Antihypertensive Drugs

Yacoub M. Irshaid, MD, PhD, ABCP

Department of Pharmacology, FOM, UJ

2016

Edited by: *Omar Saffar*

Reference

Basic & Clinical Pharmacology BG

Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

13th edition, Chapters 11 & 12

Hypertension

What is hypertension?

- **Increased blood pressure**
- **Asymptomatic which can effect the heart, brain, kidney and retina**
- **Major risk factor for atherosclerosis**
- **We start see symptoms when there is organ damage**
- **Most cases of hypertension are accidentally discovered like during clinic visits for example**
- **Treatment only reduce complications “will not prevent it”**

Hypertension

- **Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, heart failure, stroke, and dementia.**

- **Lowering of blood pressure leads to prevention of damage to blood vessels and substantially <u>reduces</u> morbidity and mortality rates.**

Hypertension

- **Diagnosis of hypertension depends on measurement of blood pressure and not on symptoms reported by the patient.**

- **Hypertension is usually asymptomatic until overt end-organ damage has already occurred.**

Hypertension

Blood Pressure Categories:

	SBP	DBP
Normal	< 120	< 80
Prehypertension	120-135	80-89
Hypertension		
Stage 1	140-159	90-99
Stage 2	≥ 160	≥ 100

Normal range is always below 120-80 regardless of age and gender

60 SBP is is okay for females, but it's not okay for males because (blood volume is different)

The actual reading by itself may be less important than in the presence of vascular damage or target organ damage.

Blood Pressure Measurement

- **How we diagnose hypertension?**
- **By Measuring blood pressure *(the right way)***
- **<u>Cuff size</u>: wrong cuff size leads to wrong reading**
- **White coat hypertension: fear (or anxiety) of doctors or medical environment leads to temporary hypertension!**

- **Before starting the measurement the patient should rest for at least 3 mins, stop talking, doctor should not talk to the patient too, after three mins the blood pressure is measured, patient should be sitting or lying comfortably , repeat the measurement for three times separately.**

Blood Pressure Measurement

- **If in these three measurements blood pressure was high, we should do further measuring by talking the blood pressure three times in one week, if BP is still high, we should give the patient these three instructions:**

1. **<u>Reduce salt intake</u> (lower Na)** ***"because salt increase water retention"***
2. **<u>Aerobic exercise</u> *(not reaching anaerobic hyperventilation)***
3. **<u>Reduce weight</u> *(normalize body weight)***

- **If BP is still high, we start to use drugs in addition to these three which are <u>essential</u> to limit complication**

Etiology of Hypertension

1. **Essential (Primary) hypertension: no specific cause of hypertension could be identified. It constitutes 85- 90% of cases.**

- **Elevation of blood pressure is usually multi-factorial.**
- **Genetic factors, psychological stress, and environmental and dietary factors (increased salt and decreased potassium or calcium intake) contribute to the development of hypertension.**

Etiology of Hypertension

2. **Secondary hypertension: Constitutes only 10-15% of cases and include renal artery stenosis, coarctation of the aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism.**

- **These are amenable to definitive surgical treatment.**

When a patient is diagnosed with Hypertension, tests must be made to exclude these causes first.

Hypertension

Physiologic regulation:

1. **Moment-to-moment:**
   - **a. Arterioles**
   - **b. Postcapillary venules**
   - **c. Heart**
2. **Long-term:**
   - **d. Kidney** **:Renin-Angiotensin system**

Hypertension

- **Baroreflexes + Renin-angiotensin-aldosterone system coordinate function at the 4 control sites.**
- **Local release of hormones from the vascular endothelium may contribute to regulation of vascular resistance:**

Baroreflexes sense high or low pressure and send impulses to the brain which will regulate the sympathetic stimulation on the heart and vessels etc..

Low blood pressure -> Baroreflexes to the brain -> increase sympathetic stimulation to the heart and vessels -> increased heart rate and vasoconstriction-> vasoconstriction activates renin angiotensin system-> water retention-> restore blood volume and pressure.

