The Cardio-VASCULAR System

- ○ Anatomy
- ○ Histology
- ○ Pathology
- ● Pharmacology
- ○ Physiology
- ○ Microbiology

Lec #: 3

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- ○ Handout
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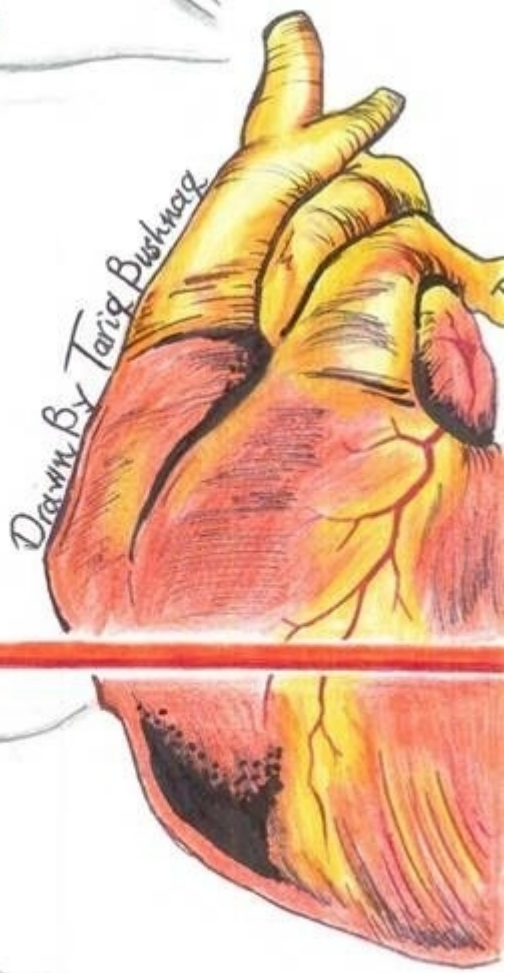

Calcium Channel Blockers and B-Blockers

Quick revision

During our previous lectures we talked about 2 classes of drugs used in treating hypertension:

1- Diuretics:

- Represented by Thiazide diuretics
- Mainly work by depleting blood sodium stores
- Have no significant side effects at low doses but they do show in long term use. The most common are **gout** (due to inhibition of urate excretion) and **hypokalemia** (which is coupled to sodium reabsorption and so the restriction of sodium dietary intake minimizes potassium loss).

2- ACE inhibitors:

- Block the ACE that cleaves Angiotensin I into Angiotensin II which is the most potent vasoconstrictor in the body. This in turn decreases the peripheral vascular resistance and allows for the decrease in blood pressure.
- Great drugs to be used in most CVS diseases like: Hypertension, Congestive heart failure and Post-myocardial infarction, however *they cannot be used in arrhythmias*. They also have great applications in treating diabetes mellitus.
- They are contraindicated in: pregnancy and **bilateral renal artery stenosis**. It was previously thought that ACEIs shouldn't be used in hypertensive patients with chronic kidney diseases however as it turned out they actually have a useful role in their treatment just not in the case of bilateral renal artery stenosis. They can also be used in unilateral kidney stenosis.
  Bottom line is that ACEIs are not contraindicated in HTN patient with kidney failure.

Calcium Channel blockers (CCBs)

These are the 3rd group of drugs to be used in earlier treatment of HTN. They are recommended agents when the preferred first-line agents are contraindicated or ineffective. (Remember in first-line therapy we use one of three choices : diuretics, ACEIS or calcium channel blockers)

❖ Mechanism of action:

Calcium enters muscle cells through special channels and produce contractility in them. There are three types of channels but the L-type is the one we're concerned with and it is distributed in the heart and the peripheral vasculature.

CCBs block these channels *(here the Dr says that they don't totally block the channels, they just increase the time of their blockage)* and stop the inward movement of Ca into the cell, I.e. lowering its concentration thus they exert their hypotensive effect through their vasodilation effect on the vessels , while it does a different effect on the heart as we won't dilate the heart for sure, it will cause a negative inotropic and chronotropic activity.

❖ Chemical Classes:

They are divided into 3 chemical classes depending on their selectivity:

1-Diphenylalkylamines represented by **Verapamil**(*effect on the vessels and the heart*):

Have no selectivity towards Ca channels wherever in the body; they block those in vessels and in the heart.
They result in hypotension (vasodilation effect)and also have a negative inotropic and chronotropic effect since they act on the heart.
A lot of limitations govern their use since they produce both negative inotropic and chronotropic effects.

