CVS
PHARMACOLOGY

Modified NO: 2

كتابة: باسل صلاح

تدقيق: ميس قشّوع

الدكتور: مالك زحلف

❖ **Remember:**

➔ Some patients develop **resistant hypertension** after being treated with **first-line therapy** for hypertension; which includes ACE inhibitors, ARB's, calcium channel blockers, diuretics, beta-blockers & alpha-1-blocking agents.

➔ Patients with **resistant hypertension** are then treated with **second-line therapy** for hypertension; which includes several options such as: clonidine & methyldopa.

➔ Furthermore, if the second-line therapy **doesn't treat** resistant hypertension ➔ then the next treatment options are most likely going to be **vasodilators!**

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- Slides
- Doctor
- Additional info
- Important

In today's lecture, we are going to study & discuss **vasodilators** & their activity as **antihypertensives :DD**

❖ **The flow of information in this lecture:**

1. Discussing vasodilators in general.
2. Discussing hydralazine (The first drug).
3. Discussing minoxidil (The second drug).
4. Discussing nitroprusside (The third drug)
5. Discussing fenoldopam (The final drug in this lecture).
6. Discussing hypertension emergency.
7. Discussing how vasodilators can lead to increased arterial pressure

Firstly, we will discuss vasodilators in general 😄

Their general MOA, side effects and drugs used in combination with them 💊

❖ **Vasodilators come in 4 types** (depending on their MOA):

1) Vasodilators which **produce NO**
➔ NO activates guanylyl cyclase ➔ which in turn increases intracellular cGMP ➔ resulting in relaxing vascular smooth muscle.
➔ for example: nitrates & **nitroprusside**.

2) Vasodilators which have **activity** towards **Ca^{2+}**
➔ they inhibit calcium transport to the interior of the smooth muscle cells ➔ leading to their relaxation (as calcium is responsible for muscle contraction).
➔ for example: **hyrdalazine**.

3) Vasodilators which **induce** more **efflux** of **K^{+}**
➔ increased K+ permeability stabilizes the membrane at its resting potential and makes contraction less likely.
➔ for example: **minoxidil** & **diazoxide**.

4) Vasodilators which are **dopamine agonists**
➔ Dopamine is normally an endogenous vasodilator.
➔ for example: **fenoldopam**.

Vasodilator

- These agents are a smooth muscle relaxants, such as Hydralazine and minoxidil.

➔ The main focus in this lecture is on **hydralazine** & **minoxidil**; as they are administered **orally**.

➔ Examples on drugs administered by **infusion**: **fenoldopam** & **nitroprusside**.

➔ Furthermore, **hydralazine** is considered a "**special drug**", as it is used in treating **African-Americans** or **black people** in general.

➔ Remember: **black people** (African-Americans) generally have a **lesser** blood pressure response to **ACE inhibitors**; so we have to utilize other options.

➔ **(hydralazine + isosorbide mononitrate)** is a well known combination of drugs, as well as it is considered as one of the **first-line therapies** to treat **heart failure** in **black people**.

Vasodilator

➔ You have to remember & keep in mind that all **vasodilators** are associated with **2** well-known **side effects**:

1) They produce **reflex tachycardia.**
2) They also have an effect of **sodium & water retention** through 2 ways:
    1. Either through a **direct** effect towards the **kidneys**.
    2. Or through the effect of **baroreceptors** (which detect changes in blood pressure) ➔ which activate **beta-1 receptors** (as a result of decreased blood pressure) ➔ which in turn will lead to **increased renin production**.

➔ **Collectively**, these **side effects** of vasodilators need to be **controlled.**

➔ This **control** can be achieved by **combining** the vasodilators (ex. Hydralazine) with other drugs, such as **diuretics** & **beta-blockers**.

Vasodilator

- They produce reflex stimulation of the heart resulting in increasing the myocardiac contractibility, heart rate, and oxygen consumption, so they may prompt angina, Myocardiac Infarction in predisposed individuals .

- They increase plasma renin concentration, which resulting in sodium and water retention.

- These unwanted effects can be blocked by the combination with a diuretics and a β blocker.

All are mentioned in the previous slide.

❖ Now, we are going to **differentiate** between **hydralazine** & **minoxidil** in regarding which drugs are most appropriately **combined** with each one of them:

1) **Hydralazine**: **thiazide diuretics** are enough to deal with sodium & water retention in the case of hydralazine.
2) **Minoxidil**: the sodium & water retention is **quite profound** in the case of minoxidil ➔ which requires a **loop diuretic** in order to deal with it.

✓ Also, you need to understand that **loop diuretics** have many **profound side effects** that must be taken care of.

✓ Examples on these side effects: **hypokalemia**, **hyponatremia**, **hypovolemia**, **hypomagnesemia** & **hypocalcemia**.

✓ However, the resulting **hypocalcemia doesn't** require medical intervention, because **Ca^{2+}** is controlled by other mechanisms in our **body**.

➔ **Despite** the type of the diuretic used with hydralazine and minoxidil; we also combine each one of them with **beta-blockers** in order to control the **reflex tachycardia**.

❖ A quick **summary** of the **combinations** of drugs used with **vasodilators** in order to deal with their **side effects**:

1) **Hydralazine** is combined with a **thiazide diuretic** & a **beta-blocker**.
2) **Minoxidil** is combined with a **loop diuretic** & a **beta-blocker**.

