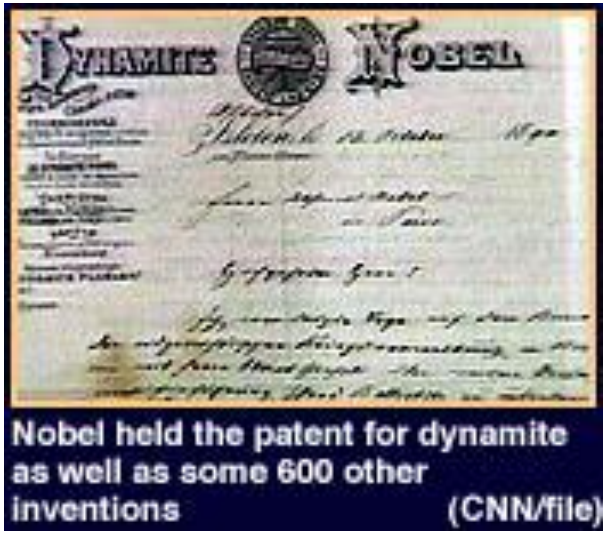
NITROVASODILATORS

THE EXAMPLE OF AN "EXPLOSIVE" DISCOVERY….

Ascanio Sobrero
(1812-1888)

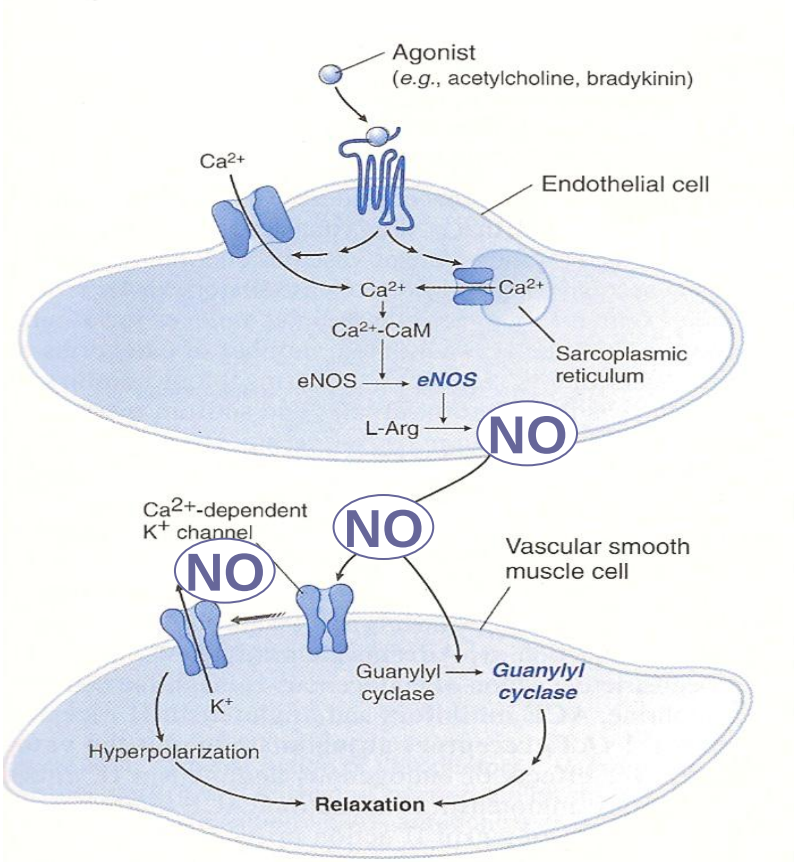
Alfred Nobel
(1833-1896)



Nobel held the patent for dynamite as well as some 600 other inventions (CNN/file)

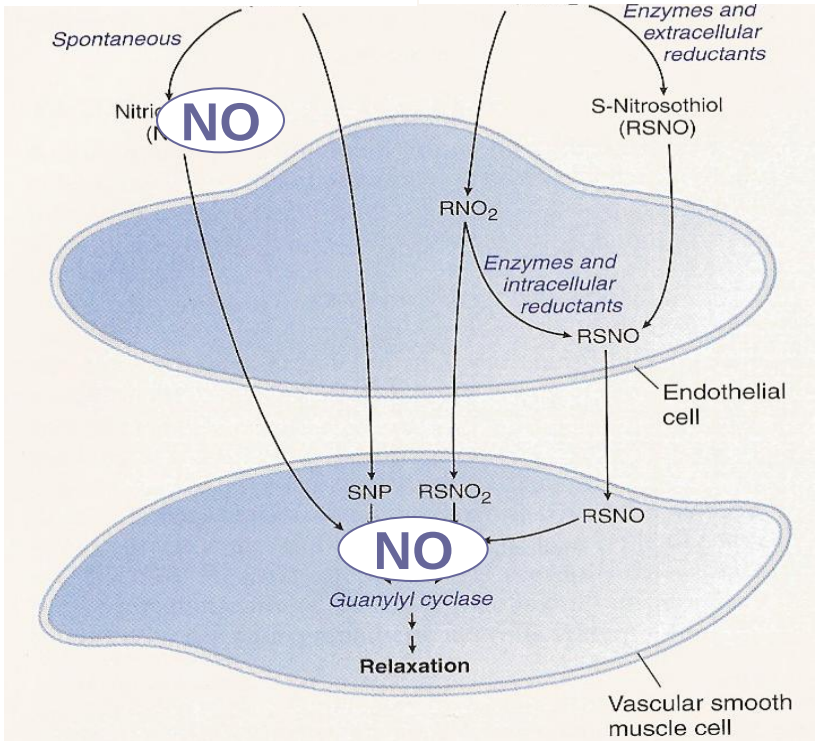
Murrel W: nitroglicerine for angina treatment
Lancet, 1879

NITROVASODILATORS



Sodium NITROPRUSSIDE

ORGANIC NITRATES



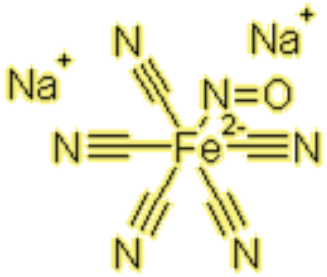
Two basic types of nitrodilators:

1. those that **release NO spontaneously** (e.g., sodium nitroprusside and molsidomine)
2. organic nitrates that **require an enzymatic process to form NO.** Organic nitrates do not directly release NO, however, their nitrate groups interact with enzymes and intracellular sulfhydryl groups that reduce the nitrate groups to NO or to S-nitrosothiol, which then is reduced to NO.

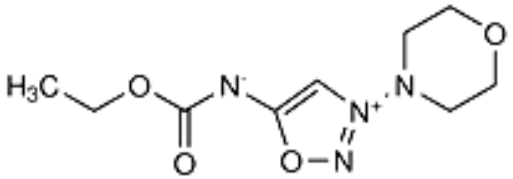
NITROVASODILATORS

NON ORGANIC NITRATES

release NO spontaneously



SODIUM NITROPRUSSIDE



MOLSIDOMINE

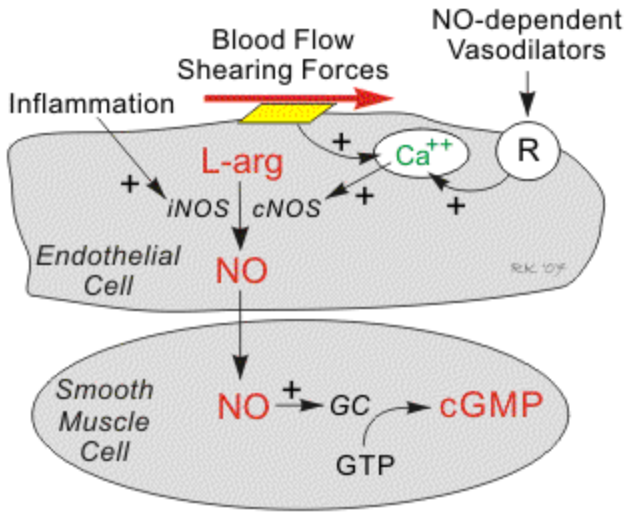
ORGANIC NITRATES

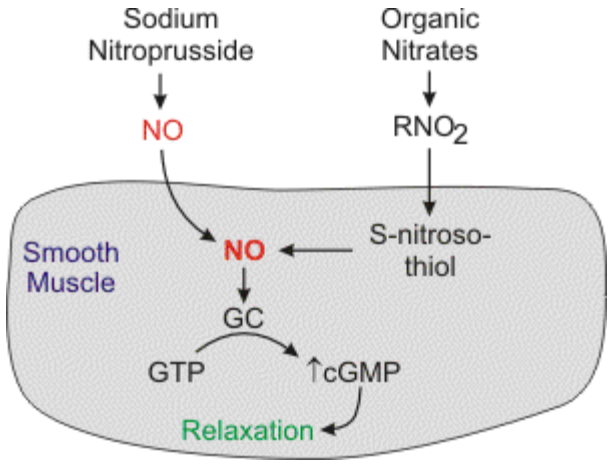
esters of nitric acid which are reduced to NO in the body.

