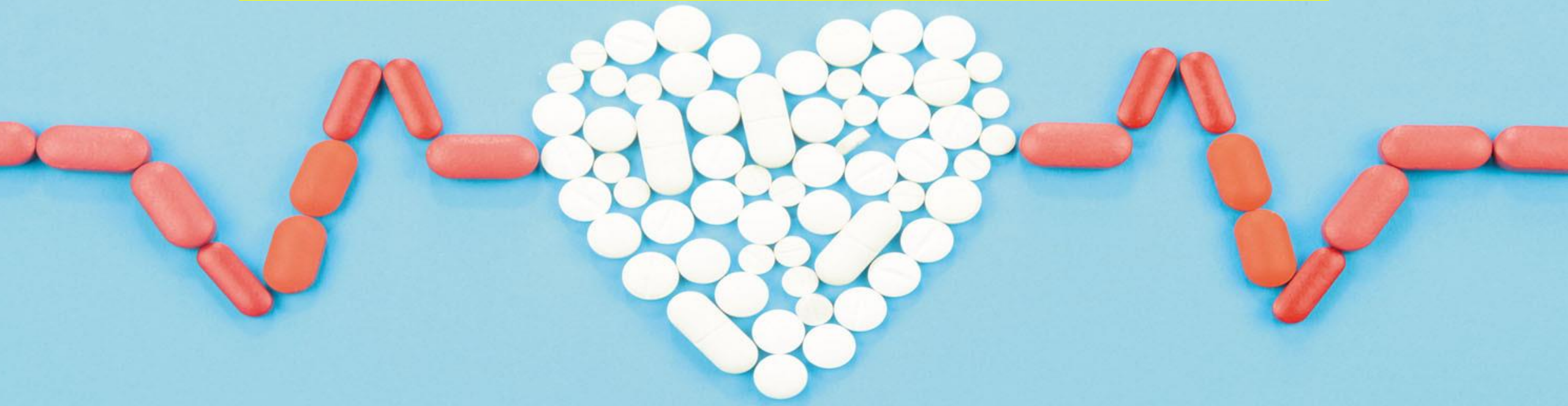
University of Anbar
College of Pharmacy
Department of Pharmacology and Toxicology

ANTIHYPERTENSIVE AGENTS



Assist.Prof.Dr.
Mohammed Mosleh Shwaish AL-Heety

HYPERTENSION

Hypertension means high blood pressure. High blood pressure is an increased pressure in blood vessels, and therefore there is less space for your blood to travel through.

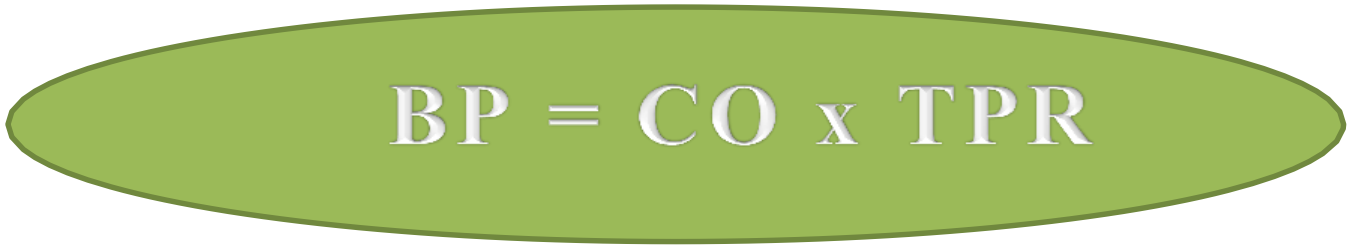
Hypertension is a major health problem with prevalence rate of 25% among adults, increasing to 50% among those above 60 years.

Hypertension causes dangerous complications (Target Organ Damage [TOD]) such as: Myocardial infarction, heart failure, aortic aneurysm, stroke and renal failure.

These complications occur commonly in high risk patients as males, elderly, smokers, diabetics, and those with high cholesterol levels.