Now, we are going to discuss hydralazine 🔥

Its MOA, special side effects & few clinical notes regarding it 💊 💪

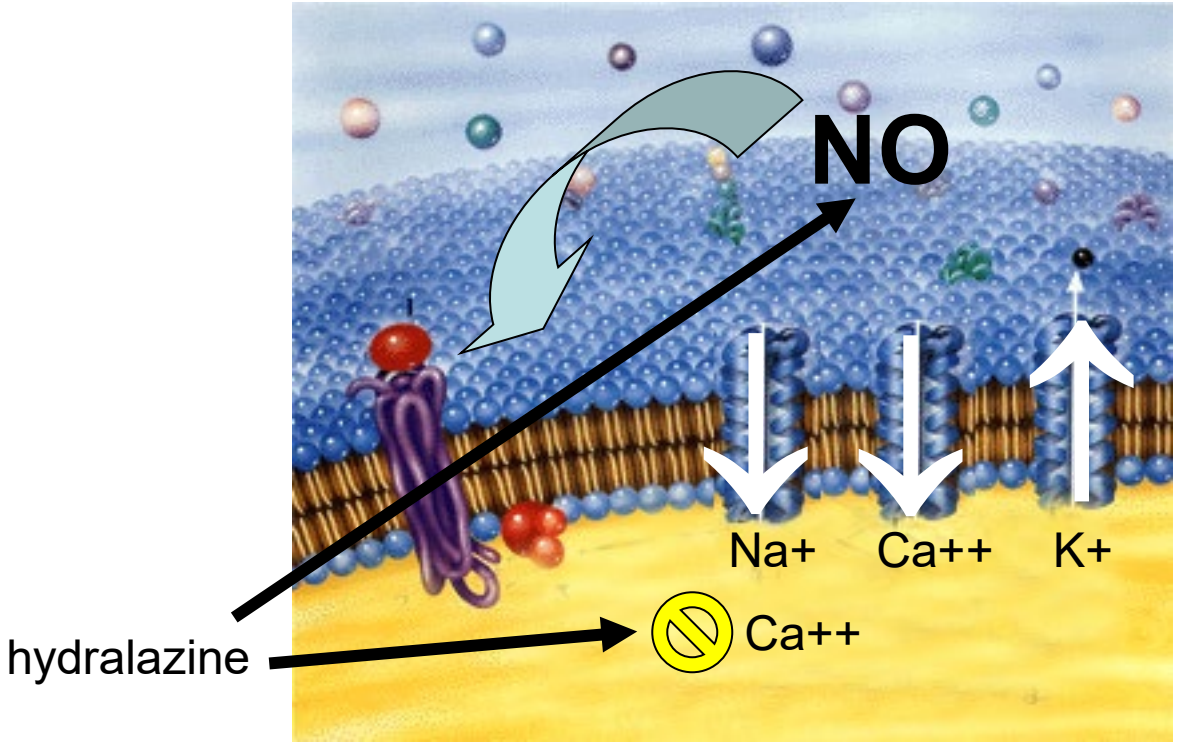
Mechanism of Action of Hydralazine

➔ In general, **hydralazine** has **2** effects/ molecular mechanisms of action:

1) Hydralazine has the ability to produce NO (nitrous oxide) ➔ NO increases **intracellular cGMP** ➔ which will result in the **dephosphorylation** of the **myosin** ➔ ultimately leading to vascular smooth muscle **relaxation**.

2) Hydralazine has the ability to **reduce** the level of the **calcium** within the **smooth muscles** (the **most important** effect of hydralazine).

➔ The effect of **decreased intracellular calcium levels** is **more important** & more linked to hydralazine than the effect of NO production.



How Does Hydralazine Reduce Calcium Levels within Smooth Muscles?

1) Some evidence suggests that hydralazine **inhibits IP3** (the molecule which **induces** the **release** of **calcium** from **intracellular storage sites** inside **vascular smooth muscles**) ➔ leading to diminished concentrations of calcium within the smooth muscles.

2) Another evidence suggests that hydralazine promotes arterial dilation through **opening high-conductance calcium-activated potassium channels**, and so on and so forth.

➔ What you must know is that hydralazine **reduces** the **concentration** of **calcium intracellularly** ➔ leading to a **nice arterial dilation** rather than venous dilation.

➔ This arterial dilation will have an activity towards the **baroreceptors** leading to **reflex tachycardia** & **reflex renin release** and **water & sodium retention**.

➔ Keep in mind that the **MOA** of hydralazine is **more towards** the **reduction** of **calcium levels** inside **vascular smooth muscles.**

❖ **Remember:**

➔ There are two major pathways/phases of **drug metabolism**:

1) **Phase1**: which primarily involves **CYTP450**, for example: metabolic reactions involving hydroxylation, dealkylation, sulfoxidation, hydrolysis, oxidation & reduction.

2) **Phase 2**: which involves **conjugation reactions** through adding certain groups to a drug in order to make it more polar & readily excreted, for example: **acetylation** & **glucuronidation**.

Special Side Effects of Hydralazine

➔ In general, **vasodilators** induce **headaches**, **reflex tachycardia** and **water & sodium retention**.

➔ Hydralazine specifically has a **special type** of **side effects**; which is known as **lupus-like syndrome** (which is more towards an **autoimmune** disease).

➔ Lupus-like syndrome is associated with the **acetylation reaction** (a **phase 2** reaction); thus, the **acetylator phenotype** is important regarding this syndrome, as it is related to the **lupus-induced cytotoxicity** of **hydralazine**.

➔ This type of side effects (lupus-like syndrome) is related to the **length** of the **period of time** in which the patient **continues administering hydralazine** ➔ if a patient keeps taking hydralazine for more than **6 months**; then they may **develop lupus-like syndrome**.

➔ Furthermore, lupus-like syndrome is **dose-dependent** ➔ if the dose is **50 mg**, then hydralazine **won't** produce **lupus-like syndrome** in anyone ➔ however, if the dose of hydralazine is **100 mg**, then there will be a **5%** chance of developing **lupus-like syndrome** ➔ and if the dose of hydralazine is **200 mg**, then there will be a **10%** increase in **induction** of **lupus-like syndrome**.

Special Side Effects of Hydralazine

➔ **Lupus-like syndrome** is **more probable** in **females** than in males, as **females** have **four times higher incidence rate** than males ➔ because the **immune system** is really **different** between males & female ➔ as **estrogen** in females **increases** the **activity** of **T-cells** (generally speaking) & **increases** the **autoimmunity** ➔ thus, generally, **autoimmune diseases** occur more in **females**, like rheumatoid arthritis (which is a white lady disease rather than a white man disease) ➔ so, **hydralazine** is **better** to be used with **males**.

➔ Furthermore, **lupus-like syndrome** is seen **more** in **caucasians** than in **black people** ➔ so, **hydralazine** is **better** to be used with **black people**.

➔ All the previous points are important to take into consideration regarding the **pharmacological effect** of hydralazine and for the **indications** of it.

Clinical Notes Regarding Hydralazine

➔ Because of the **special side effects** of **hydralazine**; it is **not considered** a **first-line therapy**.

➔ However, there are **pills** given to **heart failure patients** which contain **isosorbide dinitrate** with **hydralazine** (brand name: BiDil); as they are **widely used** to deal with **heart failure**.

➔ But, **how** is **hydralazine given** to **patients**?