- **GLYCERYL TRINITRATE (NITROGLYCERIN)**
- **ISOSORBIDE MONONITRATE AND DINITRATE**
- **PENTAERITHRITYL TETRANITRATE**
- **PROPATYLNITRATE**
- **TENITRAMINE**
- **TROLNITRATE**

NICORANDIL (*additionally acts as a potassium channel opener)*

KEY EFFECTS OF ENDOGENOUS NITRIC OXIDE (NO)





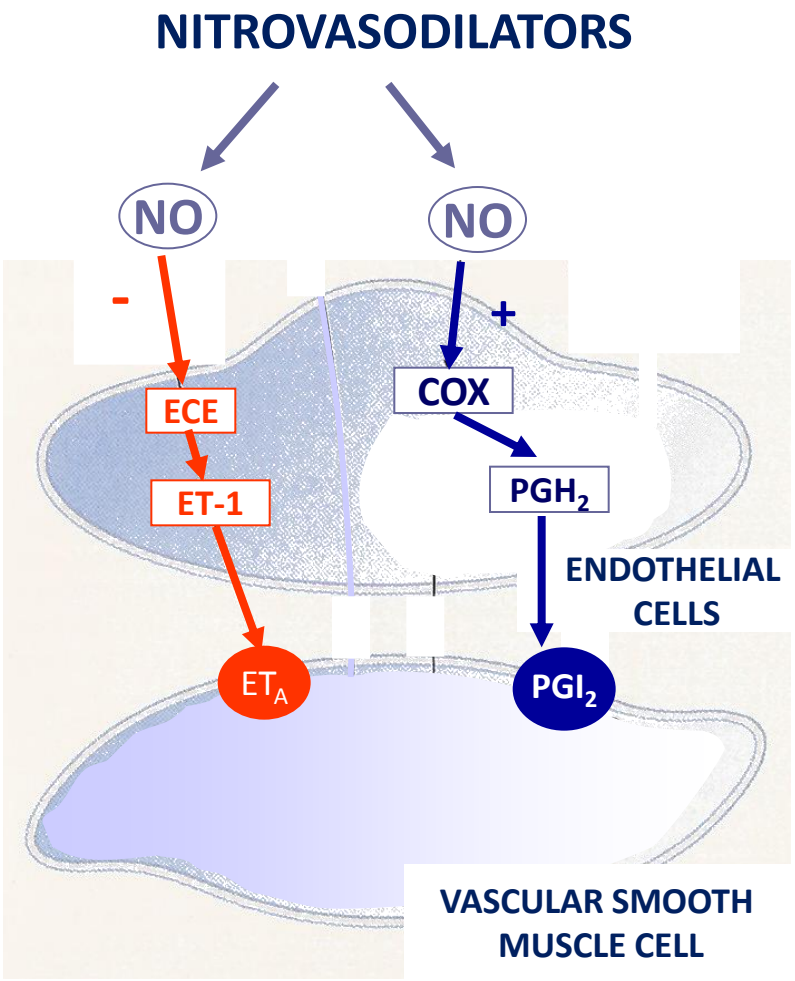
Nitric oxide (NO) is produced by many cells in the body; however, its production by vascular endothelium is particularly important in the regulation of blood flow. Because of its importance in vascular function, abnormal production of NO, as occurs in different disease states, can adversely affect blood flow and other vascular functions.

Nitrodilators are drugs that mimic the actions of endogenous NO by releasing NO or forming NO within tissues. These drugs act directly on the vascular smooth muscle to cause relaxation and therefore serve as endothelial-independent vasodilators.

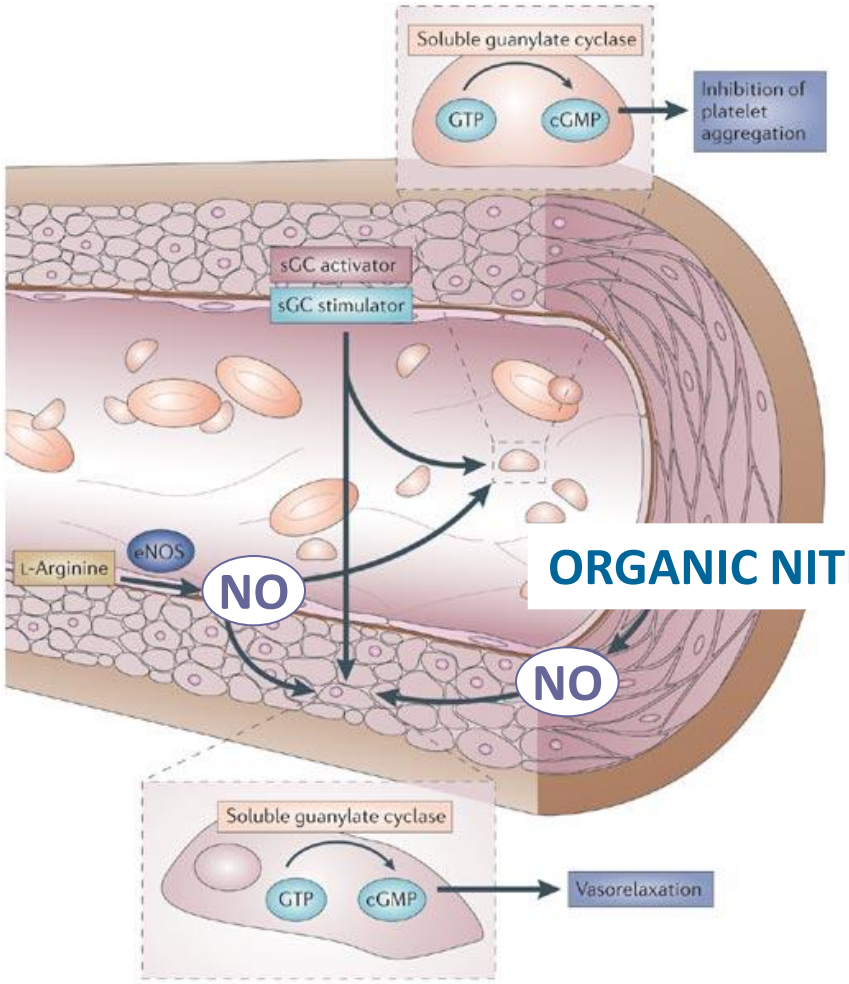
NITROVASODILATORS MODULATE ENDOTHELIAL FUNCTION

By improving NO production or mimicking NO actions, NITROVASODILATORS exert the following effects:

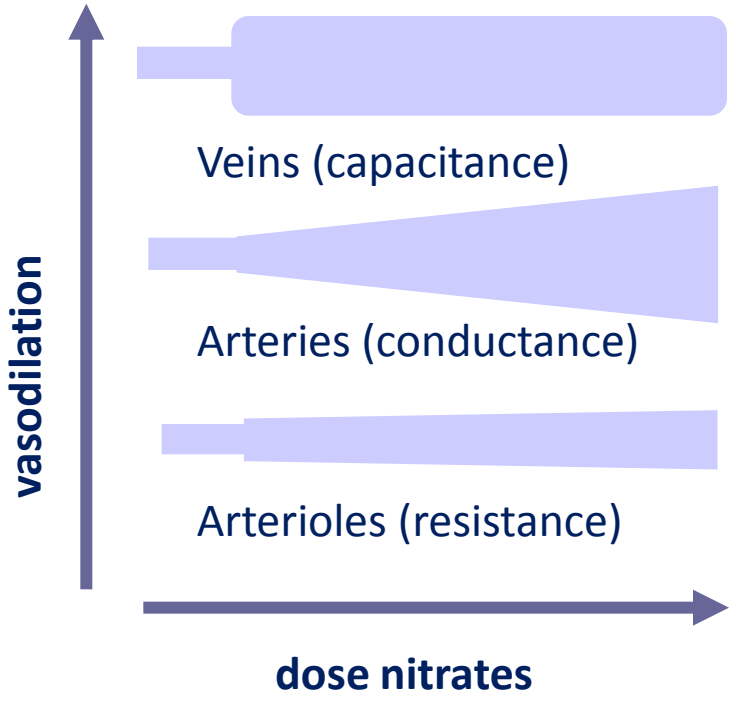
- Direct vasodilation (flow dependent and receptor mediated)
- Indirect vasodilation by inhibiting vasoconstrictor influences (e.g., inhibits angiotensin II and sympathetic vasoconstriction)
- Anti-thrombotic effect - inhibit platelet adhesion to the vascular endothelium. organic nitrates require bioconversion to release NO, which is not implemented in platelets, leading to poor anti-aggregatory effect.
- Anti-inflammatory effect - inhibits leukocyte adhesion to vascular endothelium; scavenges superoxide anion
- Anti-proliferative effect - inhibits smooth muscle hyperplasia



INITROVASODILATORS ARE ACTIVE ON VEIN AND ARTERIES



ORGANIC NITRATES



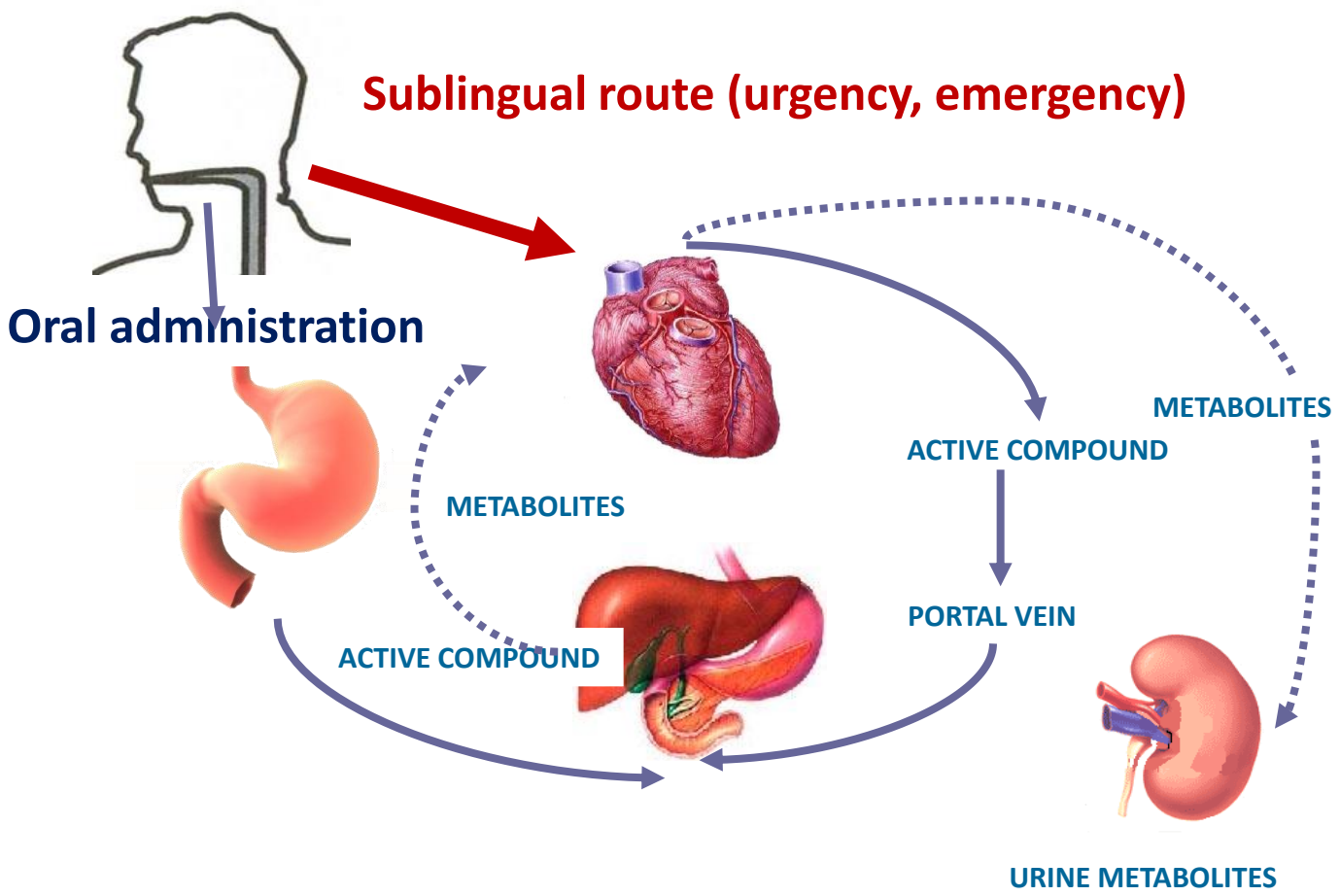
Low concentrations of nitrates preferentially dilate the veins more than the arterioles (gradient response)

MAIN PK FEATURES OF SOME NITRODERIVATES

ADMINISTRATION ROUTE	DOSE	ONSET	DURATION
Sublingual			
Nitroglycerin	**0.3-0.6 mg**	**2-5 min**	**10-30 min**
Isosorbide dinitrate	**5 mg**	**5-15 min**	**1-2 hours**
Spray nitroglicerin	**0.4 mg**	**2-5 min**	**10-30 min**
Oral			
Isosorbide dinitrate	**20-40 mg**	**30 min**	**2-6 hours**
Isosorbide 5-mononitrate	**20-40 mg**	**30 min**	**2-6 hours**
Isosorbide 5-mononitrate (S Retard)	**50-80 mg**	**30 min**	**6-12 hours**
Transdermal (patch)			
Nitroglycerin Isosorbide dinitrate	**5-40 mg**	**30 min**	**4-(24) hours**

NITROPRUSSIDE is used **intravenously** for the treatment of hypertensive crises, heart failure, and lowering of blood pressure during surgery

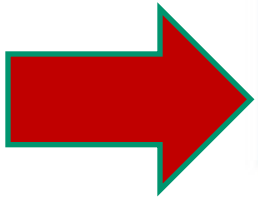
PK: INTENSE LIVER METABOLISM WHEN ORALLY ADMINISTERED REDUCES NITRATE BIOAVAILABILITY