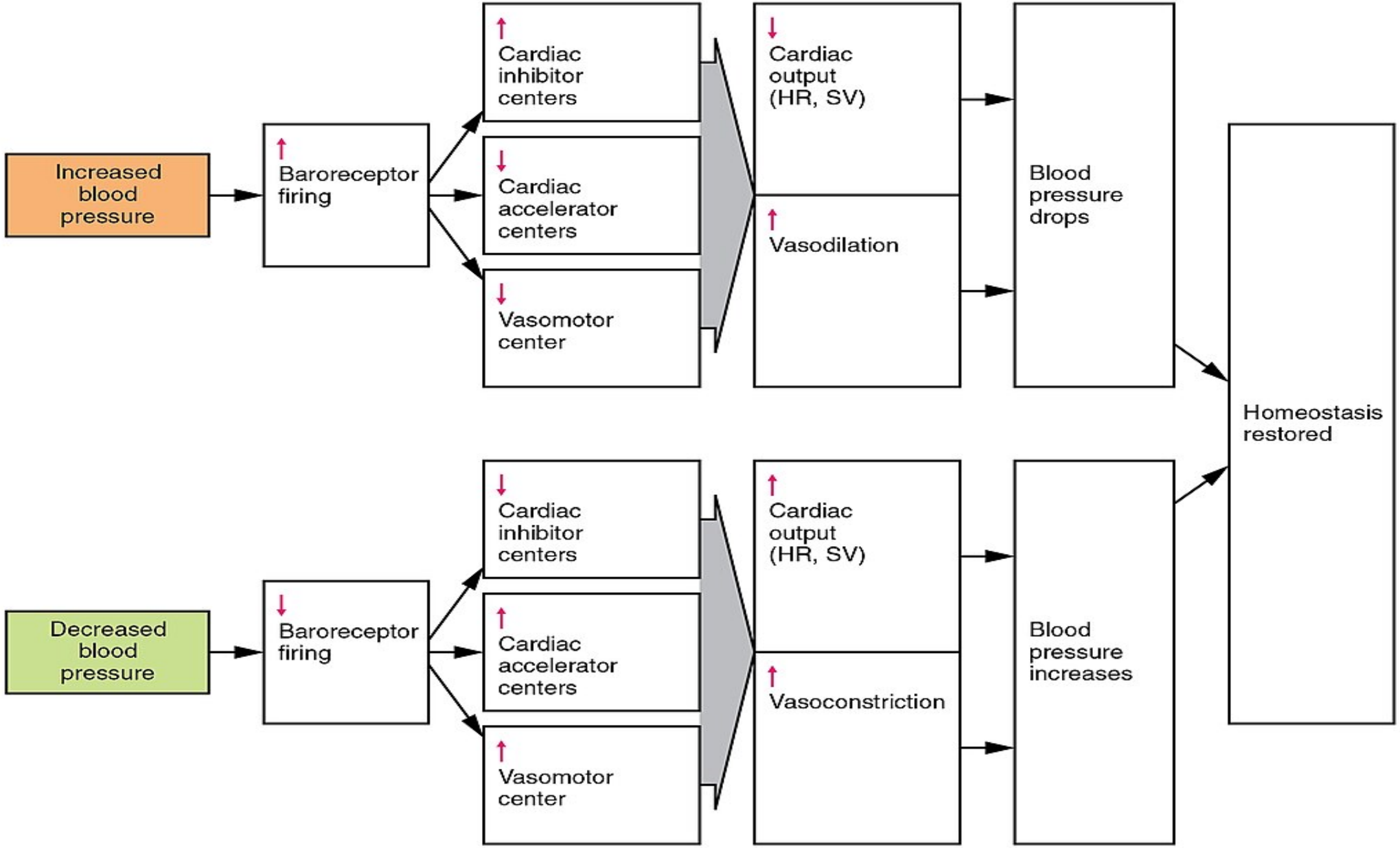
$$BP = CO \times PVR$$

Peripheral Vascular Resistance (PVR)

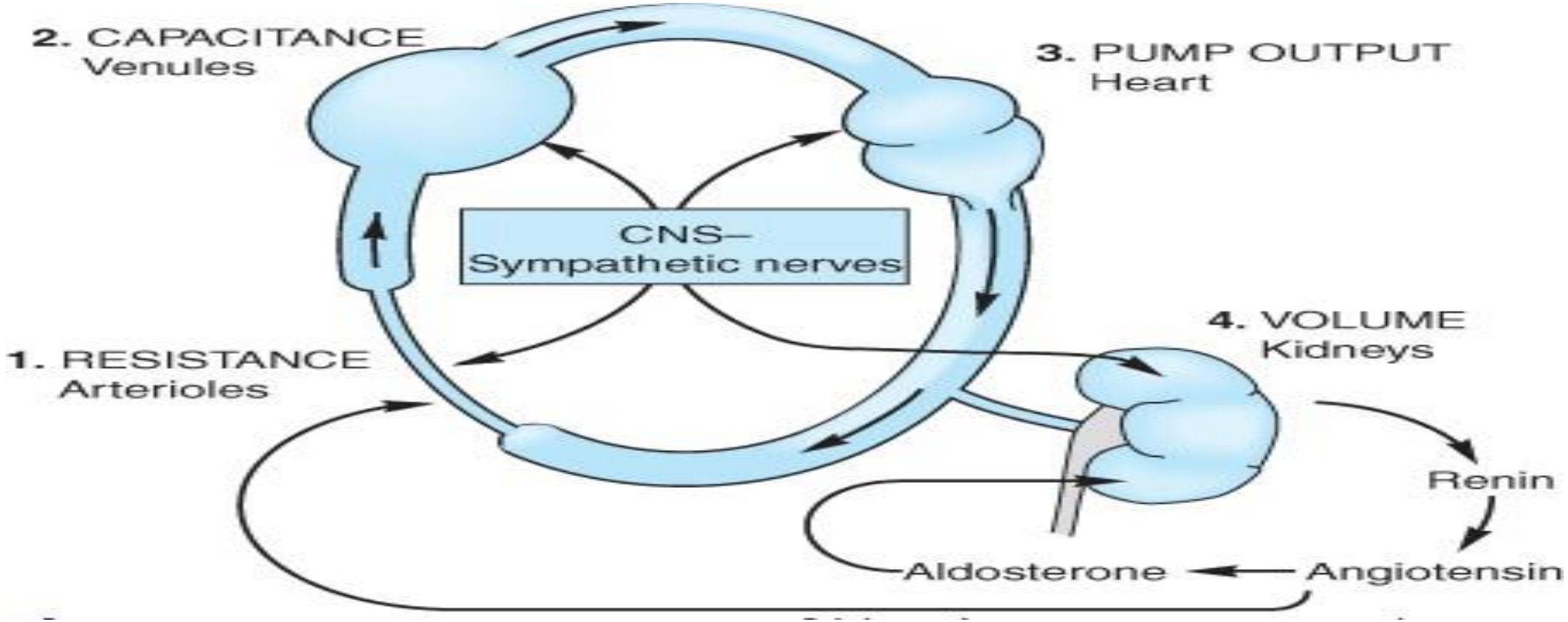


Blood pressure (BP) is determined by cardiac output (CO) and total peripheral resistance (TPR), as represented by the formula BP = CO × TPR. Cardiac output (CO) is affected by two factors, the heart rate (HR) and the stroke volume (SV), the volume of blood pumped from one ventricle of the heart with each beat (CO = HR × SV, therefore BP = HR × SV × TPR).

- The baroreceptors in the carotid sinus sense this increase in blood pressure and relay the information to the cardiovascular centres in the medulla oblongata. In order to maintain homeostasis, the cardiovascular centres activate the parasympathetic nervous system.


Increased blood pressure
↑ Baroreceptor firing
↑ Cardiac inhibitor centers
↓ Cardiac accelerator centers
↓ Vasomotor center
↓ Cardiac output (HR, SV)
↑ Vasodilation
Blood pressure drops
Homeostasis restored
Decreased blood pressure
↓ Baroreceptor firing
↓ Cardiac inhibitor centers
↑ Cardiac accelerator centers
↑ Vasomotor center
↑ Cardiac output (HR, SV)
↑ Vasoconstriction
Blood pressure increases

- CO which is dependent on myocardial contractility, heart rate, venous return and blood volume.
- TPR which is dependent on the tone of peripheral arterioles.
- CO and TPR are controlled by the sympathetic nervous system and the renin angiotensin system (RAS).
- The influx of Ca2+ into the cardiac and smooth muscles of arterioles cells- through voltage gated Ca2+ channels-increases CO & TPR respectively.



Blood Pressure Categories

American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

❁ Etiology of HPN

- Primary or essential = no specific cause (90%)
- Genetic risk
- Secondary The **cause** of hypertension is unknown and only less than 5-10% of cases are secondary to
- Hyperthyroidism
- Pheochromocytoma
- Coarctation of the aorta
- Renal vascular disease
- Adrenal cortical tumors
- Diabetes
- Obesity and dyslipidemia
- Secondary to drugs **(drug-induced hypertension)** such as:
  - Vasoconstrictors, e.g. adrenaline, noradrenaline, ephedrine & phenylephrine
  - Volume expanders, e.g. glucocorticoids, NSAIDs and oral contraceptives.

Lifestyle modification includes:

Reduced dietary intake of Na+ and fat,increased K+ intake, together with diet rich in fruits and vegetables and low-fat dairy products.
Weight reduction for overweight patients.
Regular physical exercise.
Stop smoking and reduce alcohol intake

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Hypertensive urgency

- BP ≥180/110

Emergency Hypertension

- Hypertensive urgency with end organ damage
- Ex. Hypertensive encephalopathy, angina, stroke, etc.