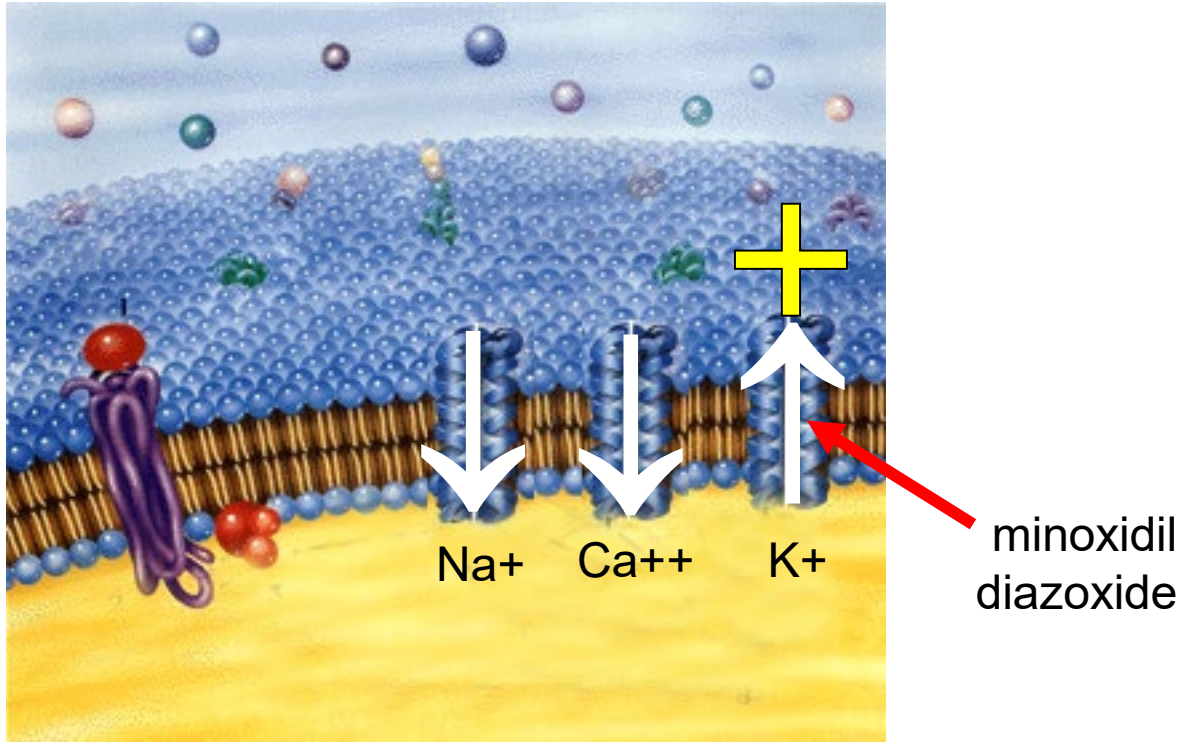
➔ We initially give the patient **25 mg's**, and if it is **insufficient**, we **gradually increase** the **dose** to **50 mg's**, and if the patient remains **unresponsive** to treatment; we **increase** the dose to **75 mg's** and **100 mg's** until the patient becomes **responsive** to treatment.

The next drug we are going to discuss is minoxidil!

Its MOA & side effects 🪮 👾

MOA of Minoxidil

➔ **Minoxidil** opens **potassium channels (ATP-dependent/ modulated potassium channels)** ➔ causing **more efflux** of **potassium** ➔ leading to **increased hyperpolarization** ➔ ultimately leading to the **relaxation** of the smooth muscles (relaxation occurs **more** at the level of **arteries** (vascular relaxation rather than venous relaxation)).



General Notes Regarding Minoxidil

Remember the general side effects of vasodilators (including minoxidil):

➔ More **renin release** & activation leading to **more sodium & water retention.**

➔ And in the case of **minoxidil**, sodium & water retention can be **controlled** by **loop diuretics** rather than **thiazide diuretics** (which are used to control water & sodium retention induced by **hydralazine**) ➔ as the water & sodium retention induced by minoxidil is **quite profound** (as it could lead to **edema formation**) & could **not** be controlled by a **thiazide** diuretic as it is **not sufficiently efficacious.**

➔ So, it may be **necessary** to use **loop diuretics** (**large doses** are required if the side effects are **profound** enough in order to prevent edema formation) especially if the patient has any degree of **renal dysfunction.**

➔ Activation of **baroreceptors** leading to **reflex tachycardia.**

➔ The **cardiac consequences** of **baroreceptor-mediated activation** of **sympathetic system** due to the administration of **minoxidil** are **similar** to those seen with the hydralazine

➔ These cardiac consequences are: **increased heart rate**, **myocardiac contractility** & **oxygen consumption.**

➔ It is **important** to fight these cardiac consequences & deal with them; and the **ideal treatment** for this side effect is using **beta-blockers**.

Main Side Effects of Minoxidil

➔ The **main side effect** of **minoxidil** is **hypertrichosis** (excessive hair growth on any part of the body) ➔ which occurs in patients who administer minoxidil for an **extended period of time**.

➔ **Hypertrichosis** is probably a **consequence** of **potassium channel activation**.

➔ Growth of hair occurs on the **face**, **back**, **arms** & **legs** ➔ so, it is particularly **offensive** to **women**.

➔ Minoxidil can be given **topically** in order to treat **loss of hair**; an **example** of topical minoxidil: **Rogaine**, it is marked as an **OTC (over-the-counter)** drug. Furthermore, Rogaine is used on the **top** of the **head** to treat **male pattern baldness** and **hair thinning & loss** in **women**; so it is used for **males** & **females**.

➔ However, in the case of **hypertension**, minoxidil is best **reserved** for the treatment of **severe hypertension** & if the patient was **unresponsive** to other **therapies**; because it is considered **offensive** to **women**.

➔ Minoxidil generally is considered a **good drug** especially in **male patients** with **renal insufficiency.**

➔ Remember: minoxidil must be **combined** with a **beta-blocker** (for the **reflex tachycardia**) & a **loop diuretic** (for the **water & sodium retention**).

Now, we are going to discuss nitroprusside

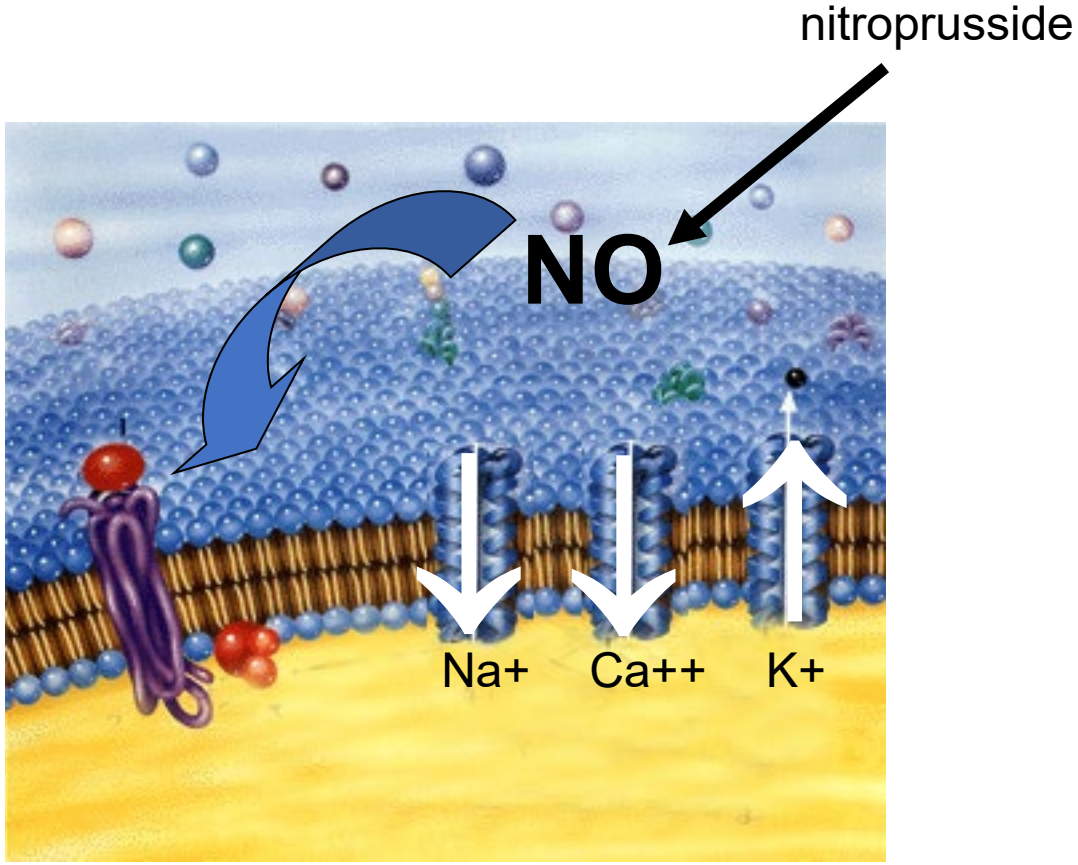
Its MOA, main toxicity and important clinical notes 🚨 ⏱️