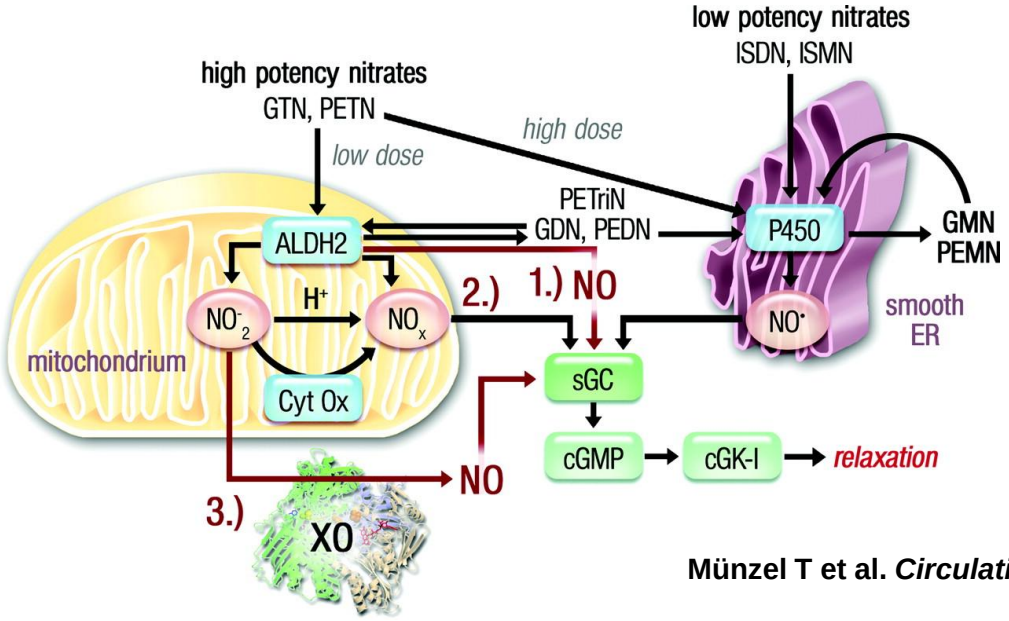
The metabolites of organic nitrates are biologically active and have a longer half-life than the parent compound. Therefore, the metabolites contribute significantly to the therapeutic activity of the compound.

AVAILABILITY of NITRATES by ORAL ADMINISTRATION

GIT availability	Route	Onset	Duration
Glyceryl trinitrate			
poor	sublingual (tablet, spray)	<5 minutes	<1 hour
	patch	30–60 minutes	prolonged
	IV infusion	<10 minutes	
Isosorbide dinitrate			
20–25%	oral tablet	15–40 minutes	4–6 hours
	sublingual tablet	<10 minutes	1–2 hours
Isosorbide mononitrate			
100%	controlled release tablet	1–2 hours	prolonged



BIOACTIVATION OF ORGANIC NITRATES



Münzel T et al. *Circulation*. 2011;123:2132-2144

In the liver, glyceryl trinitrate is metabolized by several enzymes, including glutathione-S-transferases, xanthine oxidoreductase, and the cytochrome P450.

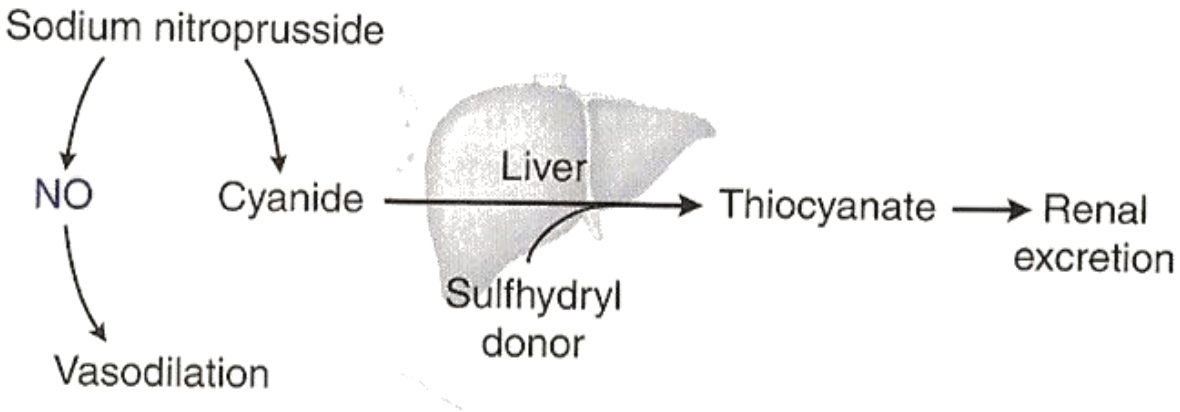
In the endothelial cells, the **reductase activity** converts the organic nitrates to nitrite and denitrated metabolites. There are 3 proposed mechanisms including:

- ***nitrogen oxide formed via a reduction of nitrite (NO2),***
- ***nitric oxide, formed directly in response to interaction with the ALDH-2,***
- ***NO2, released from the mitochondria, may be reduced by the xanthine oxidase in the cytoplasm to form NO.***

MEDICAL USE FOR NITROVASODILATORS

• HYPERTENSION

Nitrodilators are not used to treat chronic primary or secondary hypertension; however, **SODIUM NITROPRUSSIDE** and nitroglycerine are used to ***lower blood pressure in acute hypertensive emergencies*** that may result from a pheochromocytoma, renal artery stenosis, aortic dissection, etc. Nitrodilators may also be used during surgery to control arterial pressure within desired limits.



Prolonged use of **SODIUM NITROPRUSSIDE** carries the risk of ***THIOCYANATE TOXICITY*** because nitroprusside releases cyanide along with NO. The thiocyanate is formed in the liver from the reduction of cyanide by a sulfhydryl donor.

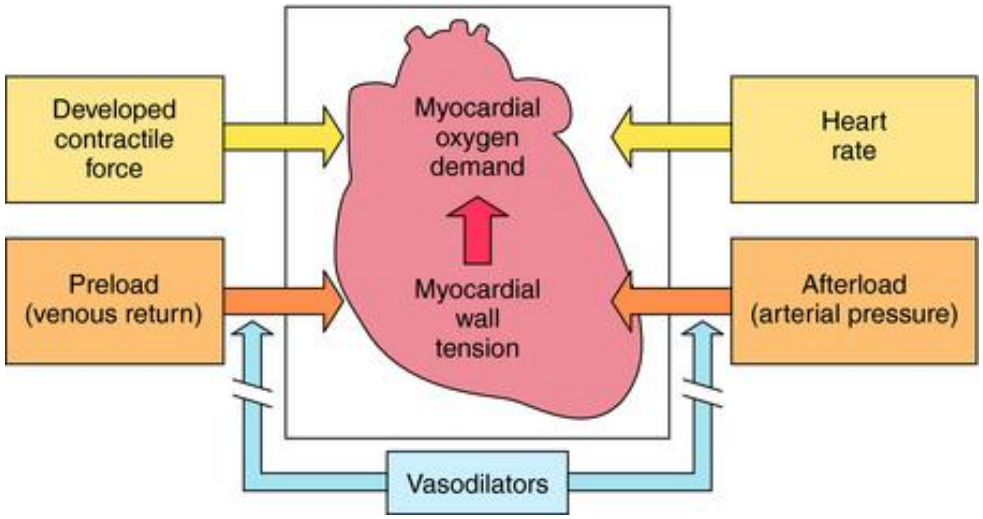
MEDICAL USE FOR NITROVASODILATORS

- **HEART FAILURE**

Nitrodilators are used in acute heart failure and in severe chronic heart failure. Arterial dilation reduces afterload on the failing ventricle and leads to an increase in stroke volume and ejection fraction.

Furthermore, the venous dilation reduces venous pressure, which helps to reduce edema.

Reducing both afterload and preload on the heart also helps to improve the mechanical efficiency of dilated hearts and to reduce wall stress and the oxygen demands placed on the failing heart.