Hypertensive emergency is a rare but life-threatening situation characterized by severe elevations in blood pressure (systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke, myocardial infarction).

Note: A severe elevation in blood pressure without evidence of target organ damage is considered a **hypertensive urgency**.

Goal

- Decrease blood pressure to 130-140/90
- **Do not decrease more than 20% of Main arterial pressure (MAP) every hour**

is the average arterial pressure throughout one cardiac cycle, systole, and diastole. MAP is influenced by cardiac output and systemic vascular resistance, each of which is influenced by several variables.

- Proper brain perfusion

Blood pressure has to be lowered rapidly (within a few hours not minutes):

Blood pressure has to be lowered rapidly (within a few hours not minutes):

- Diazoxide (a thiazide without diuretic action), Sodium nitroprusside, Labetalol, Fenoldopam.

All are given by slow IV infusion

- Recent guidelines state that the following drugs are not
- recommended:
  - ✓ Nifedipine, nitroglycerin, and hydralazine: because these agents can cause sudden, uncontrolled, and severe reductions in BP that may precipitate cerebral, renal, and myocardial ischemic events with fatal outcomes.
  - ✓ Furosemide can lead to significant volume depletion and should be used only if there is associated volume overload as in case of pulmonary edema and acute heart failure.

Treatment

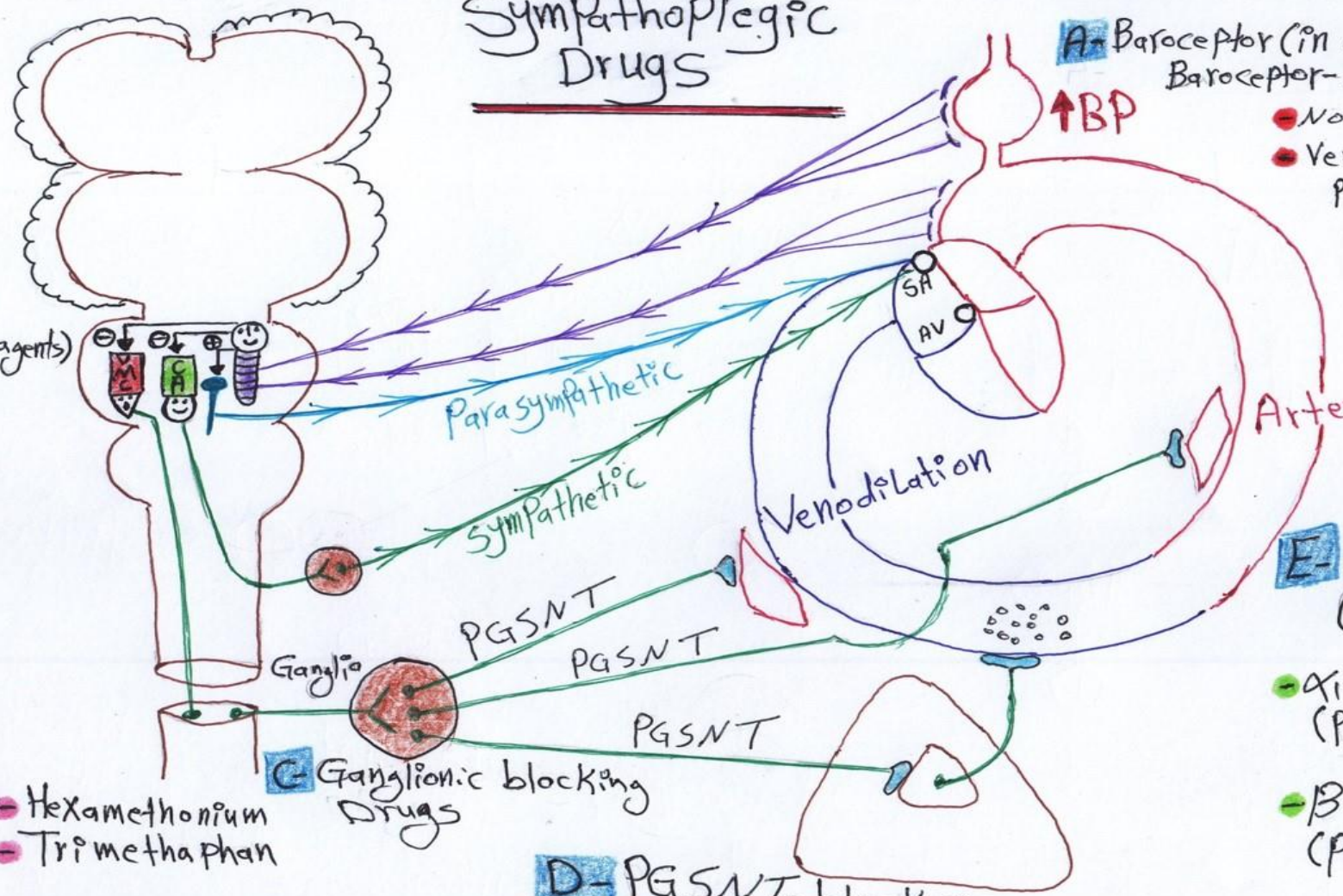
- **Pharmacologic**
  - Dependent on level of BP, presence of end-organ damage and presence of co-morbidities
  - Single/Mono-therapy vs combination therapy
- **Non-pharmacologic**
  - Diet and exercise
  - Salt restriction
  - Control co-morbidities (ex. DM)
  - Avoid other substances which may increase BP
    - Ex .cold remedies, caffeine, smoking, alcohol, contraceptives
  - Patient education

Antihypertensive agents

- 4 general mechanisms:

1) Decrease blood volume
   - Decrease sodium = Diuretics
2) Sympathoplegic agents (sympatholytic)
   - By vasodilation, ↓ cardiac function, ↑ venous pooling
   - 4 groups
3) Decrease PVR Pulmonary vascular resistance
   - Direct vasodilators
   - 4 groups
4) Inhibit RAAS
   - Block production or action of angiotensin → ↓ PVR by vasodilation and decrease aldosterone effect

Sympathoplegic Drugs



A- Baroceptor (in carotid sinus)
Baroceptor-Sensitizing agents
↑BP
- No clinical available drug
- Veratrum alkaloid (Natural product (Toxic).

