

DRUGS USED IN ANGINA PECTORIS

Course:

Integrated Therapeutics 1

Lecturer:

Dr. E. Konorev

Date:

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Materials on:

Exam #7

Required reading:

Katzung, Chapter 12

TYPES OF ISCHEMIC HEART DISEASE

- **Angina pectoris** – partial occlusion of coronary artery
 - **Classic angina:** occlusion of the coronary arteries resulting from the formation of atherosclerotic plaque
 - Most common form of angina
 - Symptoms occur during exertion or stress
 - **Unstable angina**
 - Symptoms occur at rest
 - “Unstable” plaque
 - **Variant (Prinzmetal) angina:** spontaneous vasoconstriction of coronary arteries
 - Likely genetic in origin
 - Symptoms occur at rest
 - Much less common than classic angina
- **Myocardial infarction** – complete occlusion of the coronary artery

**TYPICAL
PROGRESSION
OF EVENTS IN
ISCHEMIC
HEART DISEASE**

High Cholesterol

- Formation of atherosclerotic plaques
- **No Symptoms**

Stable Angina

- Partial occlusion of coronary artery
- **Symptoms only during exertion**

Unstable Angina

- Sudden exacerbation of partial occlusion due to unstable plaque
- **Symptoms increase in frequency and begin to occur at rest**

Acute Myocardial Infarction

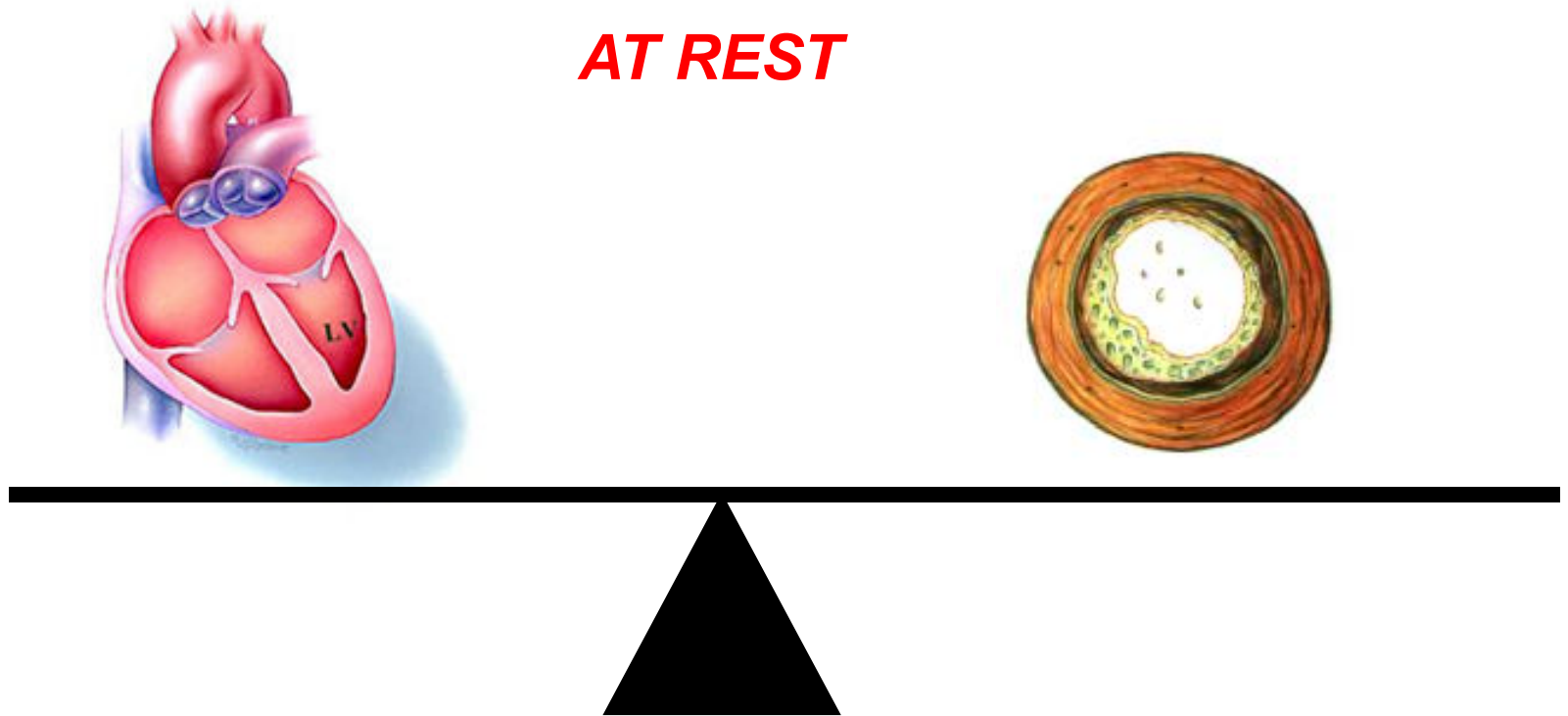
- Complete occlusion of coronary artery
- Cell death and myocardial damage

Acute Heart Failure

Congestive Heart Failure

Cardiac Arrhythmias

ANGINA – IMBALANCE BETWEEN OXYGEN DEMAND OF THE HEART AND OXYGEN SUPPLY VIA THE CORONARY ARTERIES



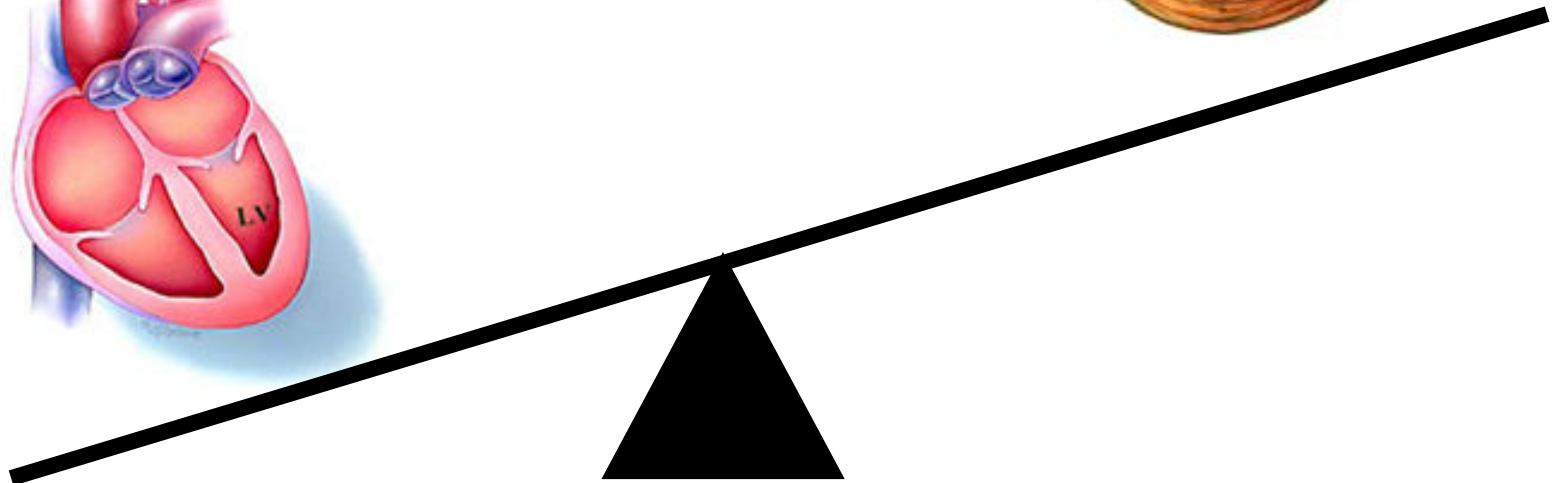
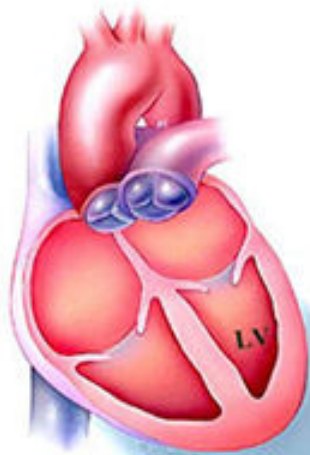
Oxygen demand of the heart = supply of oxygen through partially blocked coronary artery