Hypertension

1. **Nitric oxide: dilates**
2. **Endothelin-1: constricts**

- **In hypertensive patients, the same mechanisms operate but the control system (baroreceptors and the renal blood volume-pressure control systems) appears to be reset at a higher level of blood pressure.**

Reset at higher level means that Baroreflexes for example instead of working at 120-80 cut off point pressure , they reset to work at 140-90 cut off point

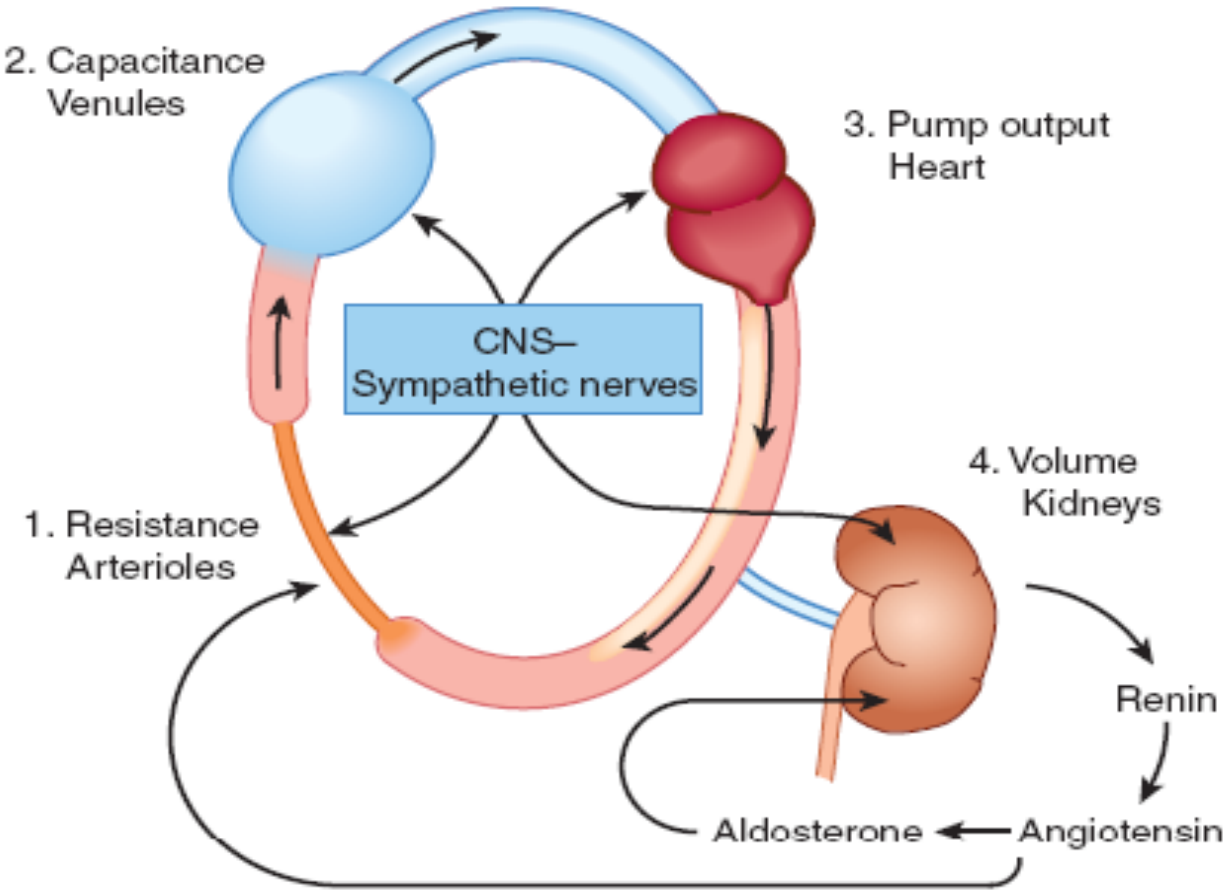

FIGURE 11–1 Anatomic sites of blood pressure control.

Postural Baroreflex

- **Baroreflexes are responsible for rapid, moment-to-moment adjustments in blood pressure, such as in transition from a reclining to an upright posture.**
- **Carotid baroreceptors are stimulated by the stretch of the vessel walls brought about by arterial blood pressure, resulting in inhibition of central sympathetic discharge (from the vasomotor center in the medulla).**
- **Conversely, reduction in stretch results in a reduction in baroreceptor activity.**

Postural Baroreflex

- **In the case of a transition to upright posture, baroreceptors sense the reduction in arterial pressure that results from pooling of blood in the veins below the level of the heart as reduced wall stretch, and sympathetic discharge is disinhibited.**
- **This reflex increase in sympathetic outflow increases peripheral vascular resistance (constriction of arterioles) and cardiac output (direct stimulation of the heart) and constriction of capacitance vessels, which increases venous return to the heart, thereby restoring normal blood pressure.**