2 – Benzothiazepines represented by **Diltiazem**(*similar to Verapamil but with moderate effect on the heart*):

Have less selectivity towards the heart that ranges between the 1st and 3rdclasses and is more selective within the vessels.

3- Dihydropyridines represented by **Nifedipine***(on the vessels with very little effect on the heart /Dipine family) :*

Amlodipine is of the same class.
Selective within vessels and have no effect on heart channels

	NIFEDIPINE*	DILTIAZEM	VERAPAMIL
coronary arteries dill	+ +	+ +	+ +
peripheral arteries dill	+ + + +	+ +	+ + +
negative inotropic	+	+ +	+ + +
slowing AV cond	↔	+ + +	+ + + +
heart rate	↑ ↔	↓ ↔	↓ ↔
↓ blood presure	+ + + +	+ +	+ + +
depression of SA	↔	+ +	+ +
increase in cardiac output	+ +	↔	↔

* and others dihydropyridines
↓ = decrease
↑ = increase
↔ = without change

This table (*important*) shows the different effects of these agents on different body parameters:

1- Coronary artery dilation: All three drugs have the same effect on the coronary arteries and can be used in angina pectoris (coronary arteries are the ones blocked in angina pectoris).

2- Peripheral artery dilation: it's the most important factor in reducing blood pressure. What do you think , who's the perfect match for this ? It's Nifedipine which has the greatest effect on the vessels (as we mentioned before) and in cases of **isolated** HTN it's the drug to be used.

3- Negative inotropic effect: Nifedipine has only little effect on it unlike Varapamil and Diltiazem.

4- Slowing AV conduction: Varapamil has the greatest effect and is used to decrease heart rate in addition to its negative inotropic effect. It's also contraindicated in bradychardic patient.

5- Cardiac output: Nifedipine has the highest effect since it decreases the **peripheral resistance** against the heart pumping which decreases the afterload and allows for greater cardiac output.

How can Nifedipine increase heart rate?

Dilation of peripheral vessels leads to decrease in venous return and pooling of blood in the lower limb. That, in addition to decrease of arterial resistance, leads to hypotension. The body responds in order to increase heart rate through a baroreceptor reflex that increases sympathetic activity and Noradrenaline release. Activation of alpha-1 receptors won't produce vasoconstriction because Ca-channels are already blocked. Beta receptor activation however causes reflex tachycardia (Reflex tachycardia may always happen with vasodilators through the baroreceptor reflex), *Remember that this doesn't happen with verapamil or diltiazem because they have negative inotropic and chronotropic effects, while nifedipine has little negative effect so reflex tachycardia is possible.*

Furthermore if you remember from pharmacokinetics, a drug with a short half-life has high fluctuations, meaning that its plasma concentrations starts off at a peak and goes down to a trough rapidly. With Nifedipine, whenever the concentration of the drug goes down, the competition on the receptors is reduced, and the drug molecules don't exert their already very little negative inotropic effect. This means that heart rate will increase at very low concentrations of nifedipine. (Notice the red boxes in the table)

This problem has been overcome by:

1-Designing a sustained release formula called a "one dose daily". Sustained release nifedipine is better than the regular 3-times-a-day nifedipine and avoids the peak and trough transition of plasma concentration. These formulas also allow for Nifedipine to be used in angina pectoris without the fear of developing tachycardia.

2- A drug with a longer half-life meaning that most of the time the activity of this drug is spent at the peak (an area the doctor described as "positive point" which is the site of tachycardia inhibition).

NORVASC is a form of Amlodipine that has a very long half-life and produces little fluctuation in plasma drug concentration due to its sustained release formula and can be used in angina. These drugs are also one dose daily drugs

❖ Uses

- Verapamil and Diltiazem are used in arrhythmias because they have an effect on the heart. They both are not great antihypertensive drugs because they have negative inotropic and chronotropic effects, however are used in patients who have palpitations/arrhythmias and suffer from HTN since they can reduce heart rate and blood pressure simultaneously.

- If a patient doesn't have arrhythmias but has HTN we prefer to use Nifedipine because it doesn't have cardiac effects.