NO SYMPTOMS

ANGINA – IMBALANCE BETWEEN OXYGEN DEMAND OF THE HEART AND OXYGEN SUPPLY VIA THE CORONARY ARTERIES

DURING EXERTION

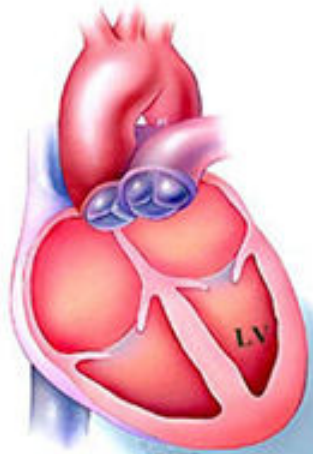
- EXERCISE
- STRESS



Oxygen demand of the heart >> supply of oxygen through partially blocked coronary artery

CHEST PAIN

APPROACHES TO TREAT ANGINA PECTORIS



TO REDUCE
OXYGEN DEMAND

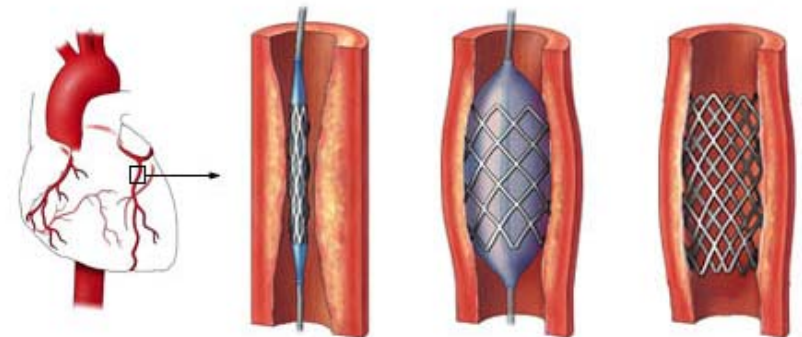
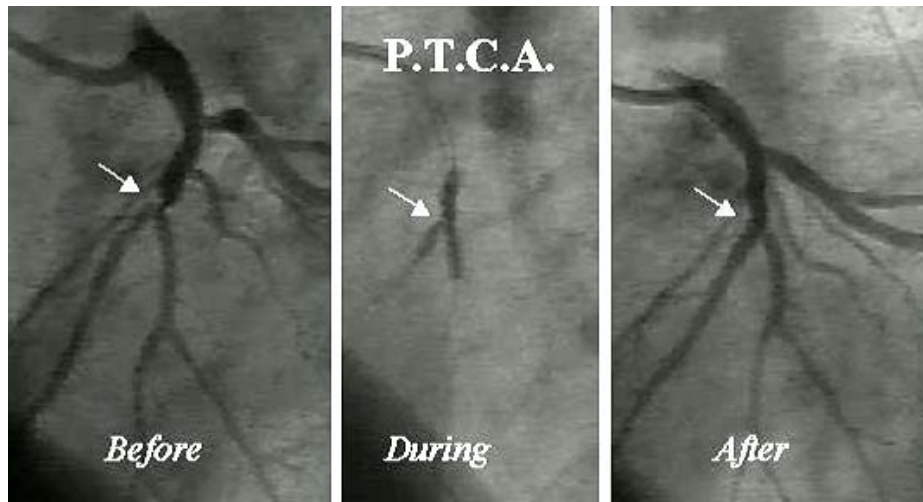
DECREASE
CARDIAC
WORK

TO INCREASE
OXYGEN SUPPLY

INCREASE BLOOD
FLOW THROUGH
CORONARY
ARTERIES

APPROACHES TO TREAT ANGINA PECTORIS

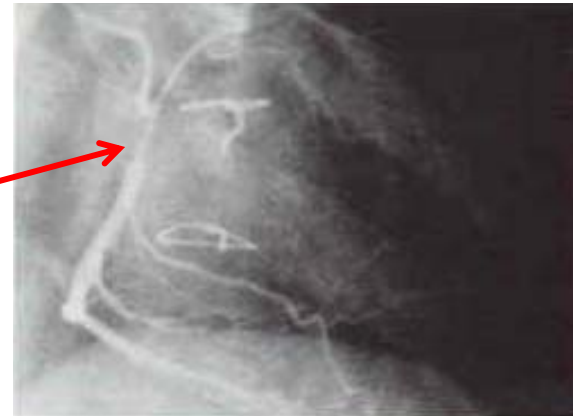
- To increase (or restore) coronary blood flow – surgical and non-surgical revascularization approaches
 - Thrombolytic therapy
 - Coronary artery bypass grafting
 - Percutaneous transluminal coronary angioplasty (PTCA)
 - Laser angioplasty – burning of plaques
 - Atherectomy – tip of catheter shears off the plaque
 - Stent – expandable tube used as scaffolding to open vessel



APPROACHES TO TREAT ANGINA PECTORIS

- To increase coronary blood flow using vasodilators
 - Useful in **vasospastic (Prinzmetal) angina**
 - To relieve coronary spasm
 - To restore blood flow into ischemic area
 - Vasodilators are used

Coronary Spasm

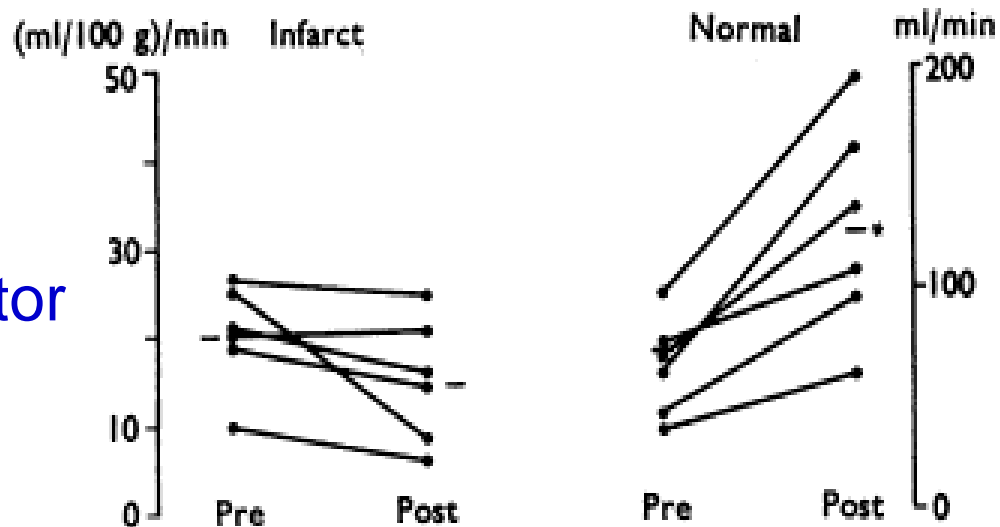


Spasm of proximal right coronary artery and its treatment with a vasodilator

APPROACHES TO TREAT ANGINA PECTORIS

- To increase coronary blood flow using vasodilators
 - **Not useful** in atherosclerotic (classic) angina
 - “Stealing” phenomenon – redistribution of blood to non-ischemic areas – associated with the dilation of small arterioles (example – **Dipyridamole**)