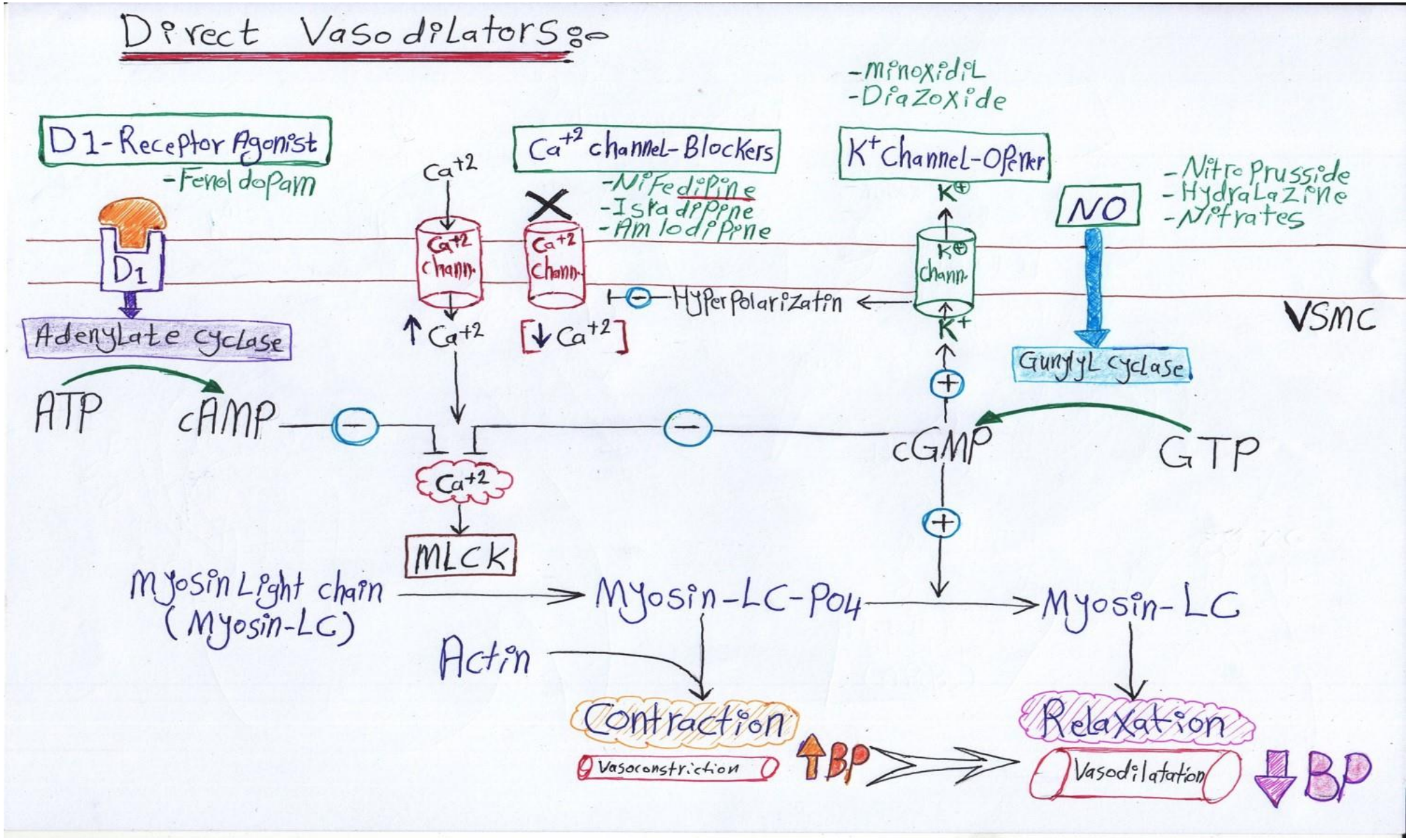
B- N.T.S
(CNS-Active agents)
α_2-Agonist
- Clonidine
- Methyldopa

C- Ganglionic blocking Drugs
- Hexamethonium
- Trimethaphan

D- PGSNT-blockers
- Reserpine
- Guanethidine
- Guanadrel

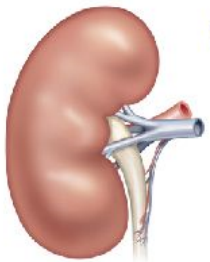
E- Adrenoceptor-blockers (α or β-blockers)
- α_1-blockers:- ≃ zosin (Prazosin, doxazosin)
- β-blockers:- ≃ olol (Propranolol, Atenolol)

= Nucleus of tractus Solitarius (N.T.S)
= Cardiac Inhibitary center
CA = Cardioaccelerator Center
VM = Vasomotor Center (V.M.C) / PGSNT = Post Ganglionic Sympethetic Nerve Terminal

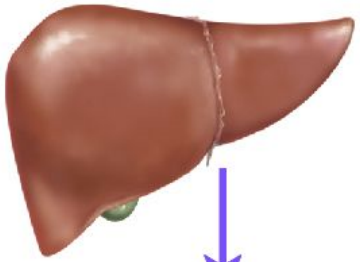

Direct Vasodilators:-
D1-Receptor Agonist
-Fenoldopam
D1
Adenylate cyclase
ATP
cAMP
Ca+2
Ca+2 Chann.
↑Ca+2
Ca+2 channel-Blockers
-Nifedipine
-Isradipine
-Amlodipine
X
Ca+2 Chann.
[↓Ca+2]
Ca+2
MLCK
Myosin Light chain
(Myosin-LC)
Actin
Contraction
Vasoconstriction
↑BP
-minoxidil
-Diazoxide
K+ channel-Opener
K+
K+ Chann.
K+
Hyperpolarization
NO
-Nitroprusside
-Hydralazine
-Nitrates
Gunylyl cyclase
cGMP
GTP
Myosin-LC-PO4
Myosin-LC
Relaxation
Vasodilatation
↓BP
VSMC

Renin-angiotensin system

Drop in blood pressure
Drop in fluid volume



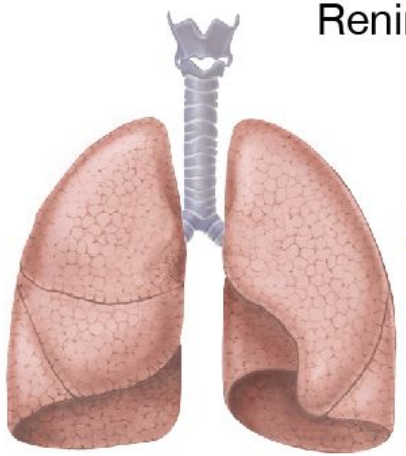
Renin release from kidney



liver

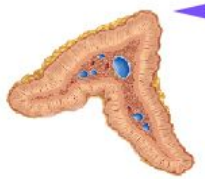
angiotensinogen

Renin acts on angiotensinogen to form **angiotensin I.**

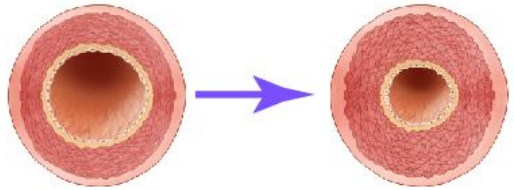


ACE (angiotensin-converting enzyme) release from lungs

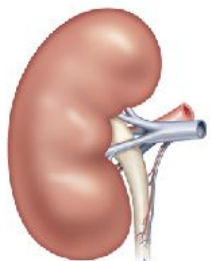
ACE acts on angiotensin I to form **angiotensin II.**