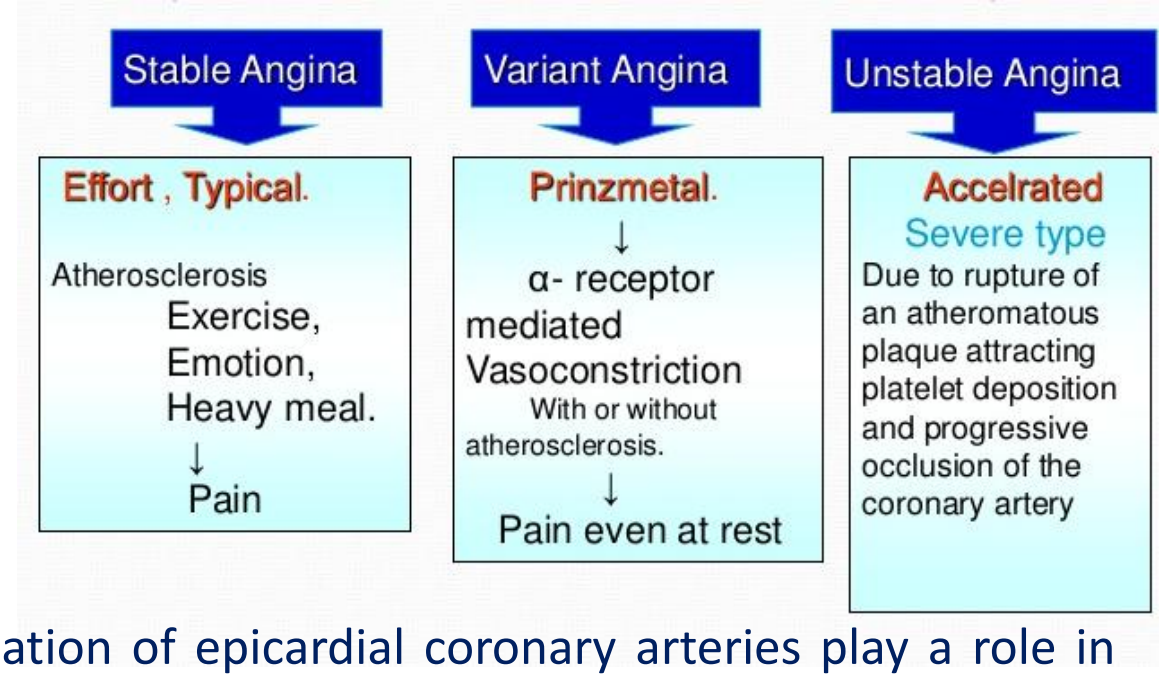


MEDICAL USE FOR NITROVASODILATORS

• ANGINA and MYOCARDIAL INFARCTION

Organic nitrates are used extensively to treat angina and myocardial infarction. They are useful in Printzmetal's variant angina because they improve coronary blood flow (i.e., increase oxygen supply) by reversing and inhibiting coronary vasospasm.

They are important in other forms of angina because they reduce preload on the heart by producing venous dilation, which decreases myocardial oxygen demand.



It is unclear if direct dilation of epicardial coronary arteries play a role in the antianginal effects of nitrodilators in chronic stable or unstable angina.

SIDE EFFECTS of NITROVASODILATORS

The most common side effects of nitrodilators are related to an excessive vasodilation and are represented by

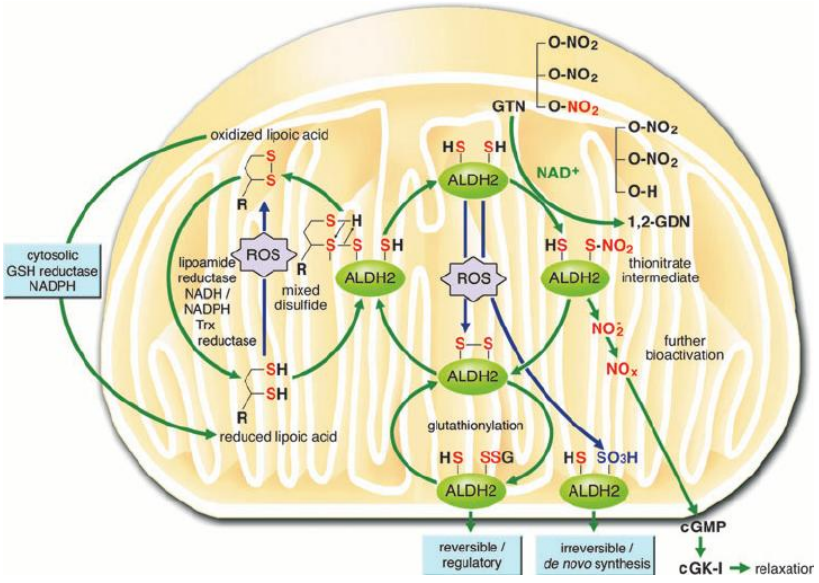
- ***HEADACHE (CAUSED BY CEREBRAL VASODILATION)***
- ***AND CUTANEOUS FLUSHING (MAINLY IN THE HEAD AND NECK REGION).***

Other side effects include
POSTURAL HYPOTENSION AND REFLEX TACHYCARDIA.
Excessive hypotension and tachycardia can worsen the angina by increasing oxygen demand.

There is clinical evidence that ***NITRODILATORS MAY INTERACT ADVERSELY WITH CGMP-DEPENDENT PHOSPHODIESTERASE INHIBITORS*** that are used to treat erectile dysfunction (e.g., sildenafil [Viagra®]). The reason for this adverse reaction is that nitrodilators stimulate cGMP production and drugs like sildenafil inhibit cGMP degradation. When combined, these two drug classes greatly potentiate cGMP levels, which can lead to hypotension and impaired coronary perfusion.

NITRATE TOLERANCE

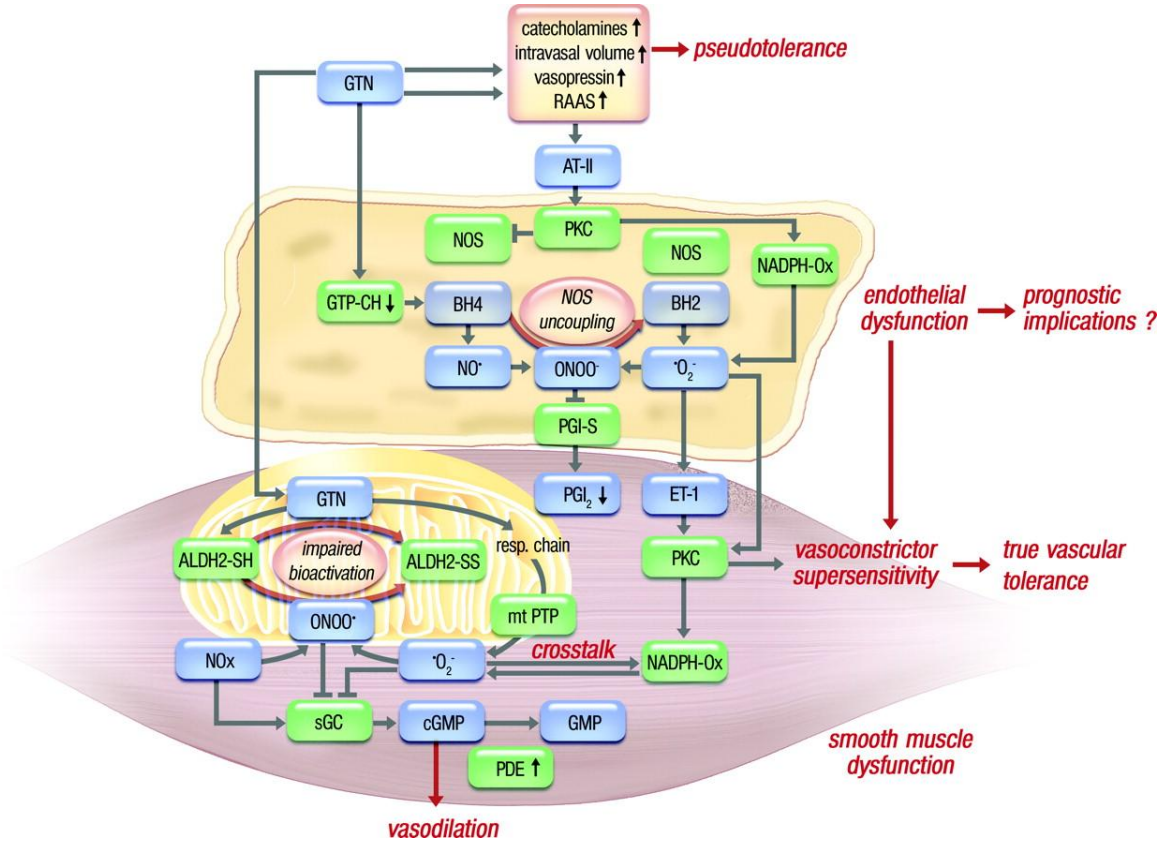
- Continuous or frequent exposure to nitrates can lead to the development of tolerance.
- The mechanism is not completely understood, but it is likely to be related to the enzymes converting the nitrates to NO
- Beyond the loss of the vasodilatory action of nitrates, a typical phenomenon associated with these changes is the worsening of anginal symptoms caused by the withdrawal of nitrate therapy, the so-called rebound effect
- Tolerance of the hemodynamic effects of GTN can be avoided by the use of schedules that allow a regenerating daily interval of at least 12 hours. Although this strategy is intrinsically flawed by the fact that patients cannot receive a 24-hour treatment (typically do not receive nitrate in the early morning hours when the incidence of acute coronary syndromes is highest), it is effective in maintaining the hemodynamic effects of the nitrate.