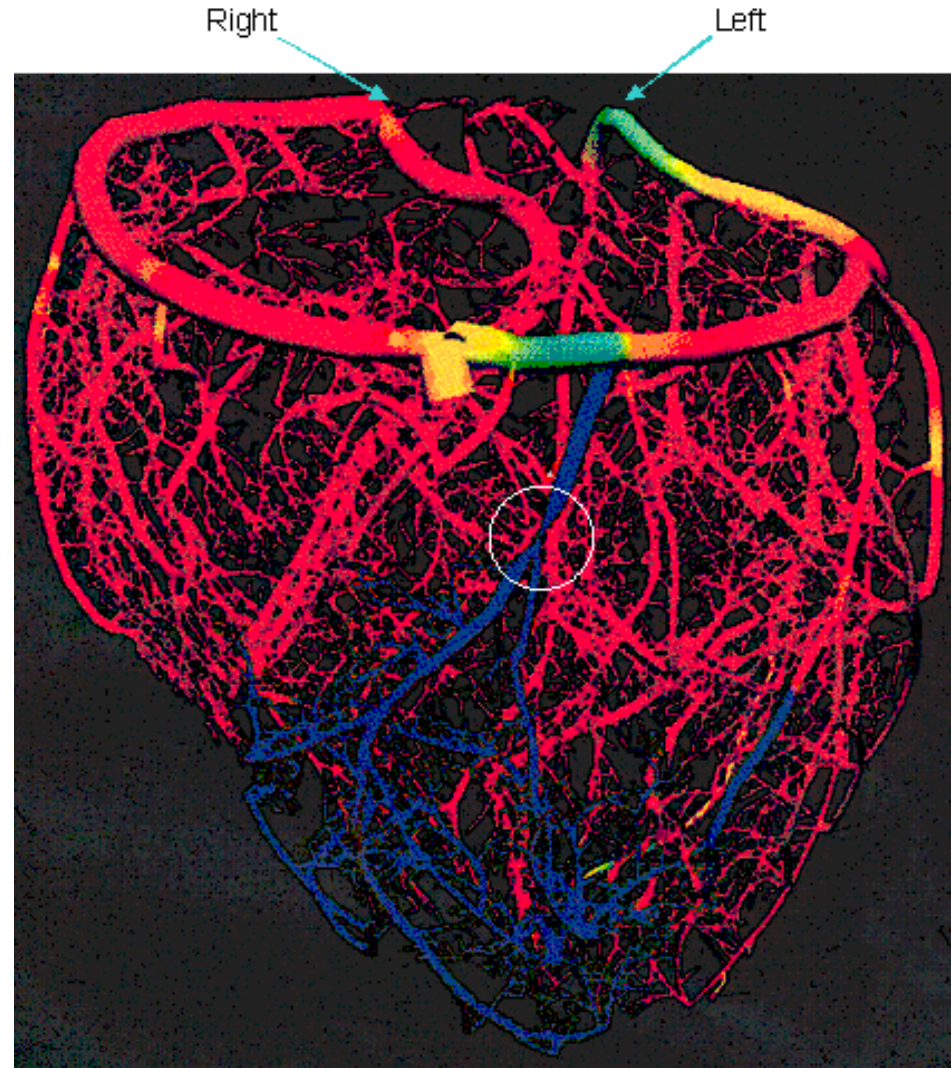
Blood flow in ischemic and remote non-ischemic myocardium: Effect of vasodilator dipyridamole (Marshall and Parratt, 1973)



APPROACHES TO TREAT ANGINA PECTORIS

Model of coronary circulation in angina pectoris

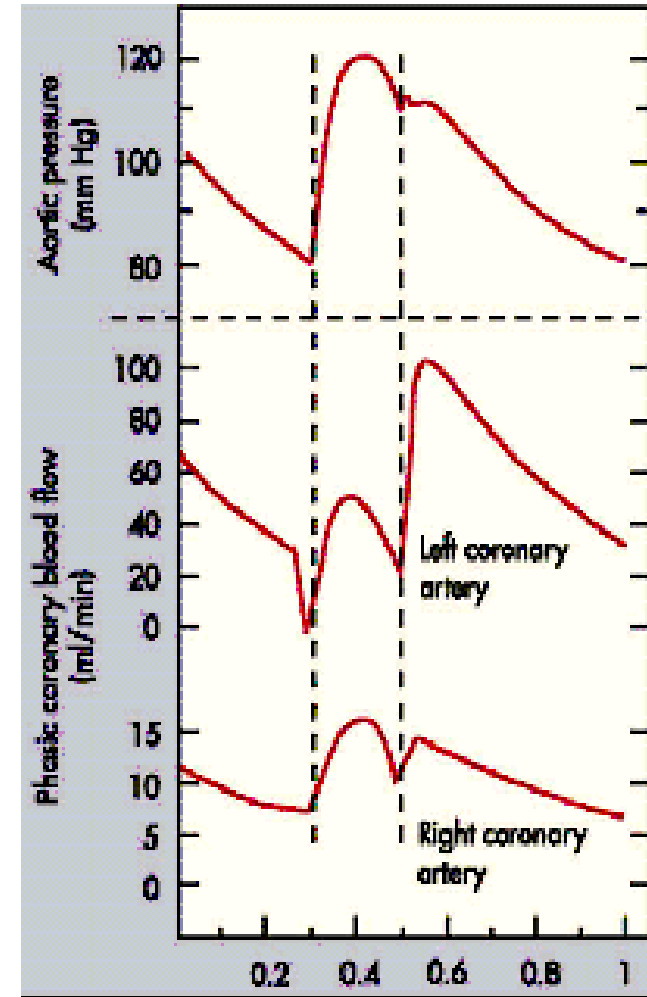
- Rapid flow is indicated by red and slow flow by blue
- Low flow blue area shows the effect of an obstruction to the flow through the descending branch of left coronary artery
- Rigid obstruction limits the flow through the area of myocardium supplied by the branch



APPROACHES TO TREAT ANGINA PECTORIS

Factors that determine coronary blood flow

- Aortic diastolic pressure
- Heart rate
- Compression force of the myocardium on coronary vessels
 - **Ejection time** – increased ejection time will diminish blood flow
 - **Intraventricular pressure** – will increase cardiac wall stress and compression force
 - **Ventricular volume** – increased volume will enhance wall stress
 - **Wall thickness** – myocardial hypertrophy will decrease coronary blood flow (hypertrophy is a risk factor for CAD)



Phasic flow in left and right coronary arteries

APPROACHES TO TREAT ANGINA PECTORIS

To reduce myocardial oxygen demand

- Determinants of myocardial oxygen demand
 - Heart rate
 - Contractility
 - Preload
 - Afterload
- Reducing oxygen demand using drug therapy
 - Nitrates and nitrites (nitrovasodilators)
 - Calcium channel blockers
 - Beta-blockers
 - Newer agents

NITROVASODILATORS

- Nitroglycerin
- Isosorbide dinitrate
- Isosorbide mononitrate – active metabolite of the dinitrate
- Amyl nitrite

Pharmacokinetics

- Significant first-pass metabolism – **high nitrate reductase activity in the liver**
- Bioavailability with oral route is low
- Other routes that avoid first-pass metabolism are used
- Partially denitrated metabolites may have activity and longer half-lives
- Denitrated metabolites are excreted by kidneys

NITROVASODILATORS

- Pharmacokinetics

Doseform, Onset and Duration of Available Nitrates

Nitrates	Dosage form	Onset (minutes)	Duration
Amyl nitrite	Inhalant	0.5	3 to 5 min
Nitroglycerin	IV	1 to 2	3 to 5 min
	Sublingual	1 to 3	30 to 60 min
	Translingual spray	2	30 to 60 min
	Transmucosal tablet	1 to 2	3 to 5 hours ¹
	Oral, sustained release	20 to 45	3 to 8 hours
	Topical ointment	30 to 60	2 to 12 hours ²
Isosorbide dinitrate	Transdermal	30 to 60	up to 24 hours ³
	Sublingual	2 to 5	1 to 3 hours
	Oral	20 to 40	4 to 6 hours
Isosorbide mononitrate	Oral, sustained release	up to 4 hours	6 to 8 hours
	Oral	30 to 60	no data