MOA & The Effects of Nitroprusside

➔ **Nitroprusside** produces **NO** ➔ NO **increases** intracellular **cGMP** ➔ leading ultimately to **dephosphorylation** of **myosin** ➔ causing smooth muscle **relaxation**.

➔ The smooth muscle relaxation **(dilation)** effect of nitroprusside affects both **arteries** & **veins** ➔ which **reduces** the **preload** (which refers to the initial stretching of the cardiac myocytes prior to contraction, which is related to the venous return) & the **afterload** (which is the pressure the heart must work against to eject blood during systole; as it is reduced due to arterial dilation), as well as **dilating** the **coronary arteries** & increasing the **perfusion** towards them.

➔ There will be **reflex tachycardia**, but it **won't** be as **strong** as the one associated with hydralazine & minoxidil.



Toxicity of Nitroprusside

➔ In general, **nitroprusside** is **not** used for **prolonged** periods of time; and that's why we **don't** take much into **consideration** the **long-term control** of **sodium & water retention** associated with nitroprusside; as it **doesn't** frequently **occur**.

➔ However, there is a **significant side effect** associated with **nitroprusside** ➔ as nitroprusside itself contains a **cyanide group** ➔ this **cyanide** group can **interact** with **thiol** groups ➔ leading to an important side effect of nitroprusside; which is **thiocyanosis**.

➔ Nitroprusside-induced thiocyanosis **occurrence** is more probable to occur when **nitroprusside** is being **administered** to the patient for **more** than **24-48 hours** and if the **infusion rate** of the drug is a bit **high** (like **5 micrograms per kilogram per day**).

➔ However, some patients develop **thiocyanate toxicity** even when they administer nitroprusside with an **infusion rate** of **2 micrograms per kilogram per day**.

➔ **Thiocyanate toxicity** leads to **lactic acidosis**; which in turn can lead to **undesirable effects** & **problems** in the patient's body. And that's why it is **not preferred** to use nitroprusside for an **extended period of time**, and the **use** of nitroprusside must be **carefully controlled**.

The Clinical Importance of Nitroprusside

➔ Nitroprusside is considered a **special drug**; as it is **administered** through **titration**.

➔ Nitroprusside works within **30 seconds** after **administration**, and it reaches its **peak hypotensive effect** within **2 minutes**. Also, its hypotensive **effect** typically **stops** within **3 minutes** after the **discontinuation** of the **infusion** ➔ indicating that **nitroprusside** is an **appropriate** & **nice emergency drug**.

➔ **Nitroprusside** is the **drug of choice** for **all patients** with **hypertension emergency**, **despite** the **cause**.

➔ Nitroprusside **works fast** with **very profound effect,** and it **finishes fast** as it can be **easily titrated** (our best drug).

➔ However, **nitroprusside** should **not** be given for **more** than **48 hours** in order to **avoid thiocyanate toxicity (thiocyanosis)**.

And for the final drug in this lecture, 💥fenoldopam💥

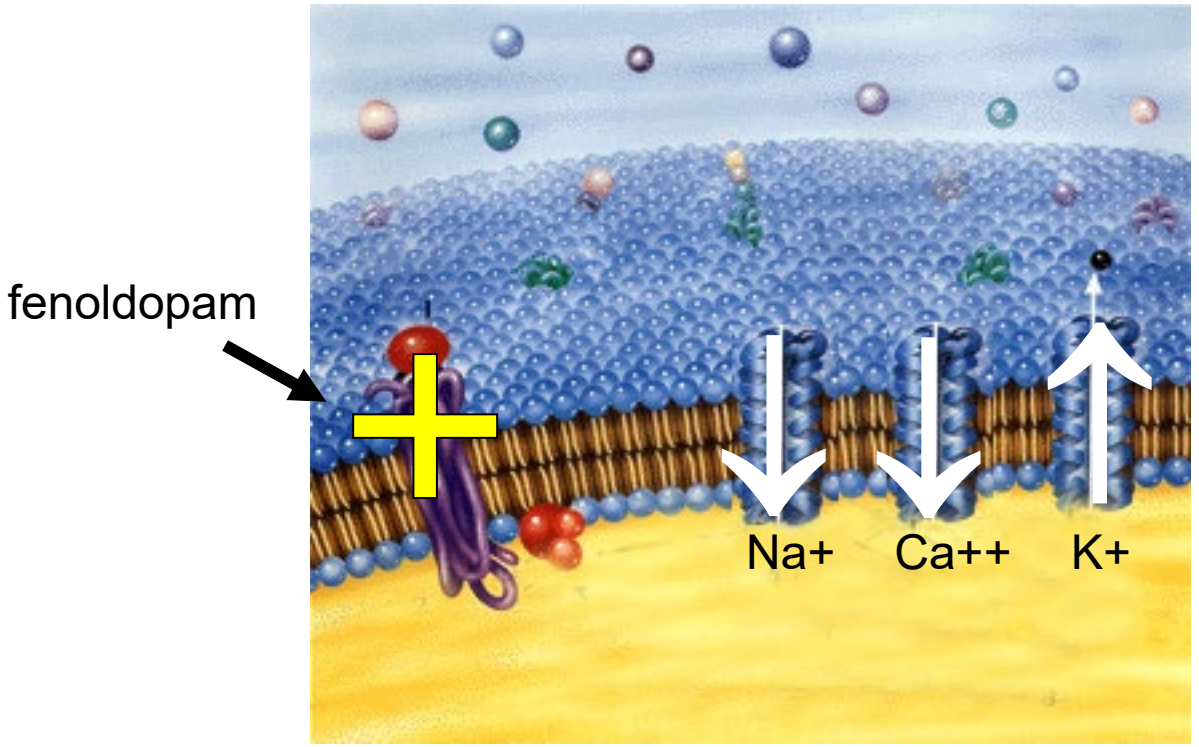
Its MOA & general notes regarding it 🚨🤝

MOA of Fenoldopam

➔ **Fenoldopam** is an **agonist** for **dopamine-1 receptors**, which are **present** on the **blood vessels**, especially the **arteries** ➔ leading to **arterial dilation**.