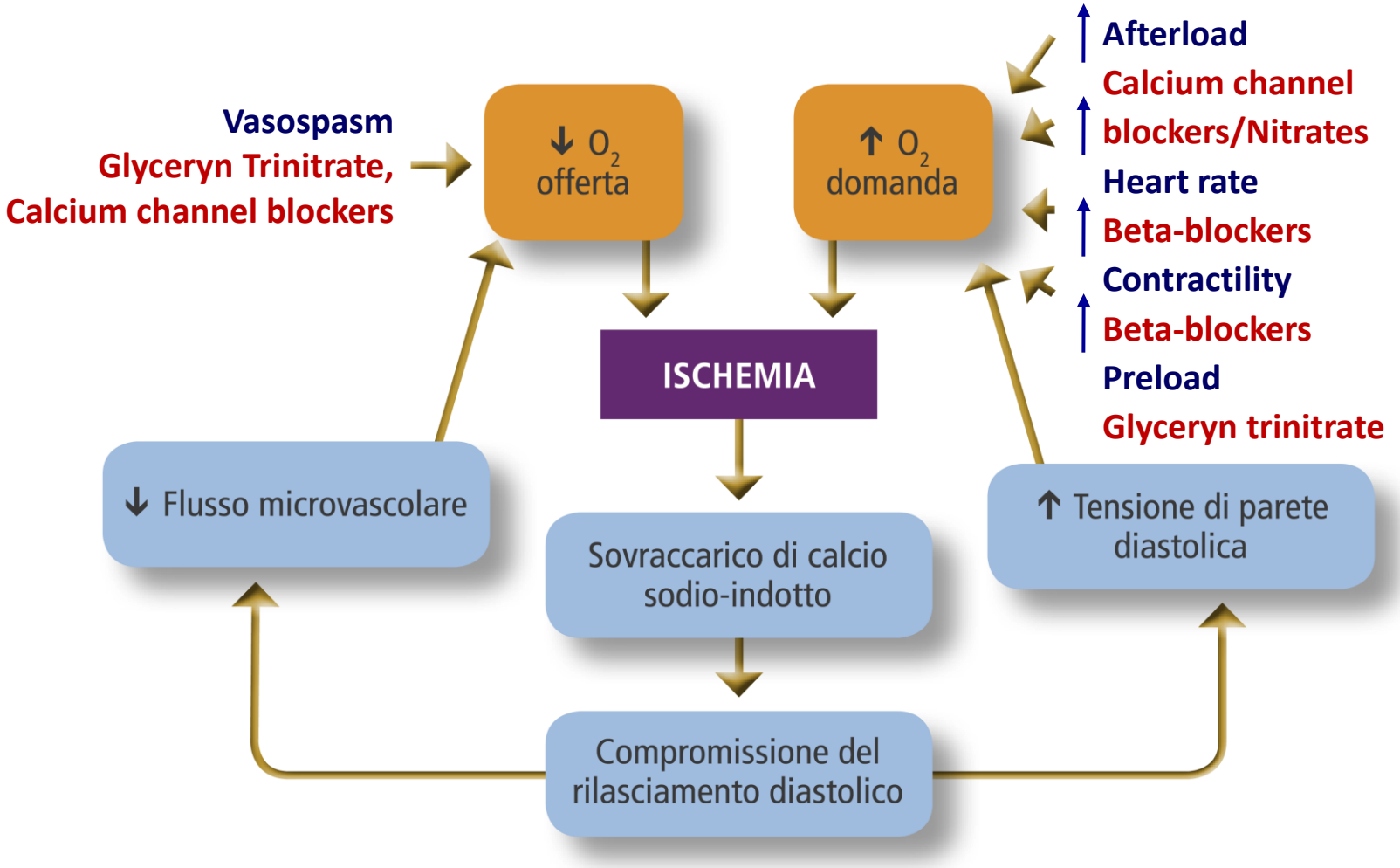
NITRATE PSEUDOTOLERANCE

- The vasodilation evoked by intravenous, oral, and transdermal nitrate therapy causes the release of catecholaminesand plasma vasopressin and increases plasma renin activity and aldosterone levels.

- Such activation of neurohormonal vasoconstrictor forces has been demonstrated in patients with coronary artery disease, patients with heart failure, and healthy subjects.



CONVENTIONAL ANTI-ANGINAL THERAPIES



NEW APPROACHES TO MYOCARDIAL ISCHEMIA

- **FASUDIL** (Rho kinase inhibition)

  RhoA/Rho kinase (ROCK) is an enzyme that plays an important role in mediating vasoconstriction and vascular remodeling in the pathogenesis of PH. ROCK induces vasoconstriction by phosphorylating the myosin-binding subunit of myosin light chain (MLC) phosphatase, thus decreasing MLC phosphatase activity and enhancing vascular smooth muscle contraction

- **TRIMETAZIDINE** (Metabolic modulation)

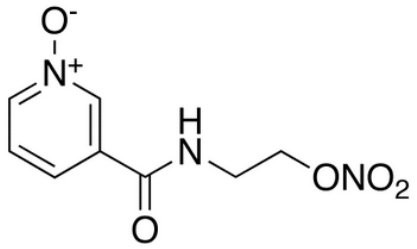
  trimetazidine shifts the metabolism from beta oxidation to glucose. In an ischaemic cell, energy obtained during glucose oxidation requires less oxygen consumption than in the beta-oxidation process. Potentiation of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischaemia.

- **NICORANDIL** (Preconditioning)

- **IVABRADINE** (Sinus node inhibition)

- **RANOLAZINE** (Late Na+ current inhibition)

NICORANDIL



The effect of nicorandil as a vasodilator is mainly attributed to its **nitrate property**. Yet, nicorandil is effective in cases where nitrates are not effective. This is due to its **K+ATP channel agonist** action which causes pharmacological preconditioning and provides cardioprotective effects against ischemia.

KCO (K Channel Opener)

Vasodilation on small arteries

Coronary arteries

REDUCED AFTERLOAD

INCREASED CORONARY FLOW

NITRATE-LIKE

Vasodilation on large vessels

Veins and venules

Epicardial arteries

REDUCED PRELOAD

INCREASED CORONARY FLOW

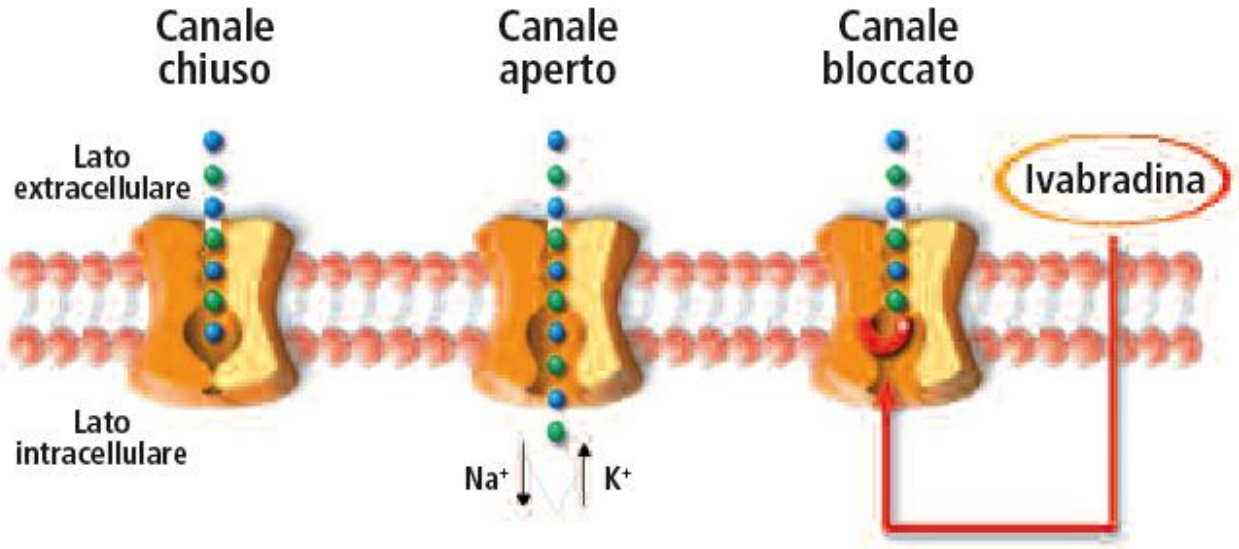
PHARMACOKINETICS: Administration by IV or OS; liver metabolism; half-life 8h.