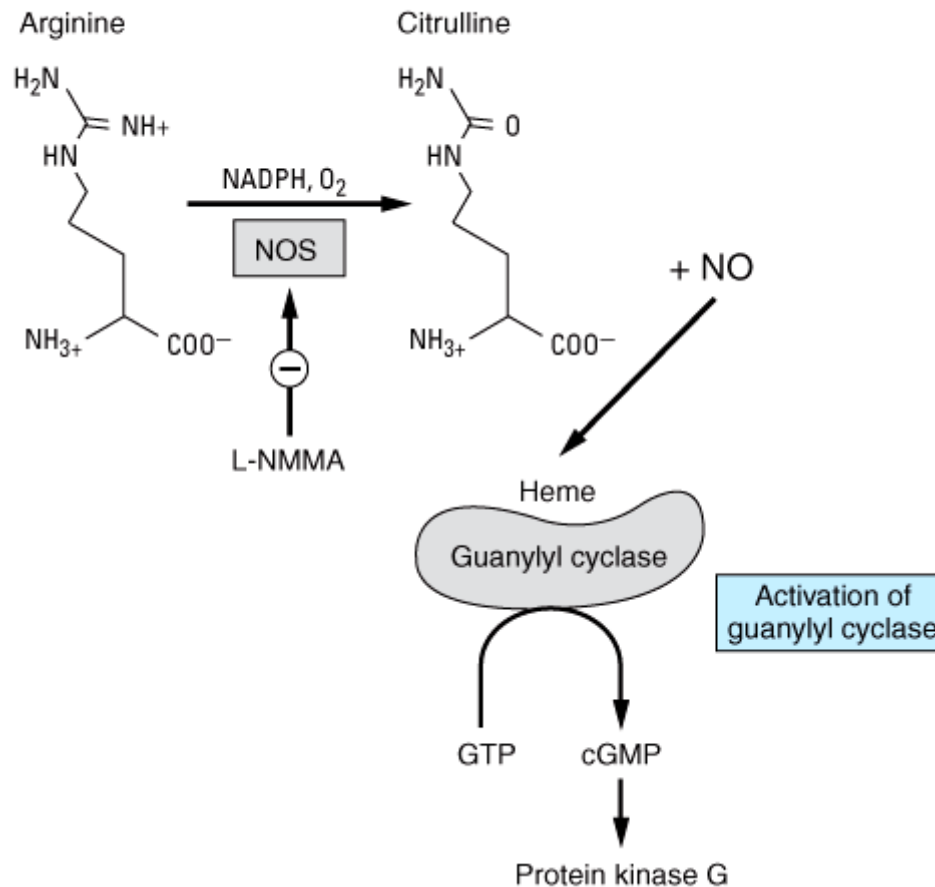
¹ A significant antianginal effect can persist for 5 hours if the tablet has not completely dissolved by this time.

² Depends on total amount used per unit of surface area.

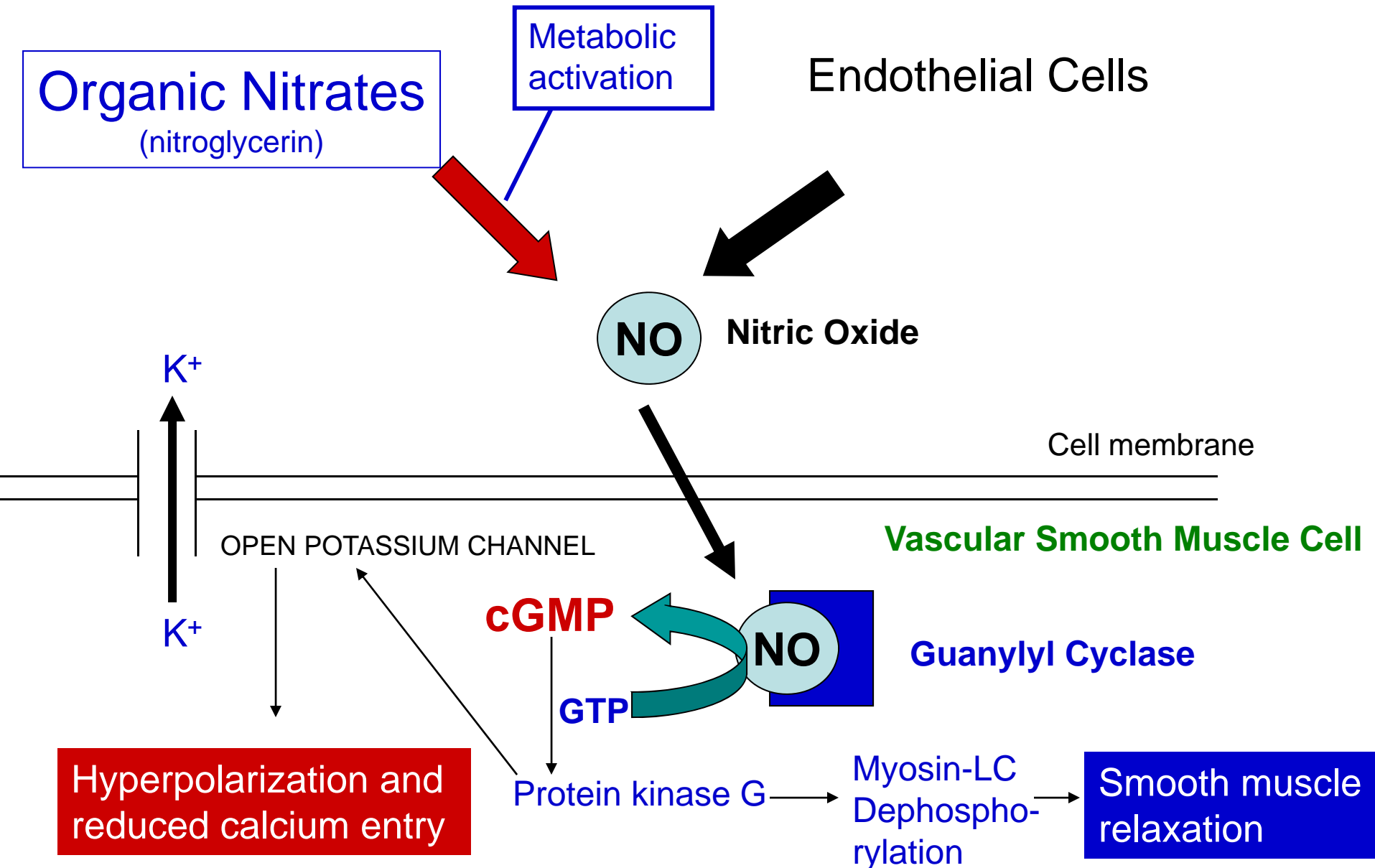
³ Tolerance may develop after 12 hours (see Precautions, Administration and Dosage).