Angiotensin II acts on the adrenal gland to stimulate release of **aldosterone.**

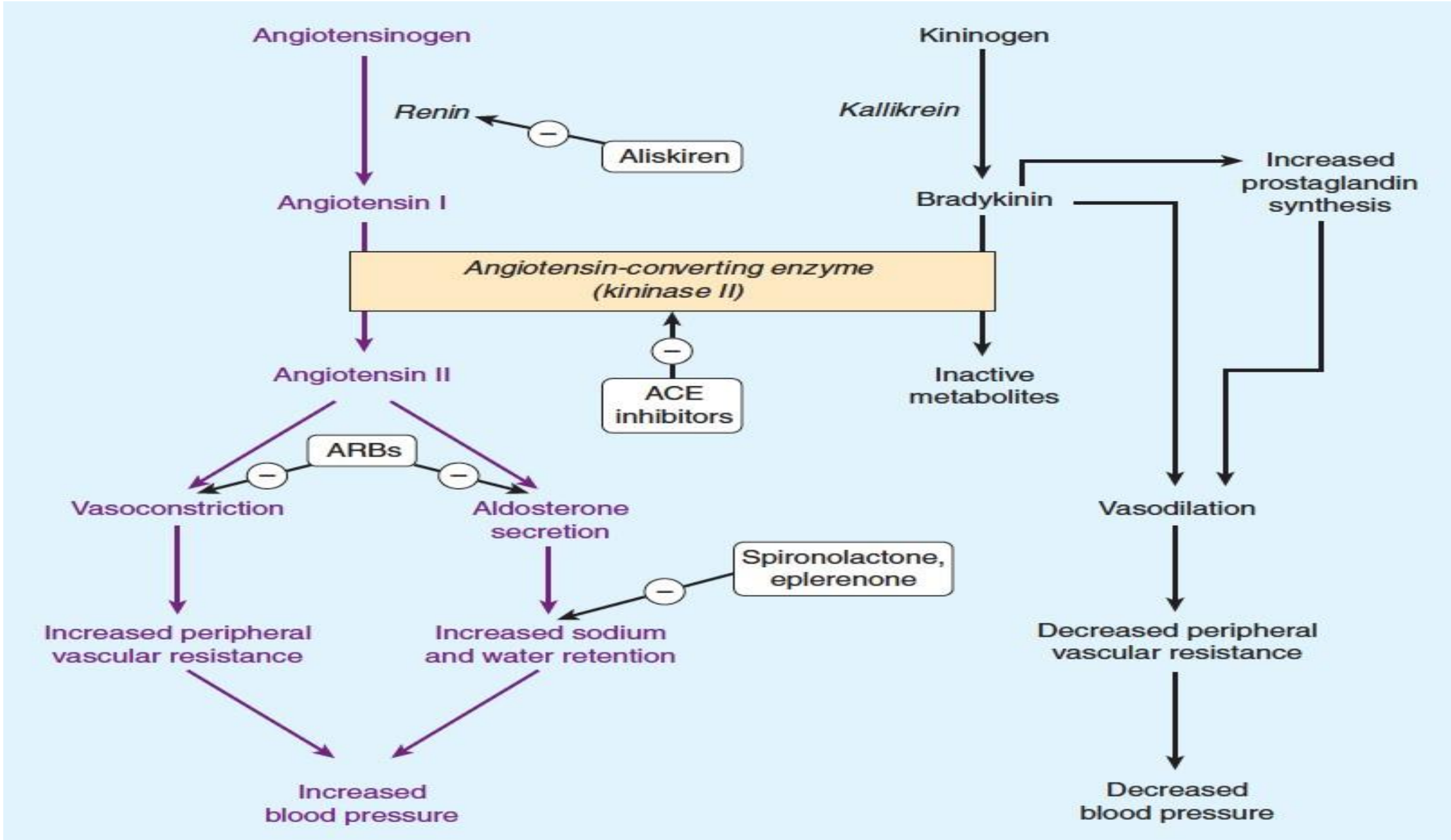


Angiotensin II also acts directly on blood vessels, stimulating vasoconstriction (narrowing).



NaCl
H_2O

Aldosterone acts on the kidneys to stimulate reabsorption of salt (NaCl) and water (H_2O).