➔ The **agonism** of **fenoldopam** is beautifully **nice** & **friendly**, especially to the **kidneys**; because **dopamine-1 receptors** are also **present** in the **arteries** of the **kidneys** ➔ so, **fenoldopam** can **activate** these **receptors** at the level of the **kidneys** also ➔ leading to **increased renal perfusion.**

➔ So, if the patient has a **kidney problem** and **hypertension emergency** ➔ they can be given fenoldopam.



General Notes Regarding Fenoldopam

➔ Fenoldopam is **administered** as **infusion** as it is **not available orally**.

➔ What's **good** about **fenoldopam** is that it **works fast** (within **5-10 minutes**).

➔ But its **half-life** is around **30-60 minutes** (can **differ** according to the **patient**).

➔ It is **not great** to administer **fenoldopam** through **titration**; as its **effects** take a **relatively longer time** to **stop** (**2 hours approximately**).

➔ It is not as great as nitroprusside. However, it is used in **hypertension emergency.**

Now, we will be discussing hypertension emergency ‼️

When does it occur & what drugs are used to deal with it ⚡

Hypertension emergency

- It is rare but life threatening, in which DBP is > 150 mm Hg with SBP > 210 mm Hg (healthy person), or DBP of > 130 mm Hg in individual with pre-existing complications, such as encephalopathy, cerebral hemorrhage, and left ventricular failure, or aortic stenosis.

➔ In **hypertension emergency**, the **systolic blood pressure** becomes **220 mmHg or more**, while the **diastolic blood pressure** becomes **130 mmHg or more**.

➔ **Hypertension emergency** occurs in patients with **pre-existing conditions**, such as: **cerebrospinal hemorrhage**, **compromised kidney function**, **cardiovascular diseases** and so on & so forth.

➔ So, the **blood pressure** must be **controlled**, especially the **diastolic blood pressure**, as it is the **main role-player** & the **main determinant** of hypertension emergency ➔ thus, diastolic blood pressure must not rise above 130 mmHg. However, sometimes & in some cases, the patient is considered to have hypertension emergency when the diastolic blood pressure rises up to 150 mmHg.

➔ The **drugs** that are used to **treat** hypertension emergency are:

1) **Nitroprusside** (a vasodilator & the drug of choice for hypertension emergency)
2) **Fenoldopam** (a dopamine-1 receptor agonist & a vasodilator)
3) **Labetalol** (an alpha & a beta-blocker)

1) Nitroprusside

- **Sodium nitropresside** (onset 1-2 min), is administered intravenously and causes sudden vasodilation and reflex tachycardia, it is effective in all patients regardless the cause.

  It metabolized rapidly (half life of minutes) and require continuous perfusion. An overdose can cause hypotension.

➔ The **ideal drug** & **the drug of choice** for **hypertension emergency** is **nitroprusside**; as it **works fast** & **finishes fast**, and it is very nicely used for **all types** of hypertension emergency (for **all causes** & **all patients**).

2) Fenoldopam

- **Fenoldopam** (onset 2-5 min), peripheral dopamine 1 receptor agonist that also given as an intravenous infusion.

  It lowers blood pressure through arteriolar vasodilation and also through specific dopamine receptors along the nephron promoting sodium excretion.

  may be particularly beneficial in patients with renal insufficiency (maintains or increases renal perfusion).

➔ The **second choice** for the **treatment** of **hypertension emergency** is **fenoldopam**, which is also a nice drug; but it is **not** quite **available** in the **hospitals**. Furthermore, fenoldopam is a **dopamine-1 receptor agonist**, and it is very good & nice to patients with **compromised kidney function** as it **increases** the **renal perfusion** and it is considered **renoprotective**.

3) Labetalol

- **Labetalol** (α and β blocker), (onset 5-10 min) does not induce reflex tachycardia, given intravenous bolus or infusion.

  Have the same β blockers contraindication (Asthma ….) and major limitation of this agent is the long half-life(3-6 hr), that prevent rapid titration.

➔ The **third choice** for the **treatment** of **hypertension emergency** is **labetalol** (or calridol, but labetalol is **better**, because when it is given by **infusion**, its effects occur with **5-10 minutes**). However, the **main issue** with labetalol is that it has a **long half-life** (around **3-4 hours**) ➔ so, it is **quite hard** to administer this drug through **titration**. But the doctor can use the proper dose for it according to their experience.

For the last topic in this lecture, we will be discussing how vasodilators can lead to increased arterial pressure 🌪️

Its more like a revision actually, but it is quite important in order to get hold of the big picture!

The side effects of vasodilators which could ultimately lead to increased arterial pressure

➔ As we said before, **vasodilators** in general are associated with **2 main side effects**:

1) **Reflex tachycardia.**
2) **Increased water & sodium retention.**

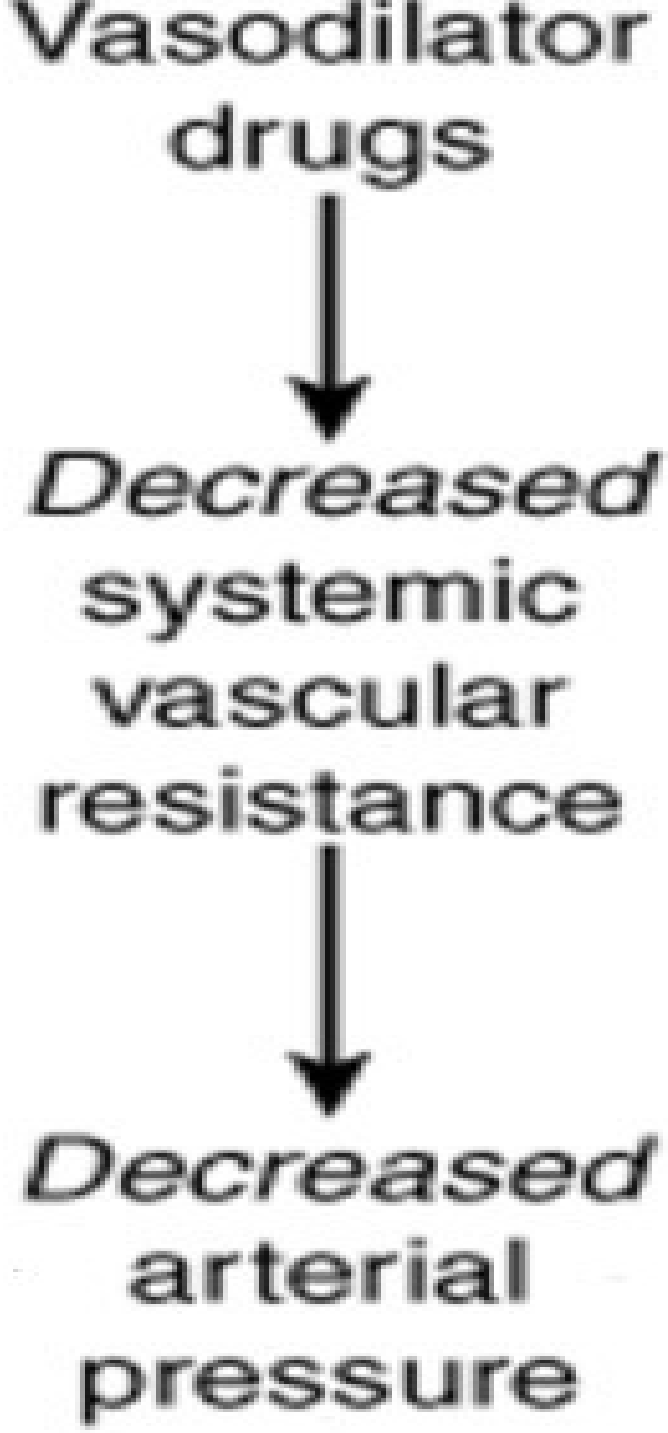
➔ These side effects in addition to the other effects caused by **reflex sympathetic nervous system increased stimulation (outflow)** ➔ can eventually lead to **increased arterial blood pressure!**