Postural Baroreflex

- **The same baroreflex acts in response to any event that lowers arterial pressure, including a primary reduction in peripheral vascular resistance (vasodilating agent) or a reduction in intravascular volume (due to hemorrhage or to loss of salt and water via the kidney).**

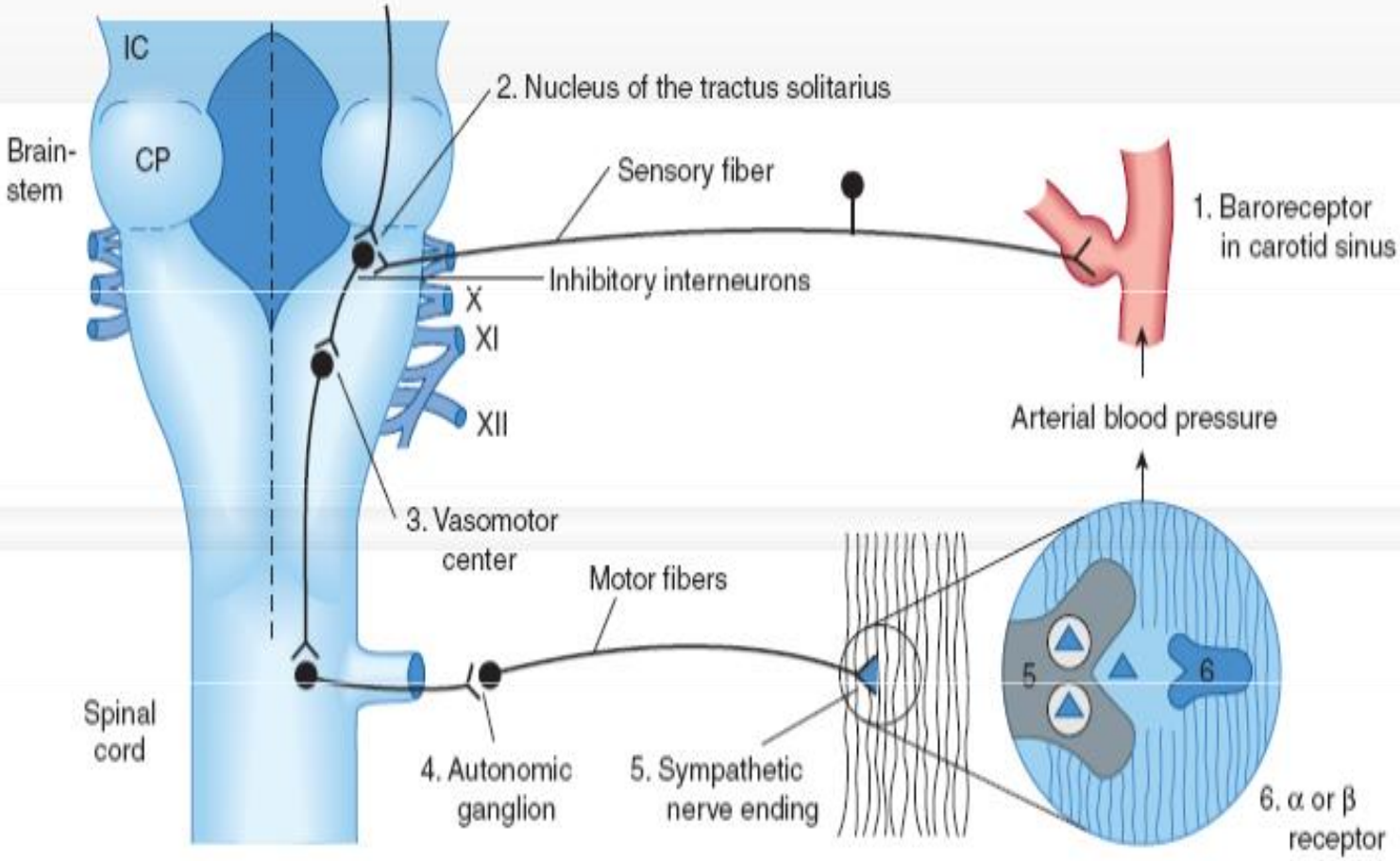

FIGURE 11–2 Baroreceptor reflex arc.

Gradual at 6 levels

Baroreceptor reflex arc. IC, inferior colliculus; CP, cerebellar peduncle.

