Doctor.021

no. 7

CVS PHARMACOLOGY

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Newer antianginal drugs

Traditionally (as mentioned in the 5th lecture), angina has been managed using beta blockers, nitrates, and CCBs (Calcium Channel Blockers). However, there are newer antianginal medications that we will be discussing in today's lecture: **Ivabradine, Ranolazine, Trimetazidine, Nicorandil**. The first three drugs are the most commonly prescribed, and some of these medications are also used in the treatment of heart failure and as antiarrhythmic agents.

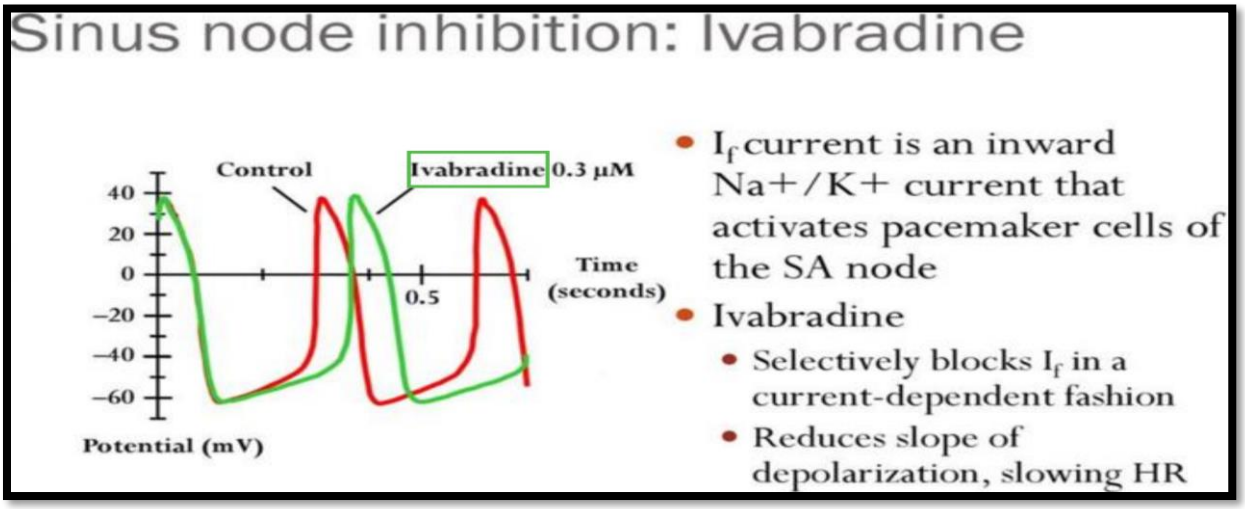
New because they were registered in the FDA by 2006. (Ranolazine specifically)

1-Ivabradine.

• Ivabradine selectively inhibits the **I_f current** (by closing the Na+ channels), an **important** current involved in generating the early phase of spontaneous diastolic depolarization in sino-atrial cells (SA node), reducing the frequency of action potential initiation and lowering heart rate.
(Ivabradine has a negative chronotropic effect on the heart, and this is the wanted effect).
• It decreases the body's demand for myocardial oxygen which is what we need in angina (remember the problem with angina is that the oxygen demand is higher than the supply), **without** any effect on blood pressure or myocardial contractility (no inotropic activity) or conduction times, and results in a reduction in angina symptoms.
• Ivabradine is metabolised by CYP3A4, there is drug interaction with CYP3A4 inhibitors **(**such as azole antifungals like **ketoconazole**, which can increase Ivabradine levels) and inducers (such as rifampicin (rifampin), which can decrease Ivabradine levels).

• note that the I_f current also called the funny current (remember physiology lectures).

• This picture below shows the effect of Ivabradine on the heart's action potential., it selectively blocks the I_f current which reduces the slope of depolarisation and slows the heart rate**, reducing the frequency of the SA node activity the heart.**



• Ivabradine **inhibits** the SA node (primary pacemaker).
• Ivabradine is **contraindicated** to be used with verapamil and diltiazem (calcium channel blockers) because these drugs inhibit CYP3A4; however, it can be used with beta blockers in HF.