ENDOGENOUS NITRIC OXIDE

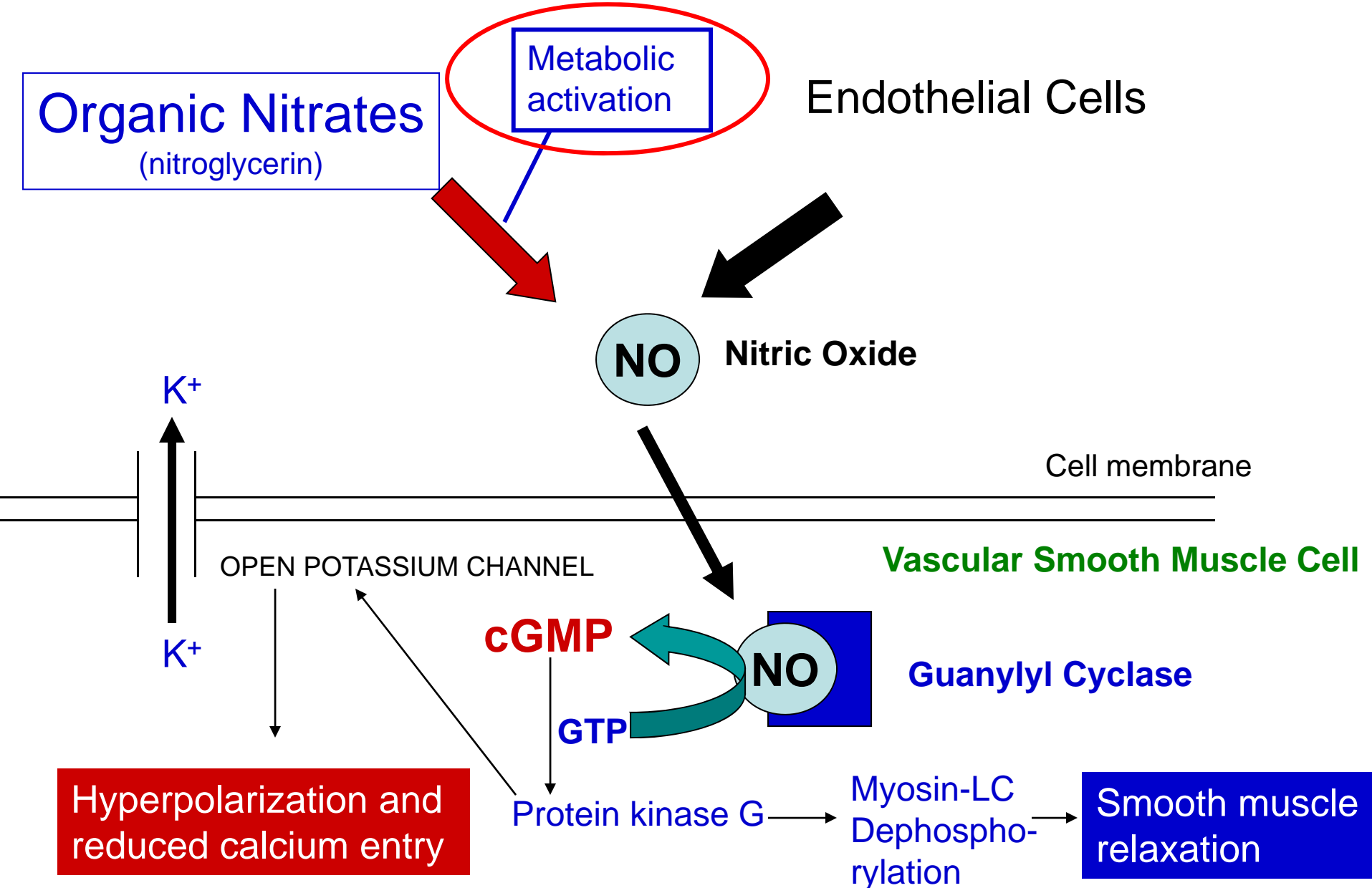
- Endothelial nitric oxide synthase produces NO, an endogenous vasorelaxing agent



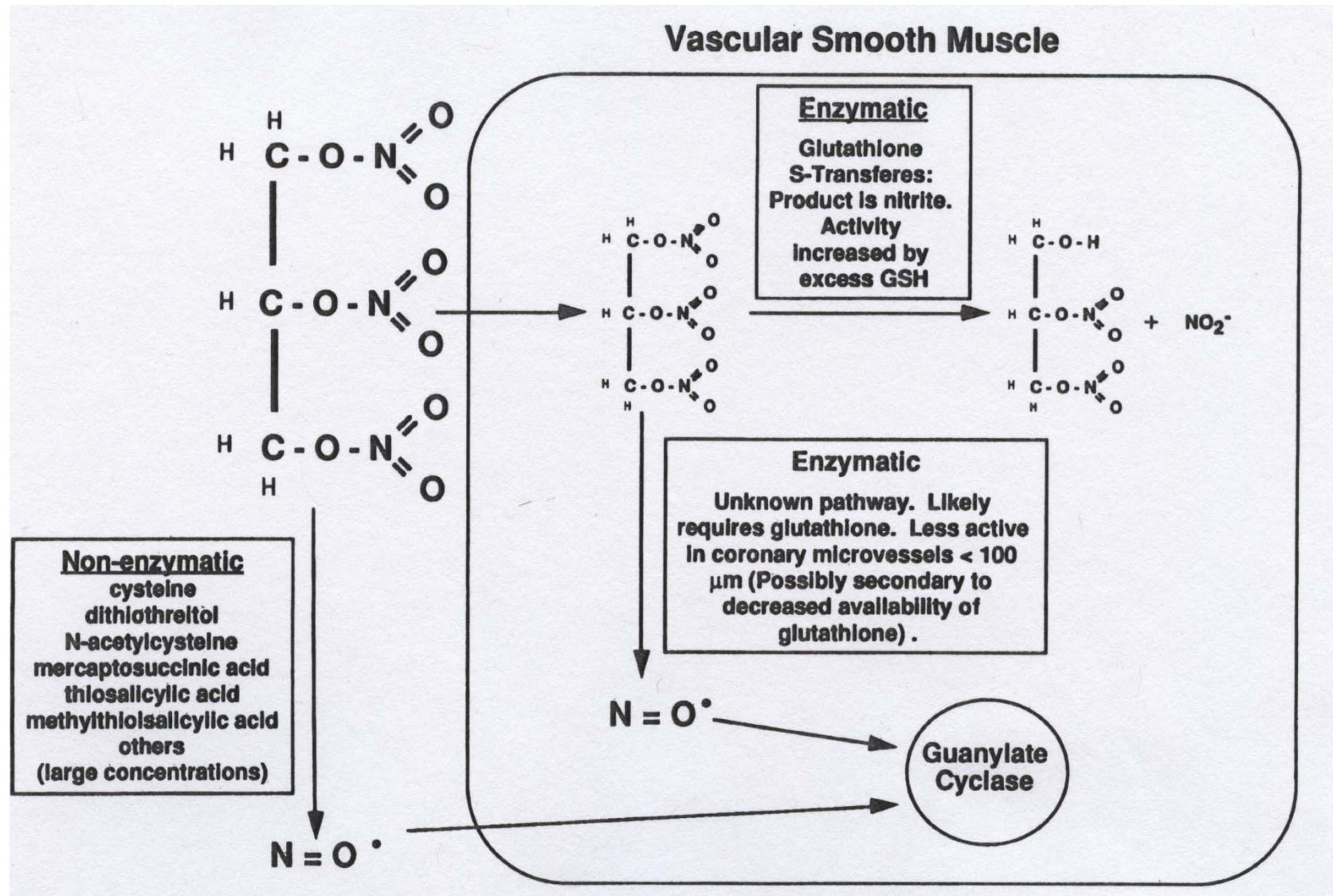
NITRATES AS NITRIC OXIDE DONORS



NITRATES AS NITRIC OXIDE DONORS



METABOLIC ACTIVATION OF NITRATES TO NO

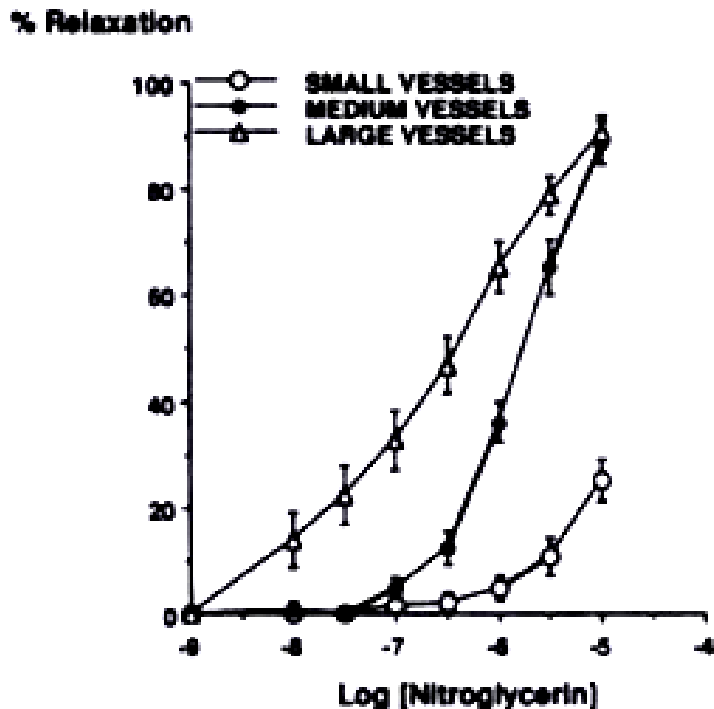


By Harrison and Bates, 1993

METABOLIC ACTIVATION OF NITRATES TO NO

- Action of nitroglycerin on vascular smooth muscle
 - Dilate veins, peripheral arteries, and large coronary arteries
 - Sensitivity of vasculature to nitrate-induced vasodilation:

Veins > Large arteries > Small arteries



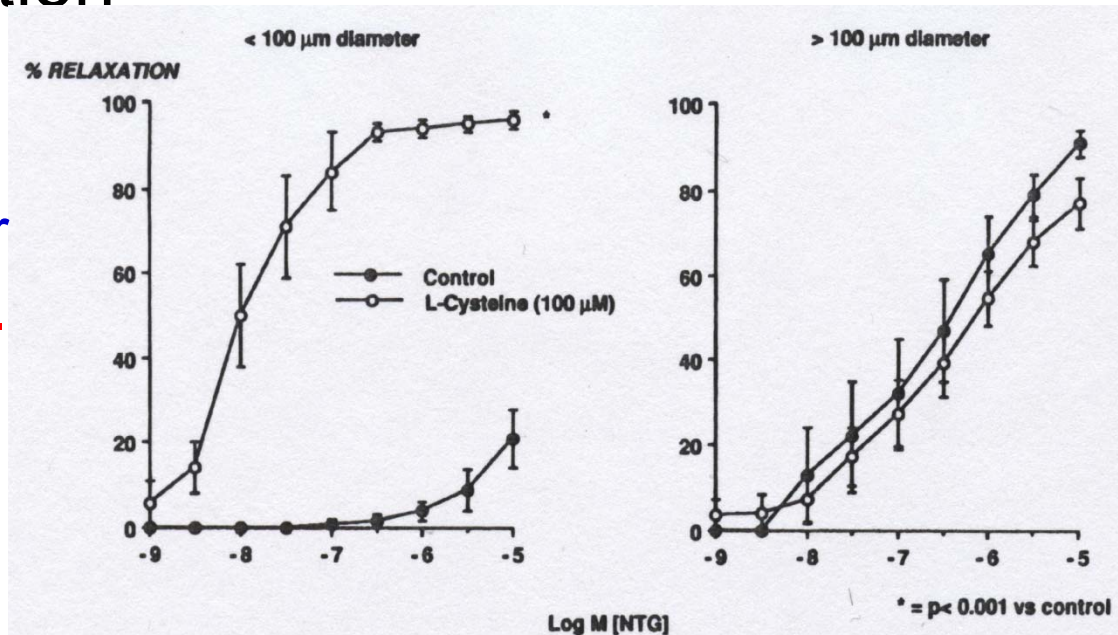
Dilation of coronary arteries of different diameters to nitroglycerin.
By Harrison and Bates, 1993

NITRATES

- Mechanism of action in angina
 - Unknown enzymatic reaction releases NO (or other active metabolite – nitrosothiol?)
 - Thiol compounds are needed to release NO from nitrates
 - Weak direct negative inotropic effect on cardiac muscle
 - Platelets – NO increases cGMP in platelets inhibiting aggregation

Effect of thiols on vascular relaxation by nitroglycerin.

By Harrison and Bates, 1993



NITRATES

- Mechanism of action in angina – decreased myocardial oxygen demand
 - NO induces relaxation of vascular smooth muscle
 - Dilation of veins (major effect)
 - Increased venous capacitance
 - Reduced ventricular preload
 - Dilation of arteries – higher concentrations of nitrates are needed, as compared to venous dilation
 - Reduced arterial pressure and afterload
 - May dilate large epicardial coronary arteries
 - There is no significant increase in coronary blood flow in atherosclerotic angina

NITRATES

- Effects of nitrates in different types of ischemic heart disease
 - Angina of effort
 - Decreased preload
 - Decreased oxygen demand
 - Vasospastic angina
 - Relaxation of vascular smooth muscle
 - Relieving coronary artery spasm
 - Unstable angina
 - Antiplatelet effect
 - Relieving the coronary artery spasm (if spasm contributed to the condition)
 - Decreased oxygen demand
 - Acute myocardial infarction
 - Antiplatelet effect
 - Decreased oxygen demand – delay of irreversible ischemic death

NITRATES

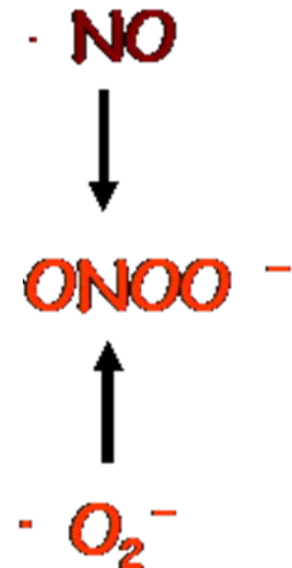
Effects on other organs

- Relaxation of smooth muscle in bronchi, GI tract, genitourinary tract

Development of tolerance

- Depletion of thiol compounds
- Increased generation of oxygen radicals
- Reflex activation of sympathetic nervous system (tachycardia, decreased coronary blood supply)
- Retention of salt and water

Increased generation of
superoxide radical
depletes tissues of NO



NITRATES

Adverse effects of nitrates

- Headache
- Orthostatic hypotension
- Tachycardia
- Nitrite reacts with hemoglobin to form methemoglobin

NITRATE DRUG INTERACTIONS

- Interaction of nitrates with drugs used for the treatment of erectile dysfunction
 - Sildenafil
 - Vardenafil
 - Tadalafil
 - Inhibit cGMP-phosphodiesterase-5, increases cGMP
 - Minimal effects on hemodynamics when administered alone in men with coronary artery disease
 - Combination with nitrates causes severe increase in cGMP and dramatic drop in BP
 - Acute myocardial infarctions have been reported

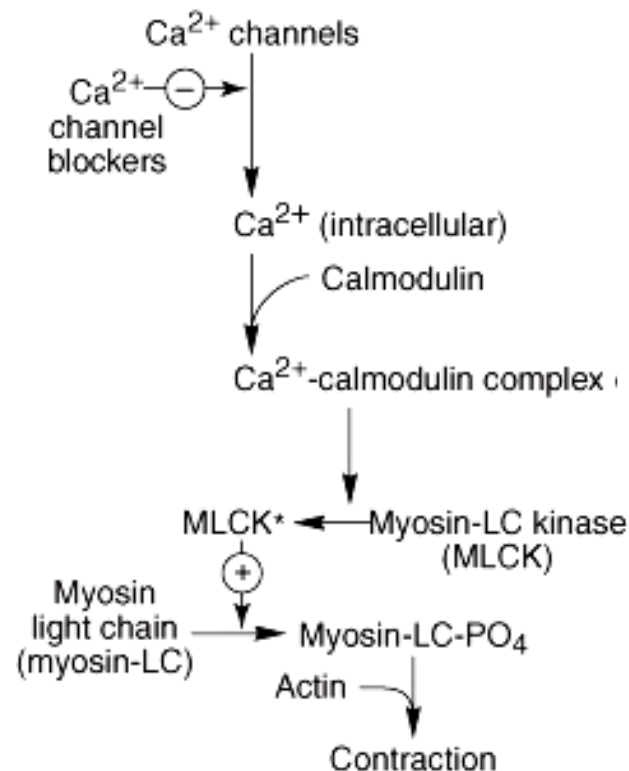
CALCIUM CHANNEL BLOCKERS

- Non-cardioactive (dihydropyridines)
 - Amlodipine
 - Nifedipine
 - Nicardipine
- Cardioactive
 - Diltiazem
 - Verapamil

CALCIUM CHANNEL BLOCKERS

Ca^{2+} mediates smooth muscle contraction; enters cells via voltage-dependent calcium channels

- Vascular smooth muscle (L-type)
- Cardiac muscle (L-type)



CALCIUM CHANNEL BLOCKERS

Anti-anginal Mechanism of CCBs

- Decreased myocardial O₂ demand
 - Dilation of arterioles
 - ↓ PVR (↓ afterload), ↓ BP
 - Arterioles more affected than veins (less orthostatic hypotension)
 - **Dihydropyridines** are more potent vasodilators
 - Decreased cardiac contractility and heart rate (observed with cardioactive CCBs)
- Increased blood supply
 - Dilation of coronary arteries relieves local spasms (this mechanism may operate in **vasospastic variant angina** and NOT in atherosclerotic angina)