Renal Response to Decreased Blood Pressure

- **By controlling blood volume, the kidney is primarily responsible for longterm blood pressure control.**
- **A reduction in renal perfusion pressure causes intrarenal redistribution of blood flow and increased reabsorption of salt and water.**

⇧BLOOD VOLUME -> ⇧BLOOD PRESSURE
⇩BLOOD VOLUME -> ⇩BLOOD PRESSURE

Renal Response to Decreased Blood Pressure

- In addition, decreased pressure in renal arterioles as well as sympathetic neural activity (via β adrenoceptors) stimulates production of renin, which increases production of angiotensin II.

Renal Response to Decreased Blood Pressure

Angiotensin II causes:

1. **Direct constriction of resistance vessels.**
2. **Stimulation of aldosterone synthesis in the adrenal cortex, which increases renal sodium absorption and intravascular blood volume.**

Renal Response to Decreased Blood Pressure

- **Vasopressin released from the posterior pituitary gland also plays a role in maintenance of blood pressure through its ability to regulate water reabsorption by the kidney.***(Vasoconstriction and water retention by working on the distal tubules in the kidney)*

Antihypertensive Agents

Include the following:

1. **Diuretics, which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by reducing blood vessels responsiveness to vasoconstrictors.**

Diuretics after a while *(first 6-8 weeks)* stop working as diuretics (due to tolerance),yet they still produce hypotensive action by depleting sodium, when sodium is lost Na-Ca exchanger function is decreased which leads to low intracellular concentration of Ca, and that will produce less vasoconstriction (vasodilation and less response to vasoconstrictors).
And that's why diuretics considered as indirect vasodilators

Antihypertensive Agents

2. **Sympathoplegic** agents, which lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in capacitance vessels.

Antihypertensive Agents

3. **Direct vasodilators, which reduce pressure by relaxing vascular smooth muscle, thus dilating resistance vessels and, to varying degrees, increasing capacitance as well.**

Antihypertensive Agents

4. **Agents that block production or action of angiotensin and thereby reduce peripheral vascular resistance and (potentially) blood volume.**