- If a patient has congestive heart failure (in which the heart can't pump enough blood towards the periphery) we don't want drugs that produce negative inotropic or chronotropic effects so Verapamil and Diltiazem are contraindicated in this case.
- We can't combine a drug that already has negative inotropic and chronotropic effects (eg. B-blockers) with Verapamil and Diltiazem since we might end up with 2nd or 3rd stage AV block due to their action on SA and AV nodes *(we can't give these drugs to a patient who's suffering from or having susceptibility toward AV block).*
- Also we can't combine them with beta blockers that affect SA & AV node conductivity. *(safe with nifedipines)*

❖ Adverse effects:

Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

The most prominent side effects associated with CCBs are:

1- Headaches: dilation of peripheral vessels causes decreased venous return and subsequently decreased brain blood perfusion leading to headaches. Another mechanism is that dilation of vessels in the brain causes a pain reflex that reads off as a headache. Mostly in Nifedipine. (This effect can be observed with most vasodilators as well)

2- Ankle swelling/edema: the decrease in arteriolar resistance that goes unmatched in the venous circulation increases hydrostatic pressures in the precapillary circulation and permits fluid shifts into the interstitial compartment especially in the legs producing ankle edema. Mostly in Amlodipine.

3- Constipation: decreasing contraction of GI tract smooth muscles leads to constipation. Mostly in Varapamil and less so in Diltiazem.

4- Gingival hyperplasia: in which the gums grow to cover the teeth. Mostly in Amlodipine. This is a very common side effect that can be linked straight away to CCBs since they are used widely in medicine to treat HTN.

5- CCBs do not affect concentrations of plasma cholesterol or triglycerides or extracellular calcium hemostasis.

Beta-adrenergic Blockers (lols family)

There are different types of B-blockers depending on their selectivity for B-receptors. Some are selective, some are non-selective and some even have activity over α-receptors. Some also have intrinsic sympathomimetic activity like pindolol and acebutolol.

Action	Adrenergic Selectivity	Examples
Selective	beta1 >beta2	Metoprolol, acebutolol, atenolol, esmolol
Non-selective and vasodilating	beta1, beta2 and alpha1	labetalol carvedilol
Non-selective	beta1 and beta2	Propranoiol, penbutolol, pindolol, timolol, nadolol, sotalol

These drugs were previously used in the 4-drug regimen used to treat HTN, however their low efficacy in reducing blood pressure forced the clinical community to eliminate them from the regimen. Heterogeneity of this group regarding their antihypertensive activity also wasn't enough to keep them as first line therapy.

They are great drugs, but they are not as great for hypertension as other drugs because their efficacy is at most 10 mmHg, and this is even less efficacious than thiazide diuretics.

The effect of B-blockers in treating HTN is not only related to their negative inotropic and chronotropic effects on the heart, it's also related to their effect on the juxtaglomerular cells in the kidney that release rennin. They work to decrease renin release and decrease blood pressure in long term use.

❖ Uses

- Angina pectoris (except for vasospastic angina patient): because they reduce the heart rate
- Atrial fibrillation: because they have negative inotropic and chronotropic activity
- Cardiac arrhythmia
- Congestive heart failure
- Essential tremor: reduction of sympathetic tone
- Glaucoma
- Hypertension
- Migraine prophylaxis: where stress plays a major role in worsening it so, we give beta blocker to reduce the stress
- Mitral valve prolapsed
- Phaeochromocytoma, in conjunction with α-blocker
- Symptomatic control (tachycardia, tremor) in anxiety and hyperthyroidism

❖ Propranolol :

- It has a higher efficacy than the other drugs.
- It's a non-selective (B1 and B2). Blocking B1 reduces cardiac output and renin release. BlockingB2however is not desirable because it reduces insulin release and causes bronchospasm.
- It's lipophilic, meaning it can cross blood brain barrier easily.
- Both these properties, being non-selective and crossing BBB, make it the drug of choice for prophylaxis against migraines

- It's also called "The Stage Drug" and can be used to reduce stage fright before speeches or big events. Stage fright is caused by sympathetic surge and can be reduced by propranolol.

❖ Atenolol& Metoprolol:

- Cardioselective drugs
- They are the most widely used blockers in treatment of HTN (affect rennin release) and have no carbohydrate effect.

❖ Pindolol & acebutolol & penbutolol :

- They are partial agonists, i.e. blockers with some intrinsic sympathomimetic activity.
- They lower blood pressure by decreasing vascular resistance and appear to depress cardiac output less than other blockers. This means they have less action on the heart but retain activity on the juxtaglomerular cells of the kidney reducing renin release.
- The clinical benefit is their use in patients with bradyarrythmias or peripheral vascular disease.

FORZA NAPOLI

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A.T. A.

And special S.O to Hala Hajjir

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