➔ Notice how in this case, we are getting the **exact opposite** of the **desired effect** (which is of course **decreased arterial pressure**).

➔ This necessitates **combining** these **vasodilators** with **other drugs** which could **control** their **side effects**, and these drugs are:

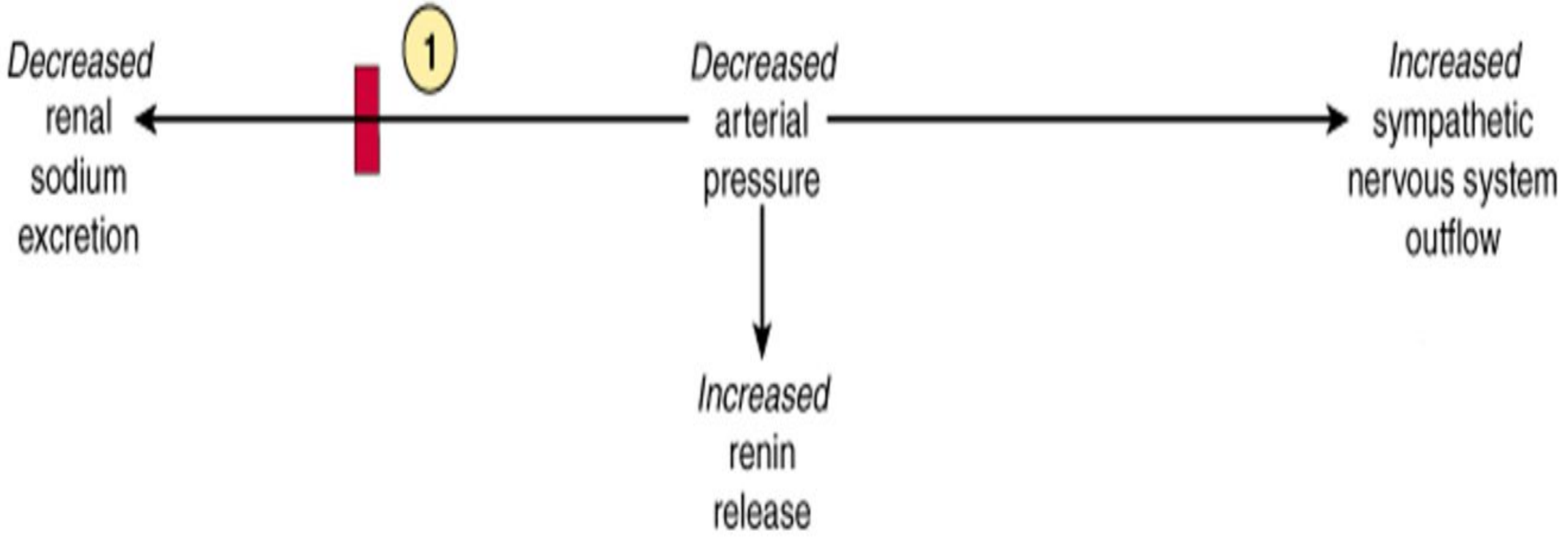
1) **Diuretics**: to deal with **increased sodium & water retention.**
2) **Beta-blockers**: to deal with the **reflex tachycardia.**

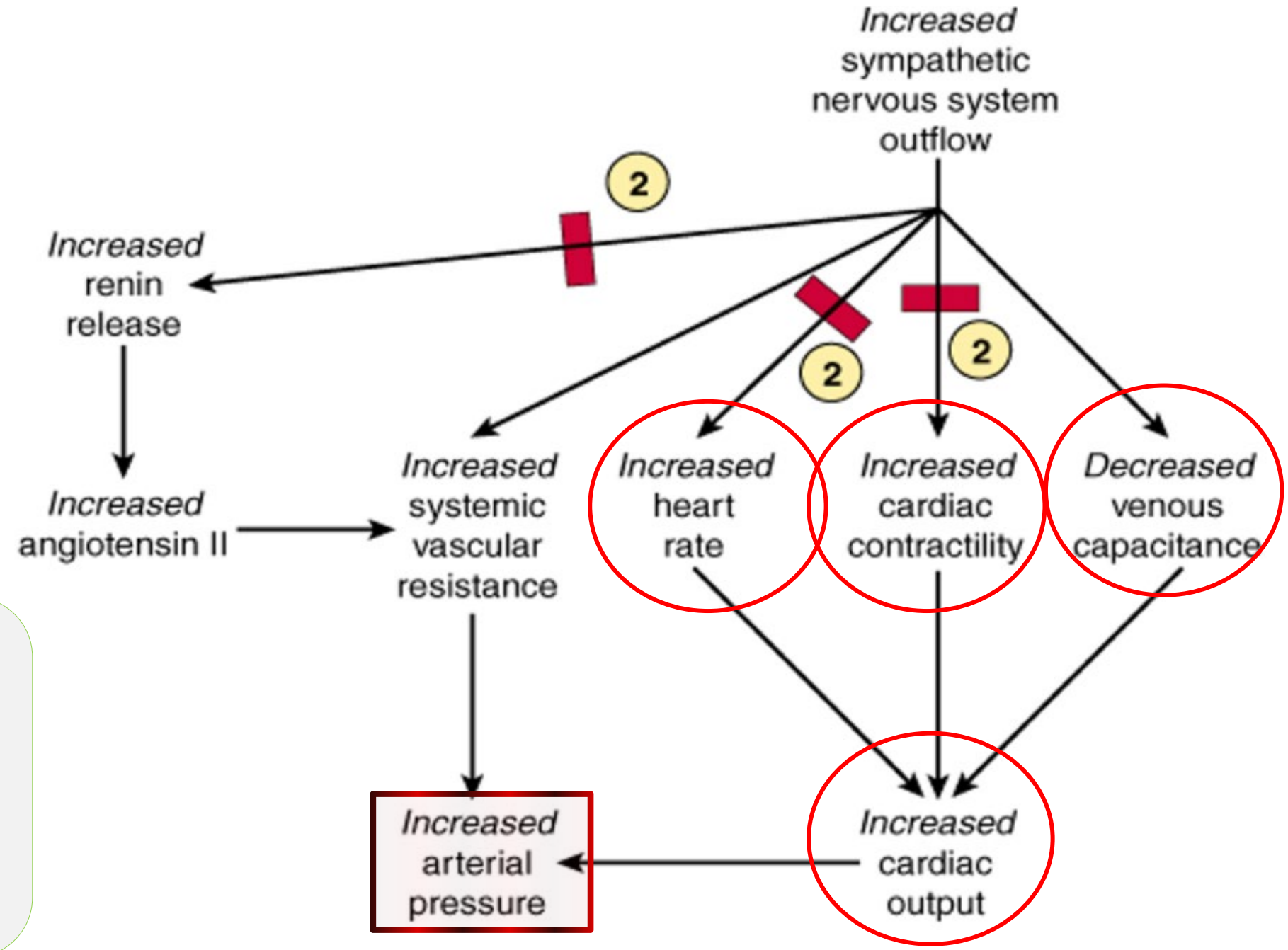
As we know, vasodilators cause **vascular smooth muscle relaxation** leading to **decreased systemic vascular resistance**, which in turn causes **decreased arterial pressure**