• Ivabradine is used in combination with beta blockers in people with heart failure with LVEF (left ventricular ejection fraction) lower than 35 percent inadequately controlled by beta blockers alone and whose heart rate exceeds 70 beats per minute(Ivabradine should be used with beta blockers, only if the heart rate of the patient was more than 70 beats per minute to avoid having bradycaria)

• Ivabradine is used in people who are not sufficiently managed with beta blockers for their heart failure, and by adding ivabradine it decreases the risk of hospitalization for heart failure. (Beta blocker alternative).

• Ivabradine is used in angina pectoris (reducing the sinus rhythm by blocking the I_f current and reducing the oxygen demand) and for heart failure (by reducing the chronotropic activity without affecting the inotropic activity**).**

Adverse effects of Ivabradine:

• Overall, 14.5% of patients taking ivabradine experience **luminous phenomena**, in which the patients described as sensations of enhanced brightness in a fully maintained visual field, the vision of the patient will have more brightness, it is a reversible issue.

•"Luminous phenomena" is a **distinctive characteristic of Ivabradine**, similar to how xanthopsia is associated with digoxin.

• This is probably due to **blockage of I_h ion channels in the retina**, which are very similar to cardiac I_f, this is called tissue selective activity.

• In a large clinical trial, bradycardia occurred in 2% and 5% of patients taking ivabradine at doses of 7.5 and 10 mg (high doses) respectively (compared to 4.3% in those taking atenolol).

• 2.6–4.8% reported headaches, remember it is a problem with nitrates, CCBs too.

• blurred vision (a special side effect, not common 1-2%).

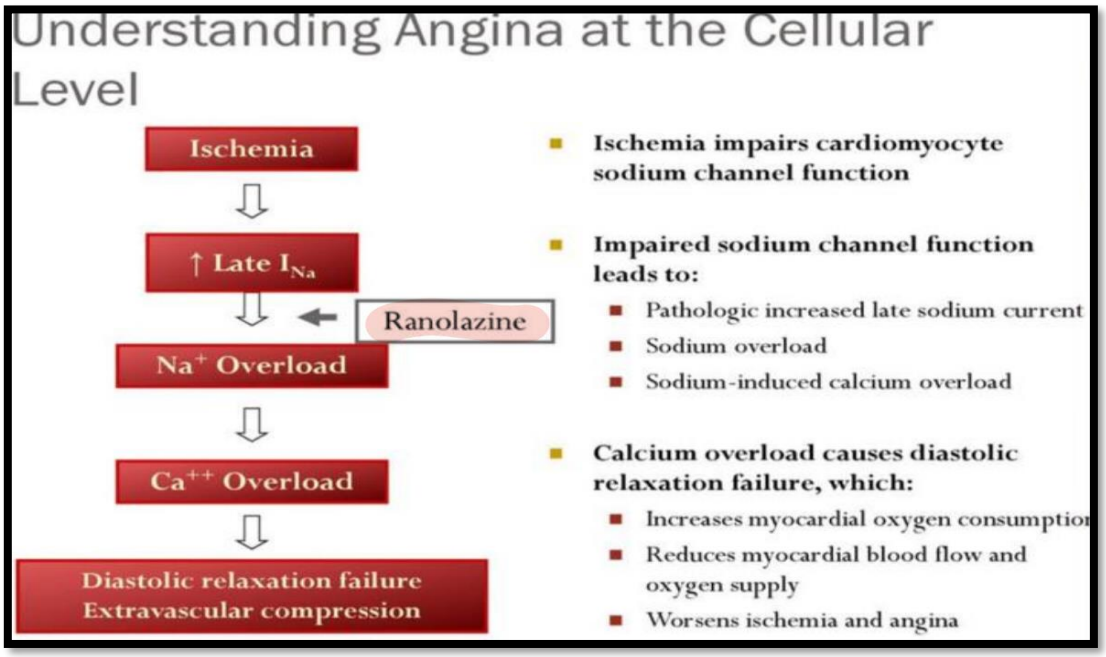
2-Ranolazine

• It selectively inhibits the late sodium influx in the myocardium (from ischemia of angina) reducing calcium overload, attenuating the ischemic abnormalities of ventricular repolarization and the resulting reduced contractility.