Blockers of Angiotensin and Aldosterone

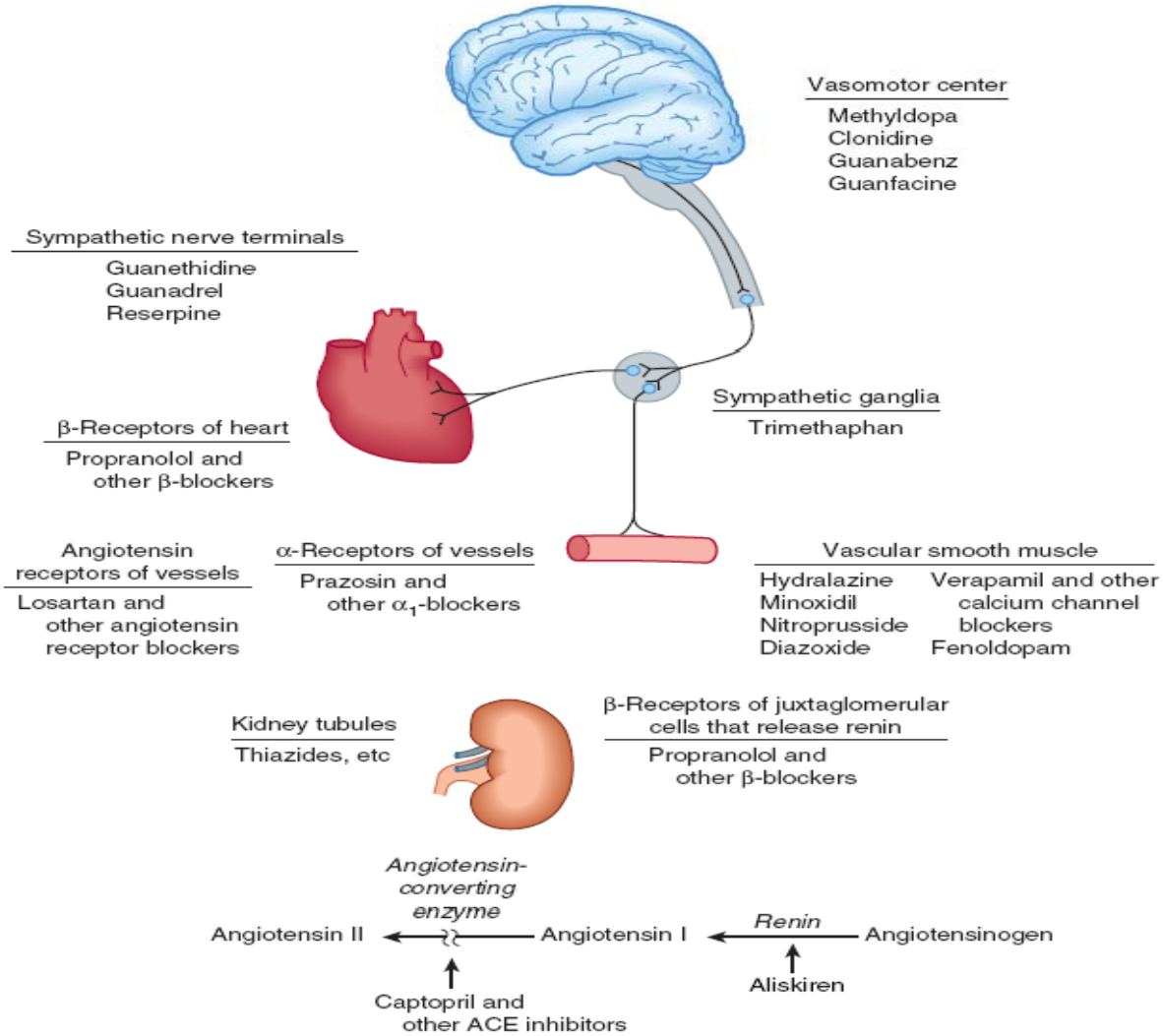

FIGURE 11–3 Sites of action of the major classes of antihypertensive drugs.

Antihypertensive Agents

Define (you should know):

1. **Systemic vascular resistance.** *vasoconstriction in the arterial side of circulation.*
2. **Cardiac output.** *Amount of blood pumped per minute*
3. **Preload.** *EDV, blood coming to the heart*
4. **Afterload.** *Systolic vascular resistance, the load that the heart faces when it pumps.*
5. **Postural (orthostatic) hypotension.** *Decrease in blood pressure when standing up in people with dysfunctional reflexes "abnormal"*

Postural Hypotension

When you stand up, blood go down to lower limbs by gravity, reduces venous return to the heart and hypotension, <u>that is if baroreceptors didn't work</u>!
But if they sense this decrease in pressure they'll send a signal to the CNS to stimulate the heart (increase force of contractility and rate) and vessel (vaso and veno –constriction) by the sympathetic system to maintain the blood pressure and keep it normal

Drugs that causes Postural Hypotension *(as an adverse effect):*
Any drug the causes arterial and venous <u>dilation</u> (vasodilators)
And also any drug or a state that causes <u>low blood volume</u>
<u>note:</u> all drugs can cause Postural Hypotension in the presence of low blood volume , yet not all drugs can cause Postural Hypotension when blood volume is normal

Postural Hypotension interferes with daily life activities so it should <u>avoided!</u>

Drugs That Alter Sodium & Water Balance

- **Dietary sodium restriction decreases blood pressure in hypertensive patients.**

- **Diuretics lower blood pressure by depleting body Na^+, thus reducing blood volume and cardiac output.**

Diuretics

First line therapy

- **After 6-8 weeks of therapy, cardiac output returns to normal but the systemic vascular resistance drops, due to decreased response to vasoconstrictors due to sodium depletion.** *Indirect vasodilators*
- **Sodium contributes to vascular resistance by increasing vessel stiffness and neural reactivity.**

Diuretics

- **This effect may be related to altered sodium-calcium exchange which increases intracellular calcium.**

- **These effects are reversed by diuretics or dietary sodium restriction. *(vasodilation)***

Diuretics

- **Indapamide also has direct vasodilator action.**
- **Thiazide diuretics are effective for mild-to-moderate hypertension in patients with normal renal and cardiac function.**

GFR >40 ml/min

- **They cause hypokalemia (all diuretics in general)**
- **Potassium-sparing diuretics are useful to avoid excessive potassium depletion.**

Potassium levels should be kept normal because hypokalemia causes Arrhythmias and hyperkalemia is dangerous also!

<u>Spironolactone:</u> is a potassium-sparing drug and also have an antagonism for aldosterone which is good for being an anti-hypertensive drug*(prevents sodium-water retention)*

GFR:

120 mL/min is normal

<60 renal dysfunction but still working

<40 renal faluire

Diuretics

- **Loop diuretics are necessary in severe hypertension with:**

1. **Multiple drugs that retain Na^+ and water.**
2. **When GFR is < 30-40 mL/min.**
3. **Cardiac failure.**
4. ***Cirrhosis when sodium retention is marked (??).***

Forget about this for now