This **decreased arterial pressure** will lead to:

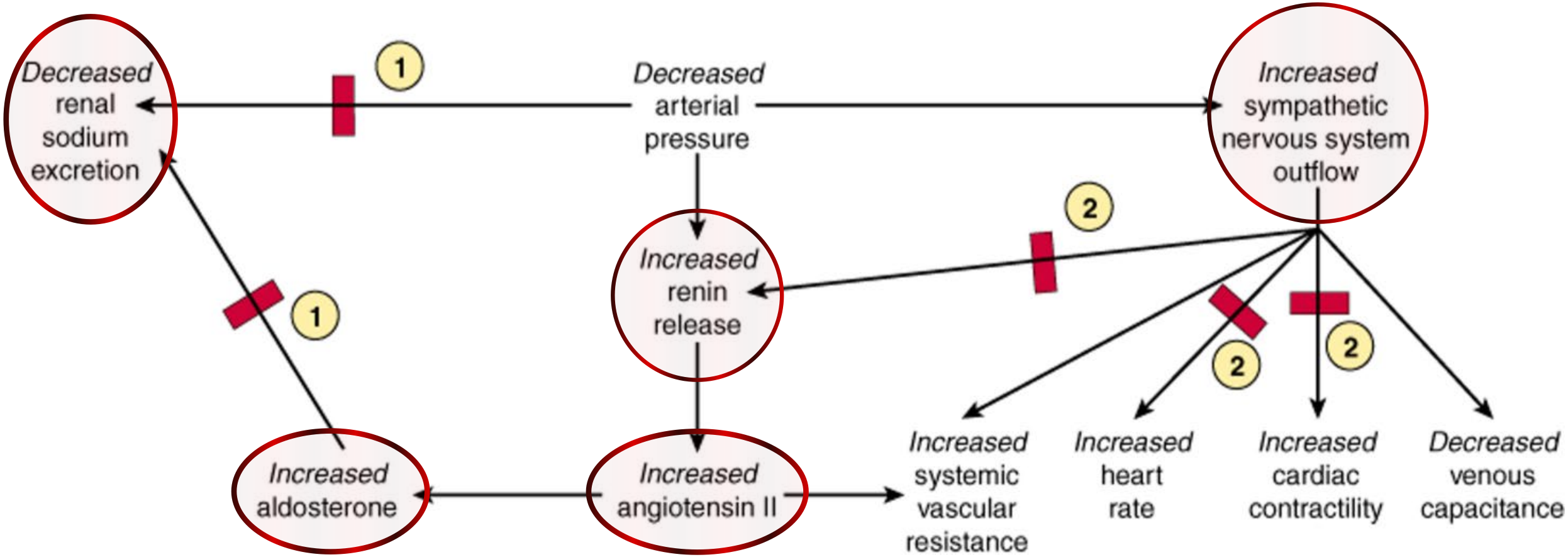
1) **increased** sympathetic nervous system outflow as a reflex
2) **Decreased** renal sodium excretion
3) **Increased** renin release