• Ischemic heart diseases, such as angina, can cause a **late influx of sodium** (which mostly does not occur under normal conditions). This influx allows more calcium to enter the heart, leading to an overload of calcium

due to the exchange between sodium and calcium. This increased calcium level can result in **higher tension** during the diastolic phase, leading to diastolic relaxation failure and extravascular compression. This is a characteristic feature of ischemic abnormality, also known as ischemic cardiac myopathy. As a result, patients with angina may experience increased tension and stiffness in the heart's walls and blood vessels, along with **reduced contractibility of the heart** due to increased ventricular repolarization. This **increased oxygen demand and consumption** (which is the underlying issue in angina) can further worsen the ischemia and angina by reducing myocardial blood flow and oxygen supply to the heart.

• ***Ranolazine selectively* inhibits the late sodium influx and the late efflux of calcium**, which reduces the ions overload and reduces the resultant stiffness in angina patients (remember it only affects the diastolic tension).

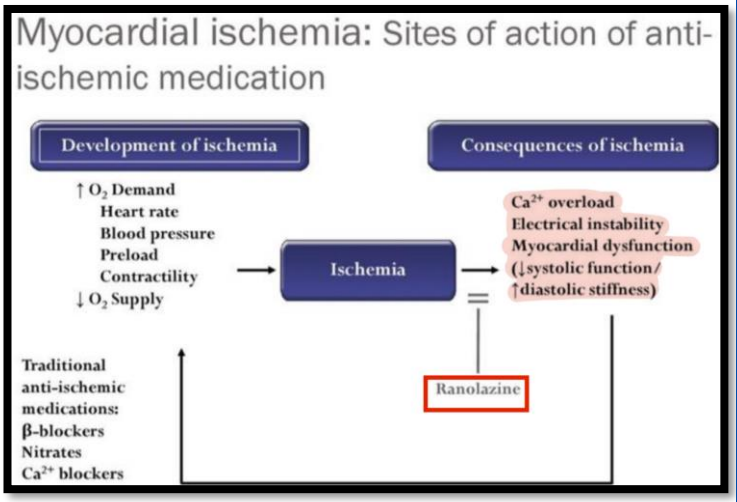


See the image below for better understanding.

• It improves exercise tolerance while reducing the frequency of angina episodes, because it reduces the demand towards oxygen and produces better contractibility, and it reduces the diastolic tension in the patient's heart.

• Can improve myocardial ischemia **without** affecting heart rate or

blood pressure or the contractibility, so it can help in angina pectoris



• Again, when ischemia occurs, the oxygen demand will increase, along with heart rate and blood pressure preload, resulting in a reduction in the oxygen supply. Traditionally, angina is treated with beta blockers, nitrates, and CCBs. However, Ranolazine is a new drug for angina that **targets the consequences** of ischemia, such as the excessive sodium and calcium levels in the late stage, electrical instability, myocardial dysfunction, decreased systolic function, and increased diastolic stiffness. **Ranolazine** effectively addresses these issues and demonstrates significant efficacy in treating myocardial ischemic disease, particularly angina pectoris. It improves contractility **without exerting positive inotropic activity**, it reduces oxygen demand, enhances perfusion through the coronary arteries toward the heart, reducing the stiffness of the heart.

• This image shows you that **beta blockers reduce everything (the heart rate, blood pressure, pump function**) and this can be reversed by the vasodilators like the nitrates especially on the blood pressure, that's why we **combine beta blockers with nitrates** as we said before.

Pharmacologic Classes for Treatment of Angina

Medication Class	Impact on HR	Impact on BP	Physiologic Mechanism
Beta Blockers	↓	↓	**Decrease pump function**
Calc Channel Blockers	↓	↓	**Decrease Pump function + Vaso-dilitation**
Nitrates	↑	↓	**Vaso-dilitation**
Ranolazine	–	–	Reduced Cardiac Stiffness

• **Calcium channel blockers** also have a negative impact on the chronotropic and inotropic activity, like the beta blockers.

• Ranolazine have no effect **on chronotropic and inotropic activity**, it reduces the cardiac stiffness only producing more perfusion to the heart and better diastolic time.

Ranolazine and QT

• Ranolazine slightly increased QT interval (in ECG) in some patients and the FDA label contains a warning for this effect, and this effect comes from the effect on the **potassium** current.

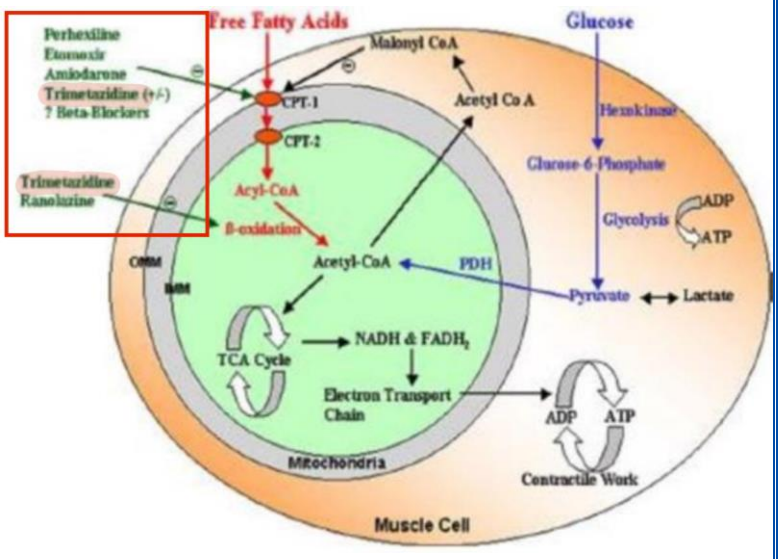
• The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of I_{kr} potassium current, which prolongs the ventricular action potential.

• The drug's effect on the QT interval is increased and becomes problematic in the setting of **liver dysfunction**; thus, it is contraindicated in persons with mild to severe liver disease.

• Ranolazine have some beta oxidation inhibiting activity (metabolic activity); however, most of its affect is on inhibiting the late Na+ influx and late overload of Ca2+.

3- Trimetazidine

• Inhibition of the reduction of adenosine triphosphate (ATP), stimulation of glucose consumption by the myocardium.



• Trimetazidine (a metabolic drug) inhibits beta oxidation for fatty acids to acytel-CoA reduction, by inhibiting Carnitine Palmitoyltransferase-1 **(CPT-1).** It switches the cardiac energy metabolism from fatty acid oxidation to glucose oxidation. And in

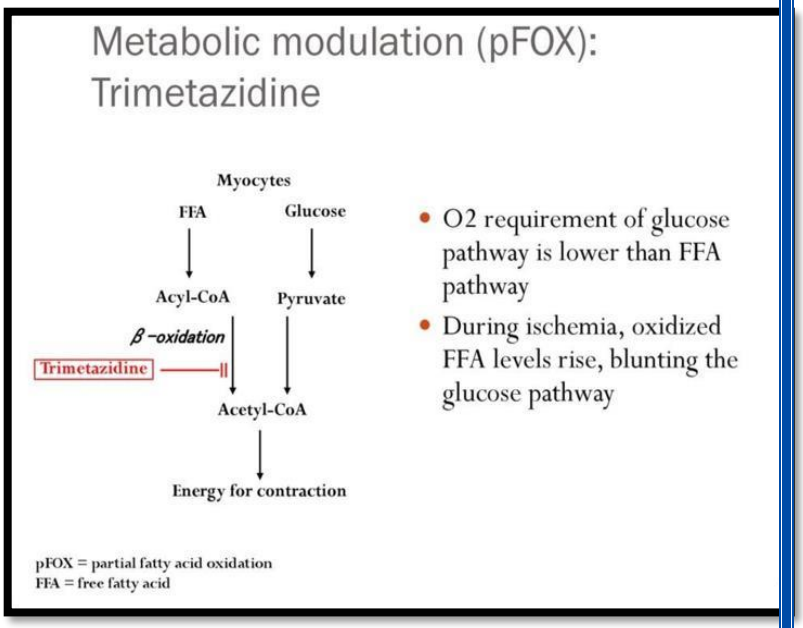
ischemic diseases where we have less oxygen, the heart will build most of its energy production from the fatty acids (80% or more), and glucose metabolism requires less oxygen, so switching the energy utilization from fatty acid to glucose oxidation, it will reduce the oxygen demand and it is much needed in angina, also it improves the performance of athletes.

•Trimetazidine has been included in the list of doping agents.

•**Doing agent** refers to a substance or method used to enhance athletic performance, often by illegal means.

• Trimetazidine has very **limited** hemodynamic effects (meaning it doesn't affect the chronotropic, inotropic activity or blood pressure).

• Trimetazidine metabolic modulation effects (pFOX): It inhibits beta oxidation and switches towards glucose → pyruvate, instead of free fatty acids → acyl-CoA, to reduce the oxygen requirements for the cell in case of ischemia and hypoxia.



- From google: fueling with palmitic acid requires ~15% more oxygen than fueling with glucose.

Side effects of Trimetazidine

•It causes symptoms of Parkinsonism. Therefore, among its main contraindications is Parkinson's disease.
• Another **rare** side effect of Trimetazidine is Extrapyramidal symptoms: symptoms such as tremor, rigidity, akinesia, hypertonia (symptoms are linked to the motor movement, many drugs produce those side effects and it is often associated with the schizophrenic and anti-psychotic drugs, we will talk about them in the CNS inshallah).
• Restless leg syndrome.
• **Not to prescribe to** patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome.

• Some research is currently being conducted to assess the effectiveness of Trimetazidine and its clinical trials. As a result, there may be potential developments in the future. However, for the purposes of this exam, it is not relevant to our focus.

4- Nicorandil.

• Nicorandil has two functioning parts, (it's a nitrate like drug with positive K+ channel effect):

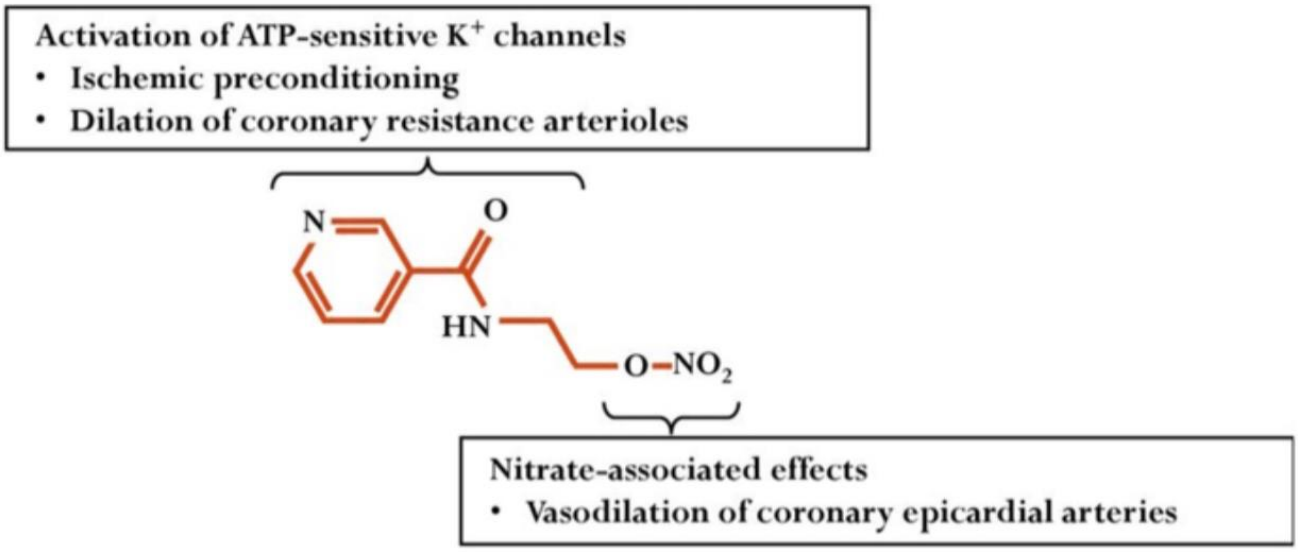
1. One part works as a **nitrate** (it ends with dil), causes vasodilation of coronary epicardial arteries (nitrate-associated effect).
2. Another part will work on the **potassium levels**, opens K+ channels, which will reduce ischemic preconditioning and cause dilation of coronary resistant arterioles (activation of ATP-sensitive K+ channels).

• It **increases** cyclic guanosine monophosphate(cGMP) and facilitates the opening of mitochondrial potassium adenosine triphosphate channels (opens potassium channels).

• Nicorandil is considered as a second-line option to treat patients with **stable angina** when they do not tolerate or cannot use beta-blockers (or calcium channel antagonists such as verapamil and diltiazem) or when they do not respond enough to first-line medications (its use is limited).

• Among the adverse effects are gastrointestinal, skin and mucosal ulcerations (especially if there is concomitant use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs). In this case, the drug should be **discontinued permanently.**

Preconditioning: Nicorandil



Thank You!

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