CALCIUM CHANNEL BLOCKERS

Organ system effects

- Smooth muscle in bronchi, uterus, and GI tract may be relaxed (not as sensitive as vascular smooth muscle)
- Skeletal muscle is not affected – it is much less dependent on transmembrane calcium fluxes
- Nonspecific antiadrenergic effect (**Verapamil, Diltiazem**) – may contribute to peripheral vasodilation
- **Cardioactive CCBs** inhibit calcium fluxes in pacemaker cells – are useful in certain types of tachyarrhythmias
- **Verapamil** has broad membranotropic action affecting sodium fluxes and other functions
 - May inhibit insulin release
 - Blocks P-glycoprotein responsible for transport of drugs and other xenobiotics out of cells
 - Reverses the resistance of cancer cells to chemotherapeutic agents

CALCIUM CHANNEL BLOCKERS

Adverse effects

- Major
 - Cardiac depression, cardiac arrest, and heart failure
 - Bradyarrhythmias, atrioventricular block
 - Short acting **Nifedipine** – vasodilation triggers reflex sympathetic activation
 - **Nifedipine** increases the risk of adverse cardiac events in patients with hypertension
- Minor
 - Flushing, dizziness, headache
 - Edema
 - Constipation

BETA-BLOCKERS

- Beta-blockers indicated in angina
 - Propranolol
 - Nadolol
 - Metoprolol
 - Atenolol
- Mechanism of action in angina – decreased myocardial oxygen demand
 - Decrease HR leads to improve myocardial perfusion and reduce oxygen demand at rest and during exercise
 - Decrease in contractility
 - Decrease in blood pressure leads to reduced afterload
- Undesirable effects in angina
 - Increase in end-diastolic volume – potential for the increased oxygen demand
 - Increase in ejection time

COMBINATION THERAPY IN ANGINA PECTORIS

Effects of nitrates alone and with β blockers or calcium channel blockers in angina pectoris
(undesirable effects are shown in italics)

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	<i>Reflex¹ increase</i>	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	<i>Increase</i>	None or decrease
Contractility	<i>Reflex¹ increase</i>	Decrease	None
Ejection time	Decrease ¹	<i>Increase</i>	None

¹Baroreceptor reflex.

BETA-BLOCKERS

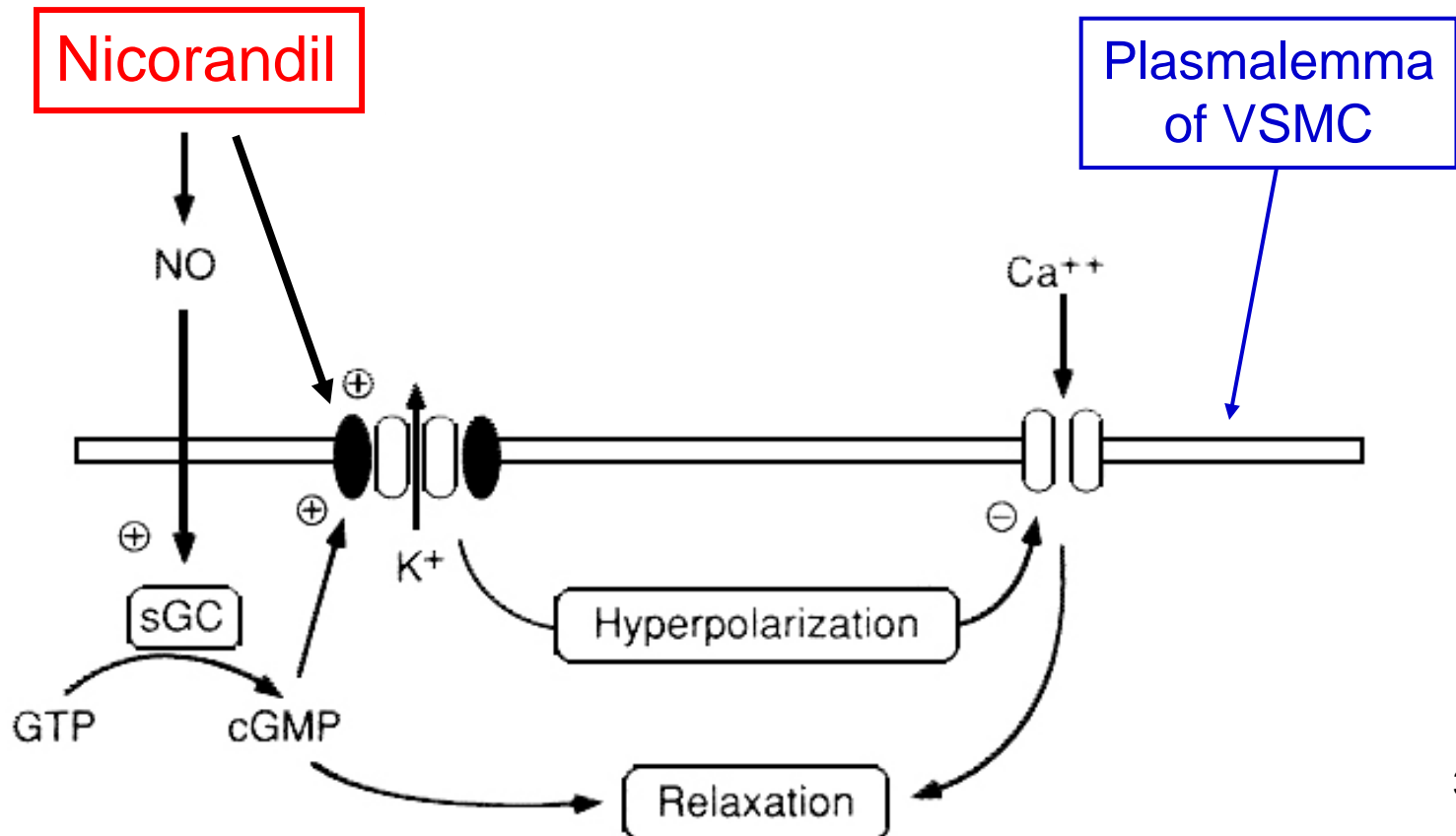
Adverse effects of beta-blockers

- Bradycardia
- Hypotension
- Bronchial constriction
- May aggravate severe unstable left ventricular failure
- Fatigue, impaired exercise tolerance
- Erectile dysfunction
- Unpleasant dreams, insomnia, depression
- Altered serum lipids (\uparrow VLDL, \downarrow HDL)
- Withdrawal syndrome

NEWER AGENTS – NICORANDIL

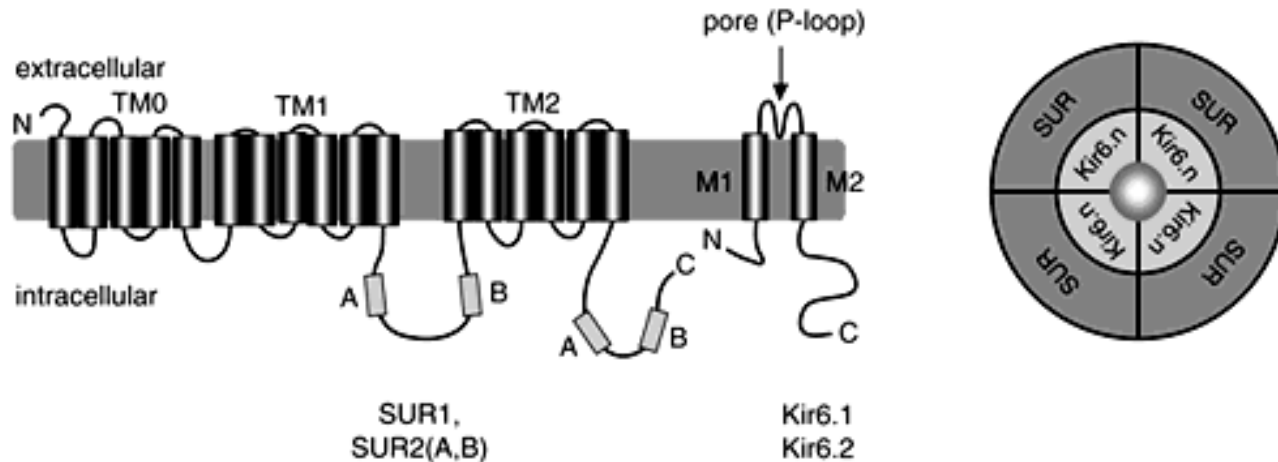
Nicorandil – bifunctional agent

- Activates potassium (K_{ATP}) channels causing hyperpolarization of vascular smooth muscle cells
- Possesses nitrate ester group ($O-NO_2$)



NEWER AGENTS – NICORANDIL

- K_{ATP} channels connect metabolic rate and energy production within the cell with electrophysiological properties
- ATP depletion will open channels causing hyperpolarization and decreased Ca influx



C

Subunits	Tissue	Function
SUR1-Kir6.2	Pancreas Hypothalamus	Insulin Leptin signaling
SUR2A-Kir6.2	Heart	Action potential
SUR1-Kir6.1(?)	Heart	Cardioprotection
SUR2B + Kir6.2 (and/or) Kir6.1	Smooth muscle	Relaxation

SUR – sulfonyleurea receptor, a regulatory subunit

Kir6.1 or 2 – potassium inward rectifying 6, a pore-forming subunit

NEWER AGENTS – NICORANDIL

Mechanism of action of **Nicorandil** in angina

- As a K_{ATP} channel opener
 - Inhibition of voltage-dependent calcium channels
 - Decreased Ca influx
 - Shortened action potential
 - Cardioprotection against irreversible ischemic injury
 - Increased resistance of myocardium to the ischemic insult due to activation of sarcolemmal and mitochondrial K_{ATP} channels

NEWER AGENTS – NICORANDIL

Mechanism of action of **Nicorandil** in angina
(continued)

- As a K_{ATP} channel opener
 - Dilation of peripheral arterioles
 - Decreased afterload
 - Decreased blood pressure
 - Dilation of coronary arteries
 - Increased coronary flow
 - Relief of coronary spasm
- As a nitrate
 - Dilation of veins
 - Decreased venous return and ventricular filling
 - Decreased preload

NEWER AGENTS

Nicorandil

- Approved in western Europe, Australia, Japan, submitted to FDA for approval in U.S.
- Large clinical trial showed the reduction in fatal and nonfatal coronary events in patients taking the drug
- Adverse effects
 - Headache
 - Flushing
 - Weakness, nausea
 - Mouth ulcers

NEWER AGENTS

Ranolazine (approved in U.S. in 2006)

- Inhibits sodium current and reduces calcium overload in myocardial cells
- Inhibits fatty acid oxidation in myocardium (inhibition of **long chain 3-ketoacyl thiolase**) – when fatty acids are oxidized instead of glucose, myocardial oxygen requirement is increased
- Clinical use of **Ranolazine**
 - Stable angina which is refractory to standard medications
 - Decreases angina episodes and improves exercise tolerance in patients taking **nitrates, or amlodipine, or atenolol**

NEWER AGENTS

Ranolazine

- **Adverse effects**

- QT interval prolongation – may trigger polymorphic ventricular arrhythmias
- Constipation
- Nausea
- Dizziness
- Headache

- **Drug interactions**

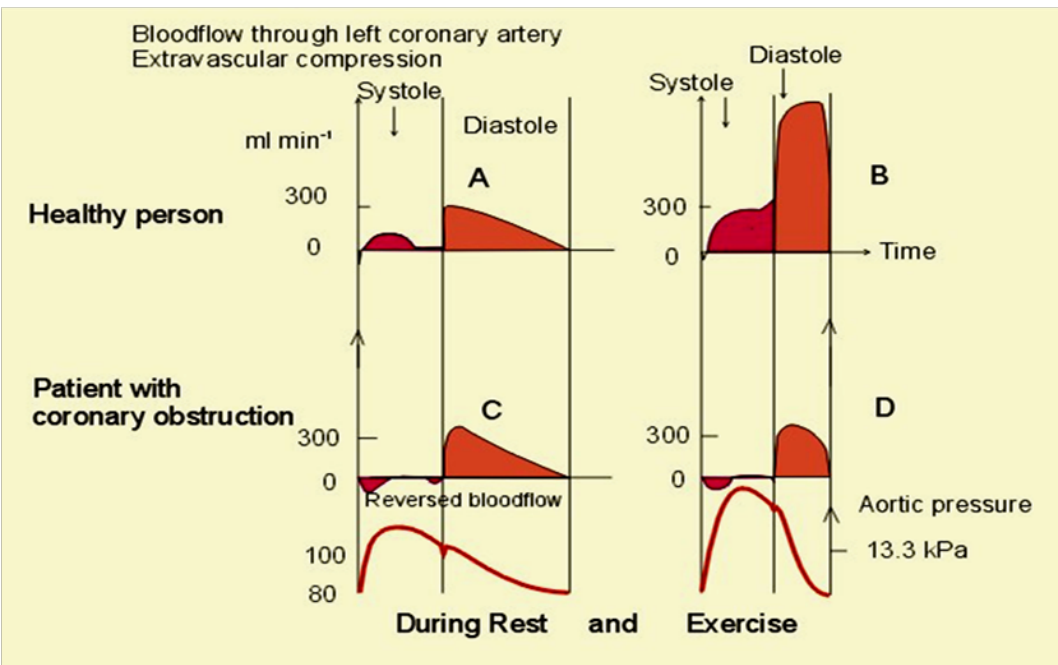
- Metabolized by CYP3A – interaction with drugs that modulate the activity of this enzyme
- Ranolazine inhibits CYP2D6 – increases half-life of Amitriptyline, Fluoxetine, Metoprolol, opioid drugs
- Drugs that prolong QT interval – certain antiarrhythmic (quinidine) and antipsychotic drugs (thioridazine) – may trigger ventricular arrhythmias

NEWER AGENTS

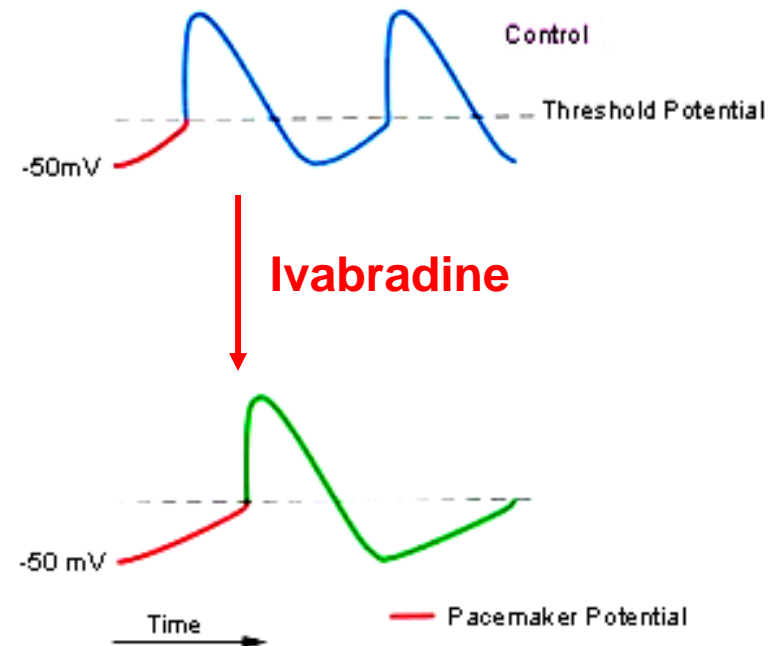
Ivabradine

- Bradycardic agent
- Inhibits I_f sodium-potassium inward current, which is activated by hyperpolarization in sinoatrial node. This current increases the slope of depolarization in pacemaker cells and increases heart rate

Heart rate and coronary blood flow



SA cells action potential



NEWER AGENTS

Ivabradine

- **Indications**

- Stable angina pectoris in patients with normal sinus rhythm when beta-blockers cannot be used
- Inappropriate sinus tachycardia

- **Adverse effects**

- Sensation of enhanced brightness of visual field
- Bradycardia
- Headaches
- Atrioventricular block
- Ventricular premature beats
- Blurred vision
- Dizziness