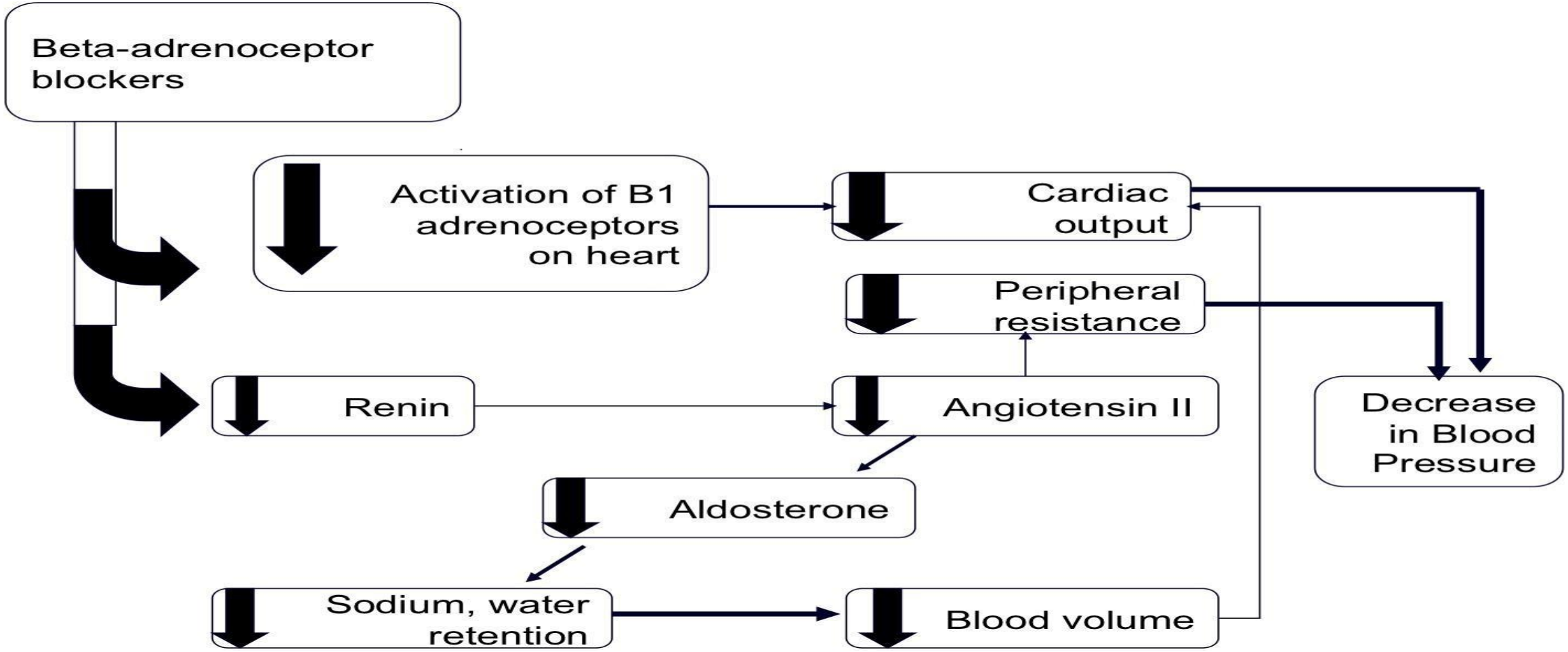

Angiotensinogen
Renin
Aliskiren
Angiotensin I
Angiotensin-converting enzyme
(kininase II)
Angiotensin II
ACE
inhibitors
ARBs
Vasoconstriction
Aldosterone
secretion
Spironolactone,
eplerenone
Increased peripheral
vascular resistance
Increased sodium
and water retention
Increased
blood pressure
Kininogen
Kallikrein
Bradykinin
Increased
prostaglandin
synthesis
Inactive
metabolites
Vasodilation
Decreased peripheral
vascular resistance
Decreased
blood pressure

β-Receptors

- Distributed throughout the body
  - concentrate differently in certain organs & tissues
- β1 receptors:
  - heart, kidney
  - stimulation increases HR, contractility, renin release
- β2 receptors:
  - lungs, liver, arteriolar smooth muscle
  - stimulation causes bronchodilation & vasodilation
  - mediate gluconeogenesis & glycogenolysis

Mechanism of Action:

- Reduction in cardiac output
- Reduction in renin secretion



Properties of Beta-blockers

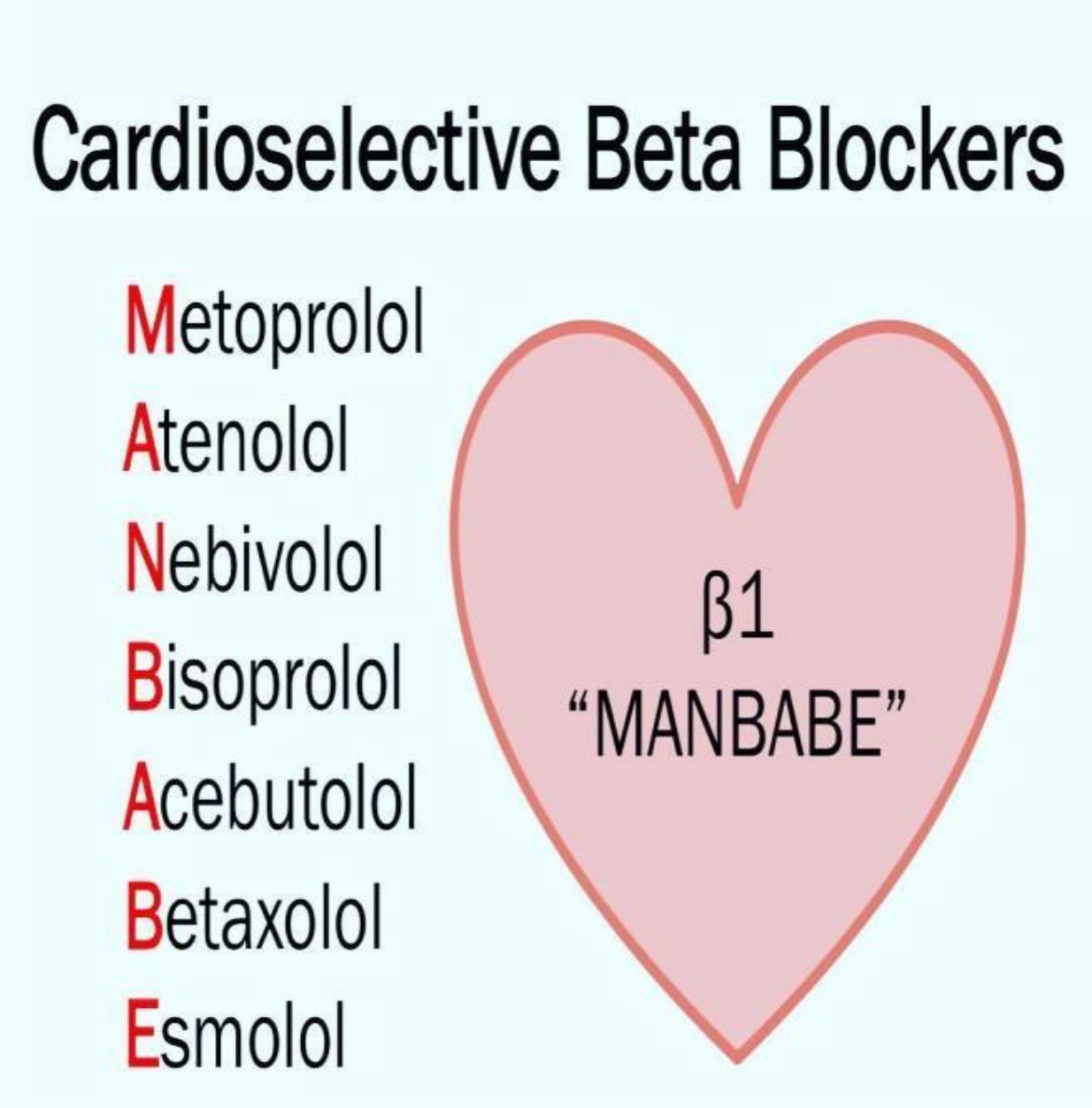
1. *β1-receptor selectivity*
2. *Intrinsic sympathomimetic activity (ISA)*
3. *Membrane stabilising activity*
4. *Pharmacokinetics*

1. β1-receptor selectivity

- Greater affinity for β1 than β2 receptors
- Inhibit β1 receptors at low to moderate dose
- Higher doses block β2 receptors
- Safer in patients with bronchospastic disease, peripheral arterial disease, diabetes
- May exacerbate bronchospastic disease when selectivity lost at high doses
- Dose where selectivity lost varies from patient to patient
- Generally preferred β1-blockers for HTN