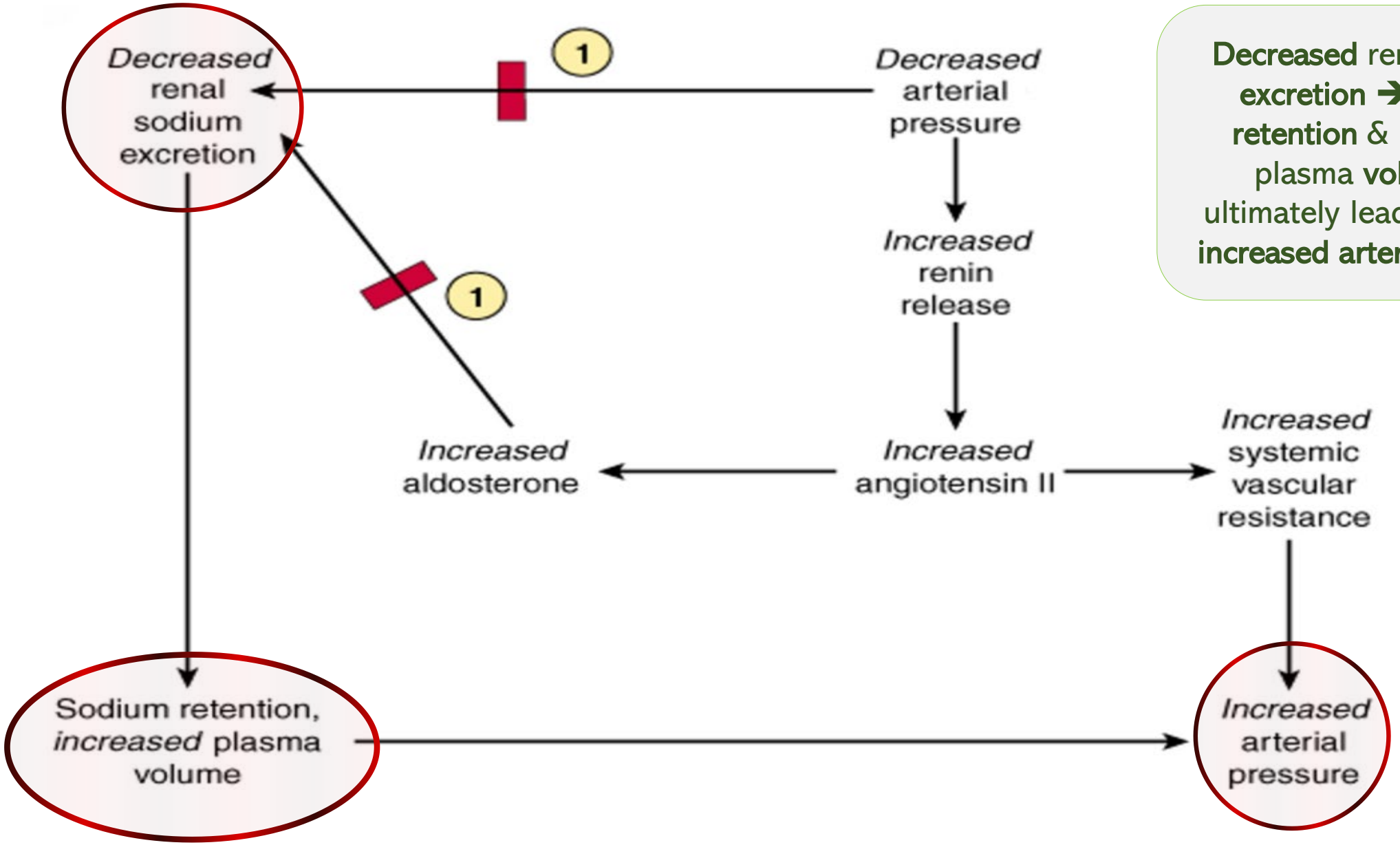




The **increased** sympathetic nervous system outflow results in **many effects** which also can directly or indirectly lead to **increased arterial pressure** (which is the opposite of the desired effect)

Increased sympathetic nervous system outflow ➔ **increased renin** release ➔ increased **angiotensin 2** ➔ increased **aldosterone** ➔ **decreased renal sodium excretion** (which is also **induced** directly by **decreased arterial blood pressure**)

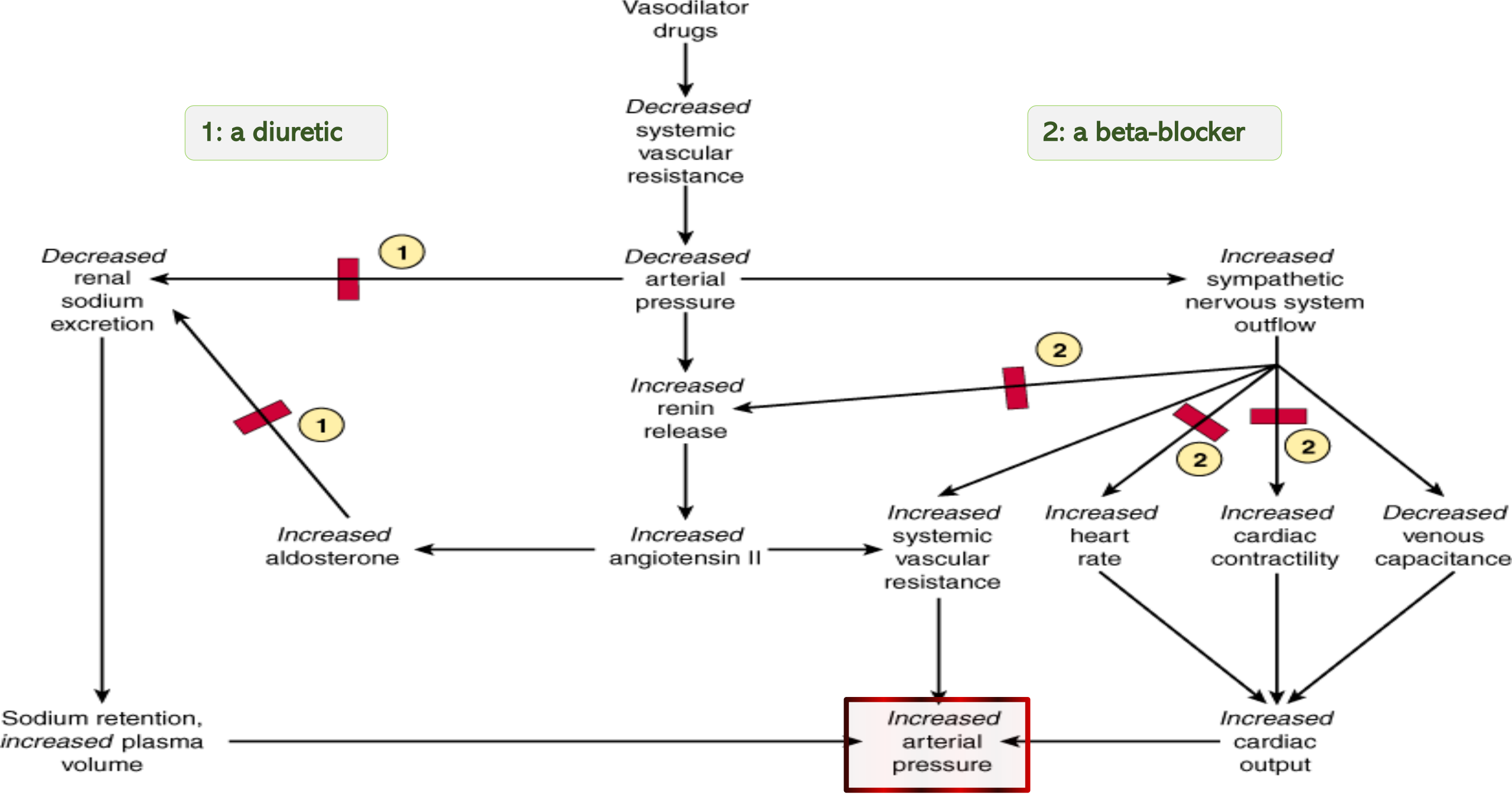




Decreased renal sodium **excretion** ➔ sodium **retention** & **increased** plasma **volume** ➔ ultimately leading also to **increased arterial pressure**

➔ Figured out how vasodilators can lead to increased arterial pressure through different pathways? Great!

➔ Now lets take a look at the big picture & how other drugs are used to **block certain steps** in order to **prevent** this increase in arterial blood pressure 👌



اللهم إني أستغيث بك، وأتضرع لك، وأتوسل إليك، بأخلص أعمالي، وأحسن أقوالي، أن تغيث أهل غزة، وتلطف بهم، وتمدهم بكل ما يحتاجون من الطعام، والشراب، والدواء، والوقود، والبركة، والصبر، والرضى، والعون، والثبات، والهدوء، والأمن، والأمان، والمأوى، والراحة، والسلام، وأن تنزل السكينة، والرحمة، والطمأنينة على قلوبهم، وأن تغنيهم بفضلك عمن سواك، وتعجل بالفرج العاجل لهم، اللهم استجب دعاءنا ولا تردنا خائبين !!

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!