MEDICAL USE: In patients symptomatic despite other treatments, usually before angioplasty.

SIDE EFFECTS: Headache, flushes, dizziness; caution in patients with gastric ulcers.

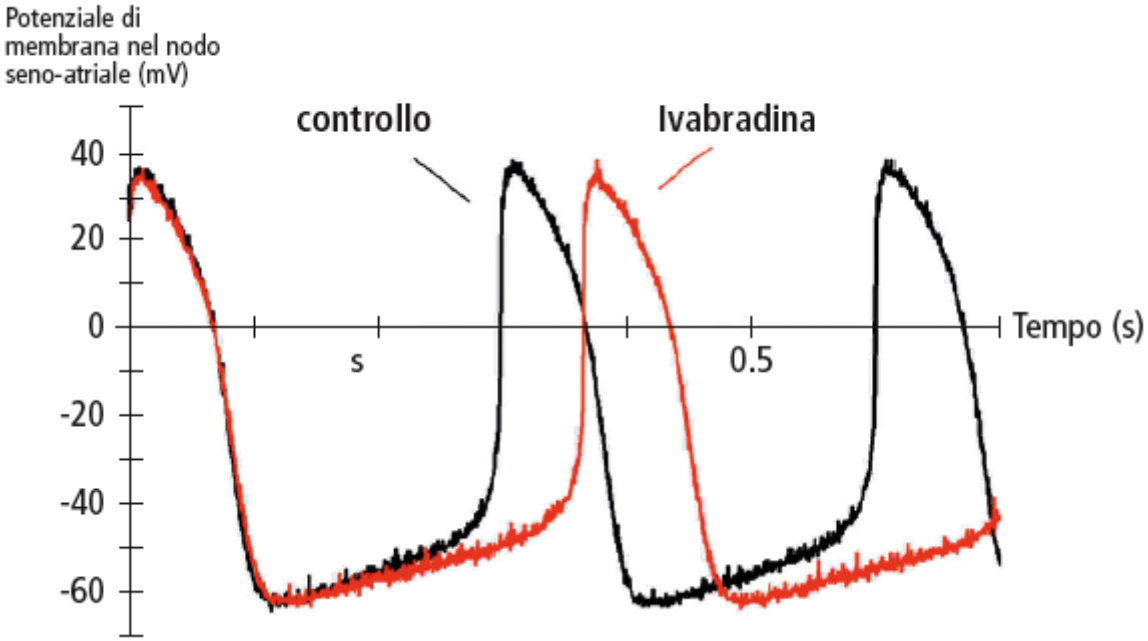
IVABRADINE

Ivabradine acts on the I_f ion current, (*f* is for "funny"- so called because it had unusual properties compared with other current systems known at the time of its discovery) which is highly expressed in the sinoatrial node.



I_f is a mixed Na^+–K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system.
It is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node.

IVABRADINE

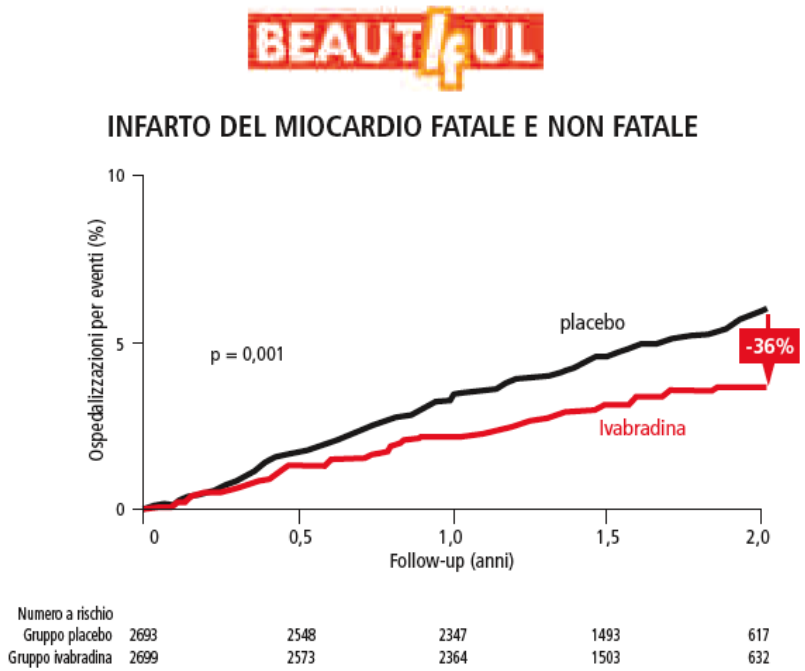


Ivabradine selectively inhibits the pacemaker I_f current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, selectively slowing the heart rate and allowing more time for blood to flow to the myocardium.

This is in contrast to other commonly used rate-reducing medications, such as beta-blockers and calcium channel blockers, which not only reduce heart rate, but also the cardiac contractility.

Given the selective decrease in rate without loss of contractility, ivabradine may prove efficacious for treatment of congestive heart failure without decreases in ejection fraction.

IVABRADINE



MEDICAL USE:

- Chest pain

For the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who cannot take beta blockers. Off-label in the treatment of inappropriate sinus tachycardia.

- Heart failure

It is used in combination with beta blockers in people with LVEF lowers than 35 percent inadequately controlled by beta blockers alone and whose heart rate exceeds 70 beats per minute.

CONTRAINDICATIONS

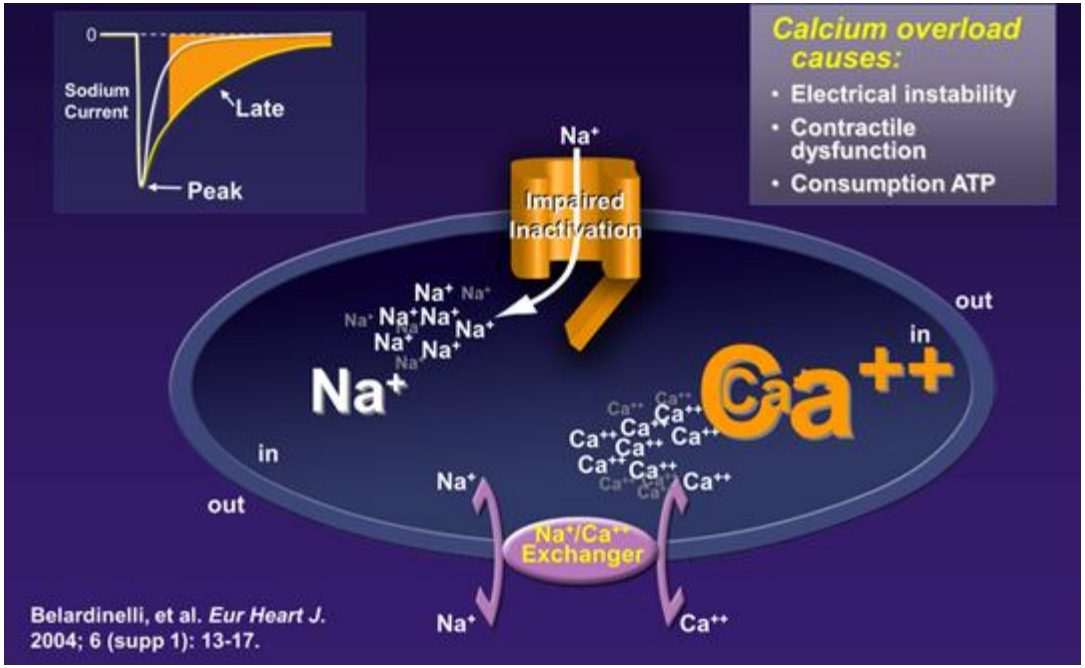
Ivabradine is contraindicated in ***sick sinus syndrome***, and should not be used concomitantly with potent inhibitors of CYP3A4, including azole antifungals (such as ketoconazole), macrolide antibiotics, and the antiretroviral drugs nelfinavir and ritonavir. Use of ivabradine with verapamil or diltiazem is contraindicated.