CARDIOSELECTIVITY

- Selective β1
  - ✓ Atenolol, Acebutolol and Metoprolol
- Nonselective β1 & β2
  - ✓ Propranolol, Pindolol, Oxprenolol, Timolol, Sotalol and Nadolol
- Mixed α- and β-blockers
  - ✓ Carvedilol, Labetolol



Overview of Beta Blockers

Non-Selective β1 & β2

- Nadolol
- Propranolol
- Timolol
- Sotalol

Cause bronchoconstriction, peripheral vasoconstriction & metabolic imbalances

with ISA

- Acebutolol
- Pindolol

Associated with less resting bradycardia & less peripheral vasoconstriction

ISA = Intrinsic Sympathomimetic Activity

Mixed β1, β2 & α1

- Carvedilol
- Labetalol

Cause vasodilation due to α1 blocking action

Cardio-Selective* β1

Preferred in angina, MI, & certain types of arrhythmias, etc

*Dose dependent

- Acebutolol
- Atenolol
- Betaxolol
- Bisoprolol
- Esmolol
- Metoprolol
- Nebivolol

HFrEF Mortality Benefit

- Carvedilol
- Bisoprolol
- Metoprolol Succinate

Intrinsic Sympathomimetic Activity (ISA) is a property of certain beta blockers that allows them to partially stimulate beta-adrenergic receptors instead of completely blocking them, as traditional beta blockers do.

How does it work?

• Regular beta blockers (like Propranolol) fully block beta-adrenergic receptors, reducing the effects of adrenaline and noradrenaline on the heart and cardiovascular system.

• Beta blockers with ISA partially block these receptors while simultaneously providing mild stimulation. In other words, they act as partial agonists.

Why is ISA important?

• Prevents excessive slowing of the heart rate (bradycardia): Beta blockers with ISA do not cause the heart rate to drop too low at rest.

• Maintains heart rate response during exercise or stress, unlike beta blockers without ISA, which may blunt this response.

• Suitable for patients who have naturally low resting heart rates or are at risk of hypotension.

Clinical uses:

• Treatment of hypertension or angina in patients with a low resting heart rate.

• Patients who require beta blockers but are prone to significant bradycardia.

Drawbacks of ISA beta blockers:

• Less effective in reducing the risk of heart attacks compared to non-ISA beta blockers.

• May not be suitable for conditions requiring full suppression of sympathetic activity, such as heart failure.

2. Intrinsic sympathomimetic activity (ISA)

Pindolol, Oxprenolol, Acebutolol, Carteolol

β -blockers may also stimulate β receptors (partial agonists) at the same time as they also block the effect of catecholamines.

- fewer falls in resting heart rate than the β -blockers without ISA
- less effective in severe angina pectoris in which reduction in heart rate is particularly desirable
- less likely to produce cold extremities

Membrane-Stabilizing Activity (MSA) in beta blockers refers to their ability to reduce the excitability of cell membranes by altering ion flow across them, particularly in cardiac cells.

How does it work?

- Beta blockers with MSA inhibit the flow of sodium and potassium ions across cardiac cell membranes.
- This modulates the action potential of cardiac cells, making them less excitable.
- The mechanism is similar to that of Class I antiarrhythmic drugs.

Significance of MSA:

- Reduces excitability of cardiac cells: Helps suppress abnormal electrical activity.
- Antiarrhythmic effects: Useful in managing or preventing certain cardiac arrhythmias.

Clinical applications:

- Cardiac arrhythmias: Such as atrial fibrillation or ventricular tachycardia.
- Post-myocardial infarction: To stabilize cardiac electrical activity and reduce arrhythmia risk.

Clinical relevance:

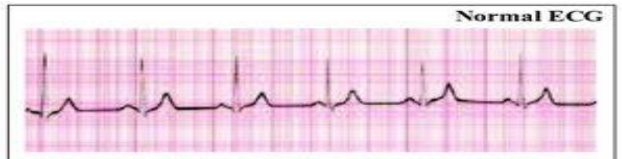
- MSA is not usually the primary consideration when choosing a beta blocker for treatment.
- The doses used in clinical practice are often too low to exhibit significant MSA effects.

3. Membrane stabilizing activity

(quinidine-like, local anaesthetic or cardiac depressant action)

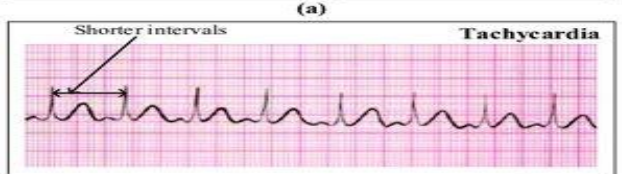
Propranolol, Oxprenolol, Acebutolol , Metoprolol (to a lesser extent)

This effect is probably clinically not important except that when applied topically for glaucoma that these agents will anaesthetise the eye therefore timolol (which does not have an MSA) is used in this condition.



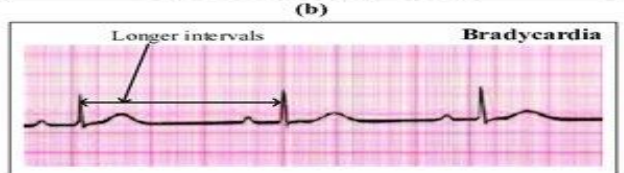
Rythm: Regular; Heart rate (bpm): 60-100; # of Ps: 1;
PR: 120-200ms; QRS: <120 ms

(a)



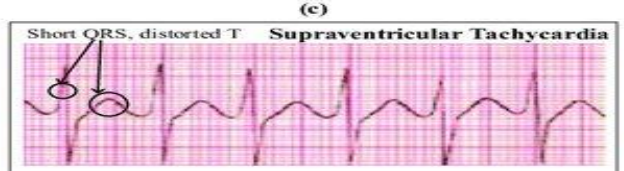
Rythm: Regular; Heart rate (bpm):>100; # of Ps: 1;
PR: 120-200ms; QRS: <120 ms

(b)



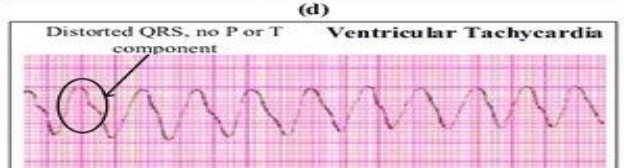
Rythm: Regular; Heart rate (bpm): <60; # of Ps: 1;
PR: 120-200ms; QRS: <120 ms

(c)



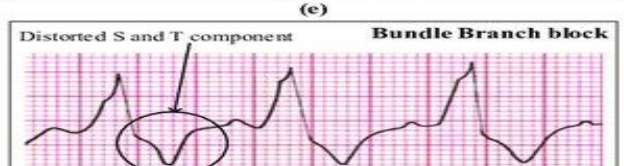
Rythm: Regular; Heart rate (bpm): >150; # of Ps: 1;
PR: -; QRS: <40 ms

(d)



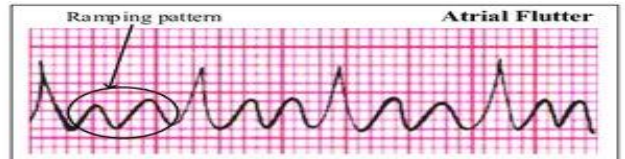
Rythm: Regular; Heart rate (bpm): >100; # of Ps: No;
PR: No; QRS: >120 ms

(e)



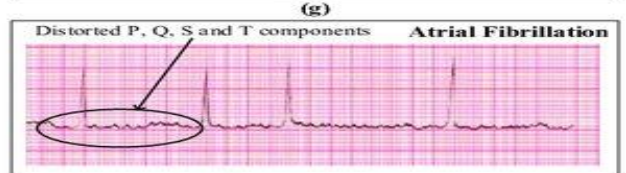
Rythm: Regular; Heart rate (bpm): Any; # of Ps: 1;
PR: -; QRS: >120 ms

(f)



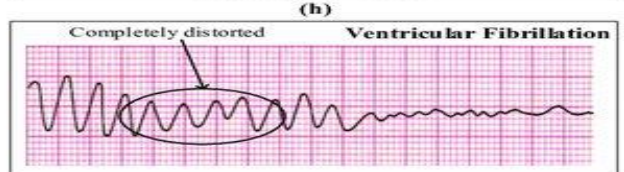
Rythm: Regular; Heart rate (bpm): Any; # of Ps: >1;
PR: No; QRS: <120 ms

(g)



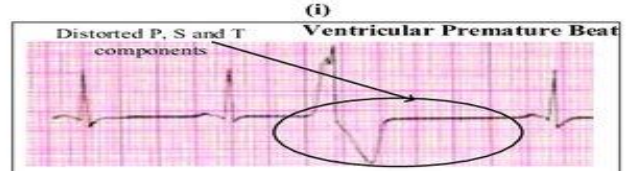
Rythm: Irregular; Heart rate (bpm): Any; # of Ps:> 1;
PR: No; QRS: <120 ms

(h)



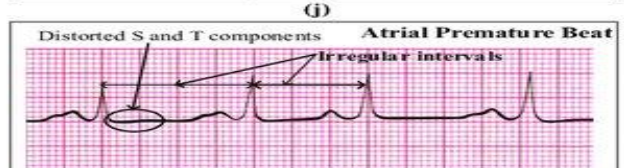
Rythm: Irregular; Heart rate (bpm): >250; # of Ps: No;
PR: No; QRS: >120 ms

(i)



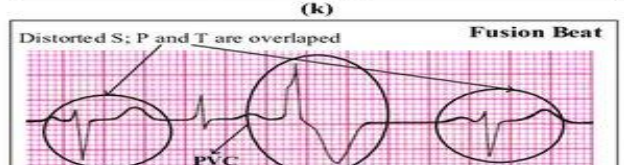
Rythm: Regular; Heart rate (bpm): -; # of Ps: No; PR: -;
QRS: >120 ms

(j)



Rythm: Regular[1]; Heart rate (bpm): Any; # of Ps: 1[2];
PR: >120ms; QRS: -

(k)



Rythm: Regular; Heart rate (bpm): Any; # of Ps: No;
PR: -; QRS: >120 ms

(l)

4. Pharmacokinetics

- Some of the metabolites of β-blockers are pharmacologically active
  - propranolol forms 4-hydroxypropranolol
- Degree of hepatic metabolism
  - 100% (propranolol, oxprenolol)
  - 50-60% (sotalol and pindolol)
  - no metabolism (atenolol).

- Elimination of β –blockers
  - Atenolol and practolol are excreted almost entirely by the kidney
  - Propranolol and metoprolol are eliminated almost entirely by the liver
  - Pindolol is partly eliminated by the liver and partly by the kidneys

Pharmacologic & pharmacokinetic properties of β-adrenergic blockers

Drug	Adrenergic receptor blocking activity	Membrane stabilizing activity	Intrinsic sympathomimetic activity	Lipid solubility	Half-life (hr)	Elimination
Acebutolol	B_1	+	+	Low	3–4	Hepatic, renal, bile
Atenolol	B_1	0	0	Low	6–9	Unchanged (50%)
Betaxolol	B_1	+	0	Low	14–22	Hepatic
Bisoprolol	B_1	0	0	Low	9–12	Unchanged (50%)
Esmolol	B_1	0	0	Low	0.15	Esterases in RBCs
Metoprolol	B_1	0	0	Moderate	3–7	Hepatic, renal
Carteolol	B_1, B_2	0	++	Low	6	Unchanged (50–70%)
Nadolol	B_1, B_2	0	0	Low	20–24	Unchanged
Penbutolol	B_1, B_2	0	+	High	5	Hepatic
Pindolol	B_1, B_2	+	+++	Moderate	3–4	Renal, unchanged
Propranolol	B_1, B_2	++	0	High	3–5	Hepatic
Sotolol	B_1, B_2	0	0	Low	12	Unchanged
Timolol	B_1, B_2	0	0	Low to moderate	4	Hepatic
Labetalol	B_1, B_2	0	0	Moderate	5.5–8	Hepatic, unchanged

Indications

A. Cardiovascular Indications:

1. Arterial hypertension
2. Arrhythmias
3. Angina pectoris
4. Coronary heart disease (e.g. after M.I)

B. Non cardiovascular indications:

1. Glaucoma
2. Thyrotoxicosis (increase numbers & sensitivity of beta receptors)
3. Migraine
4. Phaeochromocytoma (with alpha blockers)
5. Certain types of tremors
6. Esophageal varices
7. Alcohol withdrawal

Adverse effects

1. AV-block
2. Badycardia
3. Bronchoconstriction
4. Cardiac failure
5. Cold extremities (peripheral vasoconstriction)
6. Decrease HDL & increase LDL (adverse lipid profile)
7. Hypoglycemia or interference with recovery from hypoglycemia or masking of hypoglycemic symptoms (tachycardia, sweating & tremor)
8. Sleep disturbance and nightmares (e.g. propranolol- lipid soluble)
9. Sexual dysfunction

Cautions/Contraindications

1. Abrupt withdrawal (discontinuation) of β-blockers (can result in a rise in blood pressure, and in patients with heart disease, chest pain, heart attack, and even **sudden** death.)
2. AV-block (2^{nd} or 3^{rd} degree)
3. Badycardia
4. Bronchospastic diseases (Asthma, COPD)
5. Diabetes
6. Renaud's disease
7. Intermittent claudication
8. Renal or hepatic impairment
9. heart failure
10. Intermittent claudication
11. Pregnancy (fetal bradycardia and neonatal hypoglycaemia)

Thank you….