uncommon but potentially serious complication that can threaten airway function.
- These drugs can increase serum creatinine by 30% due to reduce pressure within the renal glomerulus which is not harmful.
- These drugs must not be used in pregnancy.
- Egs., Ramipril
  Captopril
  Enalapril
  Perindopril

Angiotensin Receptor Blockers

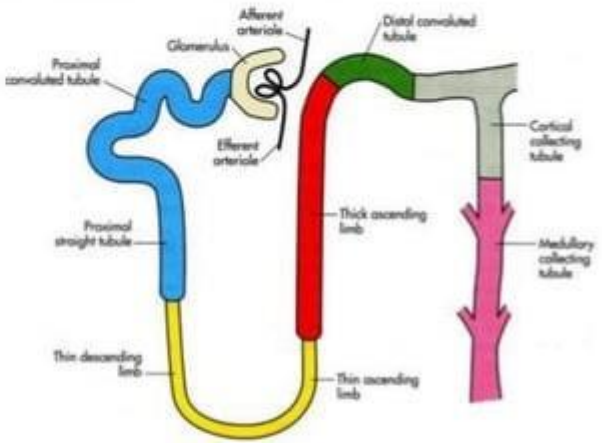
- Angiotensin receptor blockers antagonize the renin angiotensin system. They reduce blood pressure by blocking the action of angiotensin II on its AT1 receptor and thus prevent the vasoconstrictor effects of this receptor.
- Egs., Losartan
  Valsartan
  Telmisartan
  Candesartan



- Use : These drugs have the same benefits on cardiovascular and renal outcomes as angiotensin-converting enzyme inhibitors like heart failure, post–myocardial infarction, left ventricular systolic dysfunction, and diabetic and non-diabetic chronic kidney disease.
- Side Effect : They are well tolerated because they do not cause cough and only rarely cause angioedema and have effects similar to ACE inhibitors, they are generally preferred over ACE inhibitors if they are available and affordable. They also can increase serum creatinine which is not harmful.
- These drugs must not be used in pregnancy.

Diuretics

- These agents work by increasing excretion of sodium by the kidneys and additionally may have some vasodilator effects.
- 2 types of diuretics are used in the treatment of Hypertension :
  - Thiazide diuretic
  - Loop diuretic



- Clinical outcome benefits have been best established with chlorthalidone, indapamide, and hydrochlorothiazide.
- Chlorthalidone has more powerful effects on blood pressure than hydrochlorothiazide and has a longer duration of action.
- Side Effect : The main side effects of these drugs are metabolic (hypokalemia, hyperglycemia, hyperuricemia). The likelihood of these problems can be reduced by using low doses or by combining with ACE inhibitors or angiotensin receptor blockers, which have been shown to reduce these metabolic changes. Diuretics are most effective with these two combinations. Combining diuretics with potassium-sparing agents also helps to prevent hypokalemia and with calcium channel blockers are also effective.

Calcium Channel Blockers

- These agents reduce blood pressure by blocking the inward flow of calcium ions through the L channels of arterial smooth muscle cells.
- Egs.,

Nondihydropyridines :

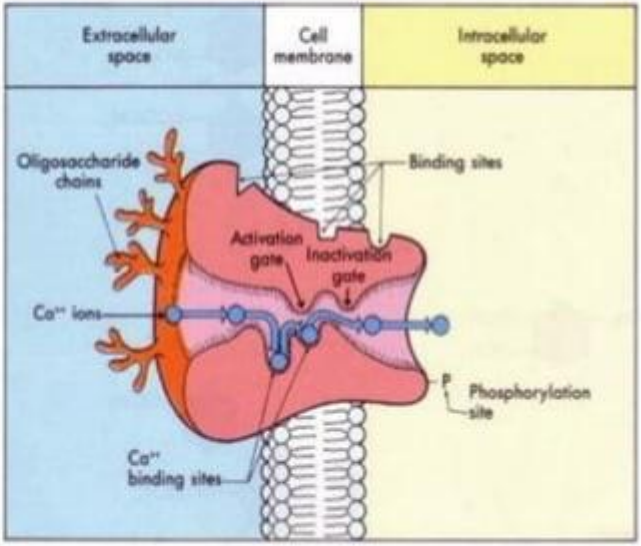
Diltiazem

Verapamil

Dihydropyridines :

Nifedipine

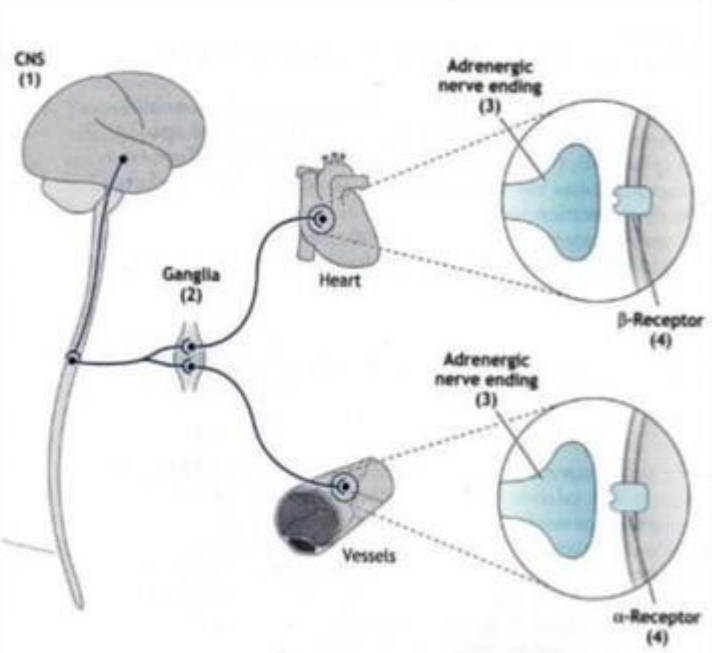
Amlodipine



- There are 2 main types of calcium channel blockers: dihydropyridines, such as amlodipine and nifedipine, which work by dilating arteries; and nondihydropyridines, such as diltiazem and verapamil, which dilate arteries somewhat less but also reduce heart rate and contractility. Hence Nondihydropyridine are not recommended in patients with heart failure.
- Side Effect : The main side effect of calcium channel blockers is peripheral edema, which is most prominent at high doses.
- They have powerful blood pressure reducing effects, when combined with ACE inhibitors or angiotensin receptor blockers.

β Adrenoreceptor Blockers

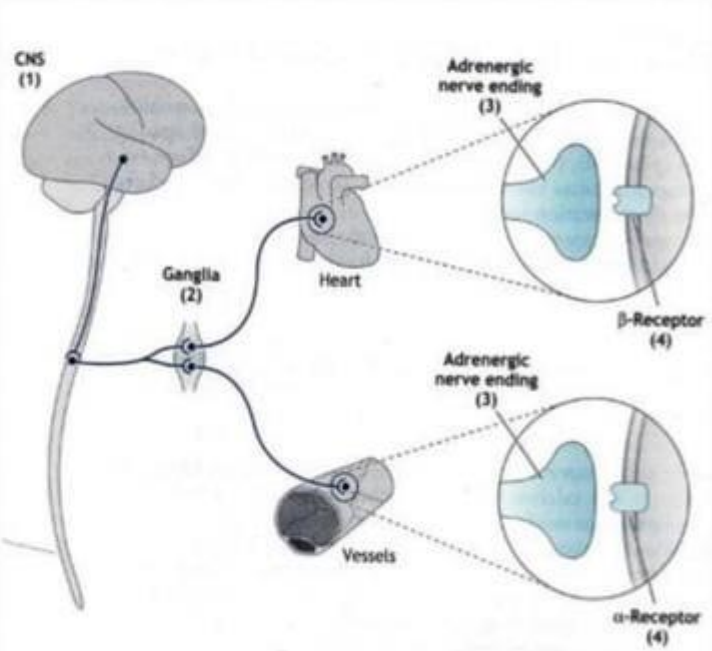
- β blockers reduce cardiac output and also decrease the release of renin from the kidney.
- Egs., Propranolol
  Atenolol
  Metoprolol
  Carvediol
  Acebtalol



- Use : They have strong clinical outcome benefits in patients with histories of myocardial infarction and heart failure and are effective in the management of angina pectoris.
- Side Effect : The main side effects associated with b-blockers are reduced sexual function, fatigue, and reduced exercise tolerance.
- Many of these agents have adverse effects on glucose metabolism and therefore are not recommended in patients at risk of diabetes, especially in combination with diuretics. They may sometimes also be associated with heart block.
- The combined α and β blocker, LABETALOL, is widely used intravenously for hypertensive emergencies and is also used orally for treating hypertension in pregnant and breastfeeding women.

α Adrenergic Blockers

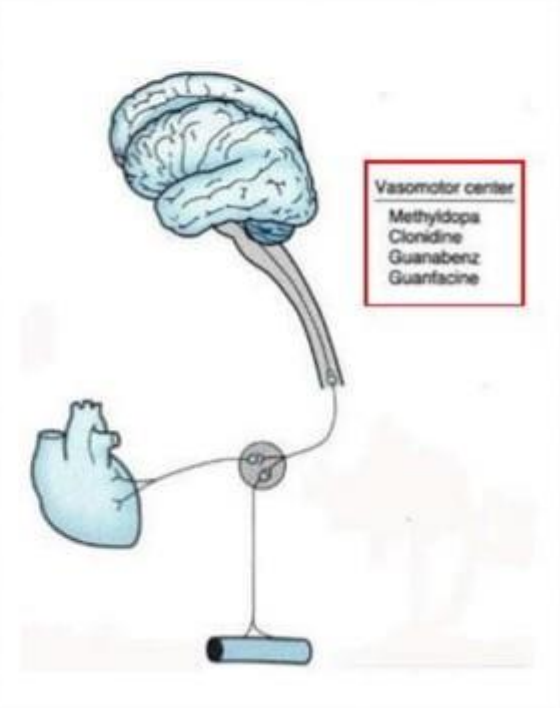
- α Blockers reduce blood pressure by blocking arterial α adrenergic receptors and thus preventing the vasoconstrictor actions of these receptors.
- Egs., Prazosin
  Terazosin
  Doxazosin



- Use : These drugs are less widely used as first-step agents than other classes because clinical outcome benefits have not been well established. However, they can be useful in treating resistant hypertension when used in combination with agents diuretics, β blockers, and ACE inhibitors.
- To be maximally effective, they should usually be combined with a diuretic. Since α blockers can have somewhat beneficial effects on blood glucose and lipid levels, they can potentially neutralize some of the adverse metabolic effects of diuretics.
- The α blockers are effective in treating benign prostatic hypertrophy and so can be a valuable part of hypertension treatment regimens in older men who have this condition.

Centrally Acting Agents

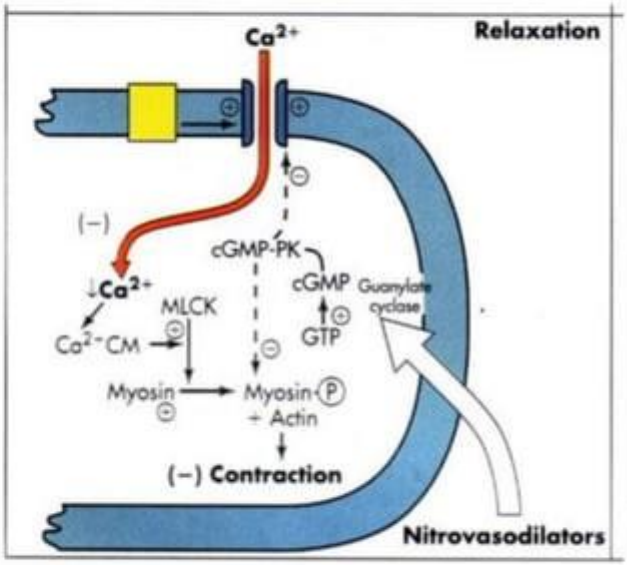
- These drugs, the most well-known of which are clonidine and methyldopa work primarily by reducing sympathetic outflow from the central nervous system.
- Egs., Methyldopa
  Clonidine
  Clonidine patch



- Side Effect : Bothersome side effects such as drowsiness and dry mouth have reduced their popularity.
- Treatment with a clonidine skin patch causes fewer side effects than the oral agent, but the patch is not always available and can be more costly than the tablets.
- In certain countries, including the United States, α methyldopa is widely employed for treating hypertension in pregnancy.

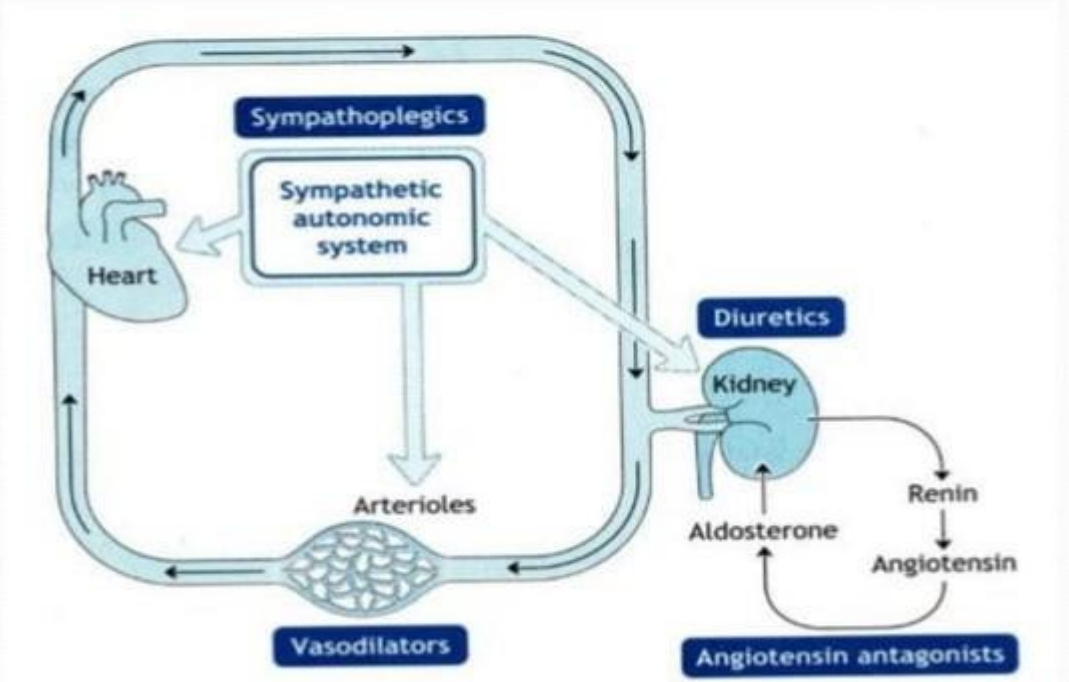
Direct Vasodilators

- Because these agents often cause fluid retention and tachycardia, they are most effective in reducing blood pressure when combined with diuretics and β blockers or sympatholytic agents. For this reason, they are now usually used only as fourth-line or later additions to treatment regimens.
- Egs., Hydralazine
  Minoxidil



- Hydralazine is the more widely used of these agents. The powerful drug minoxidil is sometimes used by specialists in patients whose blood pressures are difficult to control. Fluid retention and tachycardia are frequent problems with minoxidil, as well as unwanted hair growth (particularly in women). Furosemide is often required to cope with the fluid retention.

Overall Mechanism of Action



Drug Class	Agents of Choice	Comments
Diuretics	HCTZ 12.5-50mg, chlorthalidone 12.5-25mg, indapamide 1.25-2.5mg triamterene 100mg *K+ sparing* – spironolactone 25-50mg, amiloride 5-10mg, triamterene 100mg furosemide 20-80mg twice daily, torsemide 10-40mg	Monitor for hypokalemia Most SE are metabolic in nature Most effective when combined w/ ACEI Stronger clinical evidence w/chlorthalidone Spironolactone - gynecomastia and hyperkalemia Loop diuretics may be needed when GFR <40mL/min
ACEI/ARB	*ACEI:* lisinopril, benazapril, fosinopril and quinapril 10-40mg, ramipril 5-10mg, trandolapril 2-8mg *ARB*: candesartan 8-32mg, valsartan 80-320mg, losartan 50-100mg, olmesartan 20-40mg, telmisartan 20-80mg	SE: Cough (ACEI only), angioedema (more with ACEI), hyperkalemia Losartan lowers uric acid levels; candesartan may prevent migraine headaches
Beta-Blockers	metoprolol succinate 50-100mg and tartrate 50-100mg twice daily, nebivolol 5-10mg, propranolol 40-120mg twice daily, carvedilol 6.25-25mg twice daily, bisoprolol 5-10mg, labetalol 100-300mg twice daily,	Not first line agents – reserve for post-MI/CHF Cause fatigue and decreased heart rate Adversely affect glucose; mask hypoglycemic awareness
Calcium channel blockers	*Dihydropyridines*: amlodipine 5-10mg, nifedipine ER 30-90mg, *Non-dihydropyridines*: diltiazem ER 180-360 mg, verapamil 80-120mg 3 times daily or ER 240-480mg	Cause edema; dihydropyridines may be safely combined w/ B-blocker Non-dihydropyridines reduce heart rate and proteinuria
Vasodilators	hydralazine 25-100mg twice daily, minoxidil 5-10mg terazosin 1-5mg, doxazosin 1-4mg given at bedtime	Hydralazine and minoxidil may cause reflex tachycardia and fluid retention – usually require diuretic + B-blocker Alpha-blockers may cause orthostatic hypotension
Centrally-acting Agents	clonidine 0.1-0.2mg twice daily, methyldopa 250-500mg twice daily guanfacine 1-3mg	Clonidine available in weekly patch formulation for resistant hypertension

Maintenance Therapy & Reassessment

- Fixed drug combinations should be avoided in the initial stages till optimal control is achieved as fine adjustment in dosage of individual components may be required.
- Once the patient is on a stable maintenance dose of drugs, combination therapy may be used to improve compliance.
- Some drug combinations should be avoided:–
  - Two drugs of same class
  - Diuretics with β-blockers: Reported to increase incidence of new onset diabetes mellitus
  - β-blockers with verapamil: Precipitates conduction blocks

Table 6.2 Effective drug combinations

First drug		Second drug	Comment
Effective combination			
ACE inhibitor or ARB*	plus	Calcium channel blocker	Particularly useful in presence of diabetes and/or lipid abnormalities[124]
ACE inhibitor or ARB*	plus	Thiazide diuretic	Useful in presence of heart failure or post stroke
ACE inhibitor or ARB*	plus	Beta-blocker	Recommended post myocardial infarction or in patients with heart failure†
Beta-blocker	plus	Dihydropyridine calcium channel blocker	Useful in presence of symptomatic coronary heart disease
Thiazide diuretic	plus	Calcium channel blocker	
Thiazide diuretic	plus	Beta-blocker	Not recommended in presence of glucose intolerance, metabolic syndrome or established diabetes
Combinations to use with care			
Diltiazem	plus	Beta-blocker	Due to risk of heart block, but risk is less than with verapamil
ACE inhibitor or ARB	plus	Potassium-sparing diuretic	Due to risk of hyperkalaemia
Combinations to avoid			
ACE inhibitor	plus	ARB	Increased risk of renal dysfunction[120]
Verapamil	plus	Beta-blocker	Due to risk of heart block

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker


140 160 180
120 200
100 220
mmHg
80 240
60 260
40 280
20 0 300
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