SIDE EFFECTS

Luminous phenomena (by patients described as sensations of enhanced brightness in a fully maintained visual field). This is probably due to blockage of I_h ion channels in the retina, which are very similar to cardiac I_f. These symptoms are mild, transient, and fully reversible. ***Bradycardia, headaches, AV block, ventricular extrasystoles, dizziness and/or blurred vision***.

RANOLAZINE

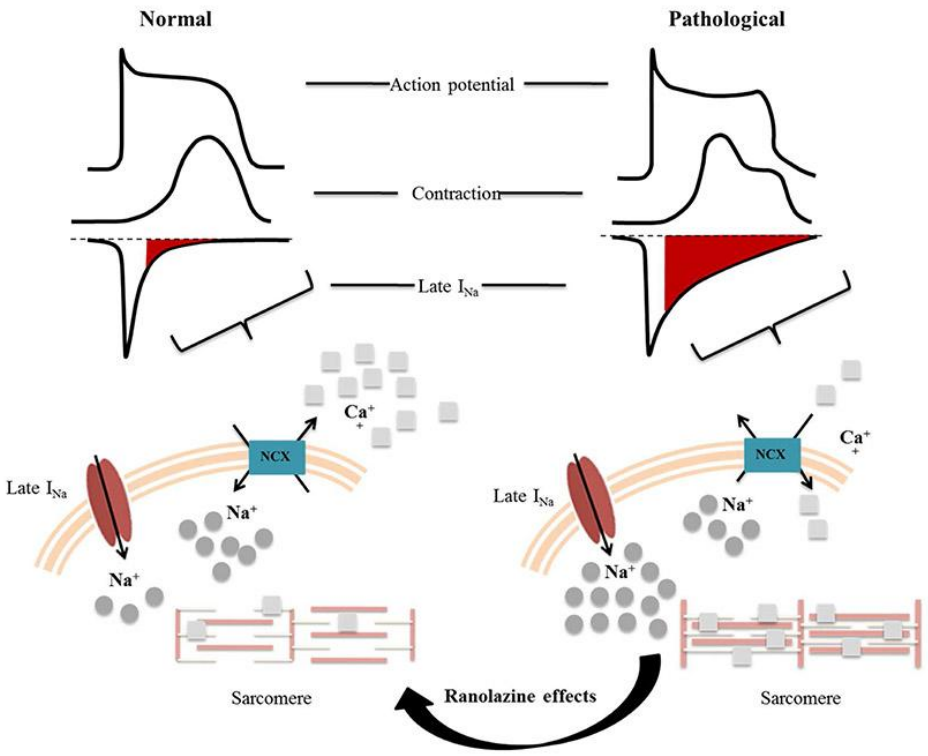
Ranolazine inhibits persistent or late ***inward sodium current (I_{Na})*** in heart muscle in a variety of voltage-gated sodium channels.



Inhibiting this current leads to ***reductions in elevated intracellular calcium levels.*** This in turn leads to reduced tension in the heart wall, leading to reduced oxygen requirements for the muscle.

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

RANOLAZINE



PHARMACOKINETICS

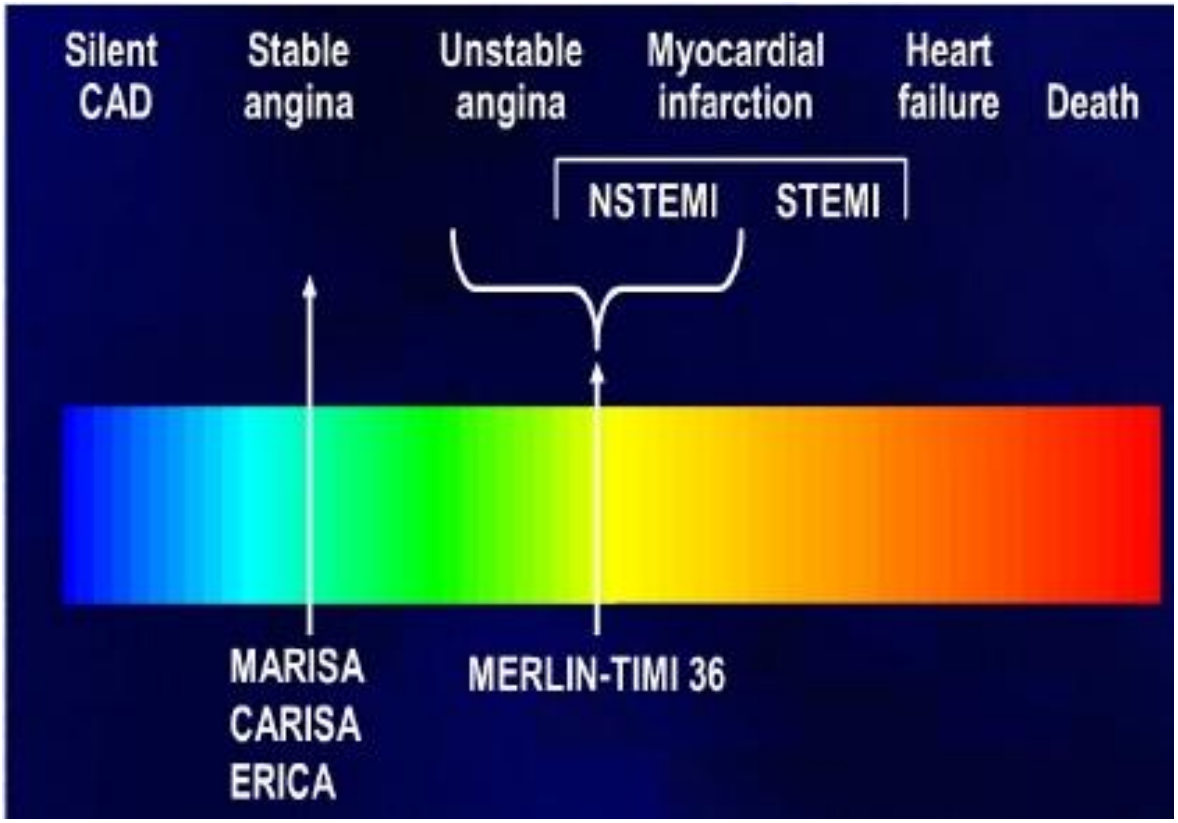
Ranolazine is metabolized mainly by the CYP3A enzyme. It also inhibits another metabolizing enzyme, cytochrome CYP2D6.For this reason, the doses of ranolazine and drugs that interact with those enzymes need to be adjusted when they are used by the same patient.

Ranolazine should not be used with drugs like ketoconazole, clarithromycin, and nelfinavir that strongly inhibit CYP3A nor with drugs that activate CYP3A like rifampin and phenobarbital.

SIDE EFFECTS

The most common side effects are dizziness and constipation. Other side effects include headache and nausea.

RANOLAZINE



MARISA = Monotherapy Assessment of Ranolazine In Stable Angina
CARISA = Combination Assessment of Ranolazine In Stable Angina
ERICA = Evaluation of Ranolazine in Chronic Angina
MERLIN-TIMI = Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes