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College of Medicine

DRUGS FOR CORONARY ARTERY DISEASE

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify clinical uses for nitrates, beta-blockers, calcium channel blockers, and I_{Na} inhibitors.
2. Explain the mechanism of action of nitrates, beta-blockers, calcium channel blockers, and I_{Na} inhibitors and how this relates to the underlying pathophysiology of their clinical use.
3. State adverse effects and contraindications to nitrates, beta-blockers, calcium channel blockers, and I_{Na} inhibitors.
4. Describe the clinically important drug interactions of nitrates, beta-blockers, calcium channel blockers, and I_{Na} inhibitors.

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INTRODUCTION

Coronary Artery Disease

CORONARY ARTERY DISEASE (CAD)

Imbalance between myocardial oxygen demand and supply from coronary arteries

Causes

- Atherosclerosis of coronary arteries (most common)
- Others: Embolus, vasculitis, vasospasm

Stable ischemic heart disease

Acute coronary syndrome

- ST-elevation MI (STEMI)
- Non-ST elevation MI (NSTEMI)
- Unstable angina

ANGINA

Angina pectoris is primary symptom of ischemic heart disease

Caused by transient episodes of myocardial ischemia

Due to imbalance in myocardial oxygen supply-demand relationship

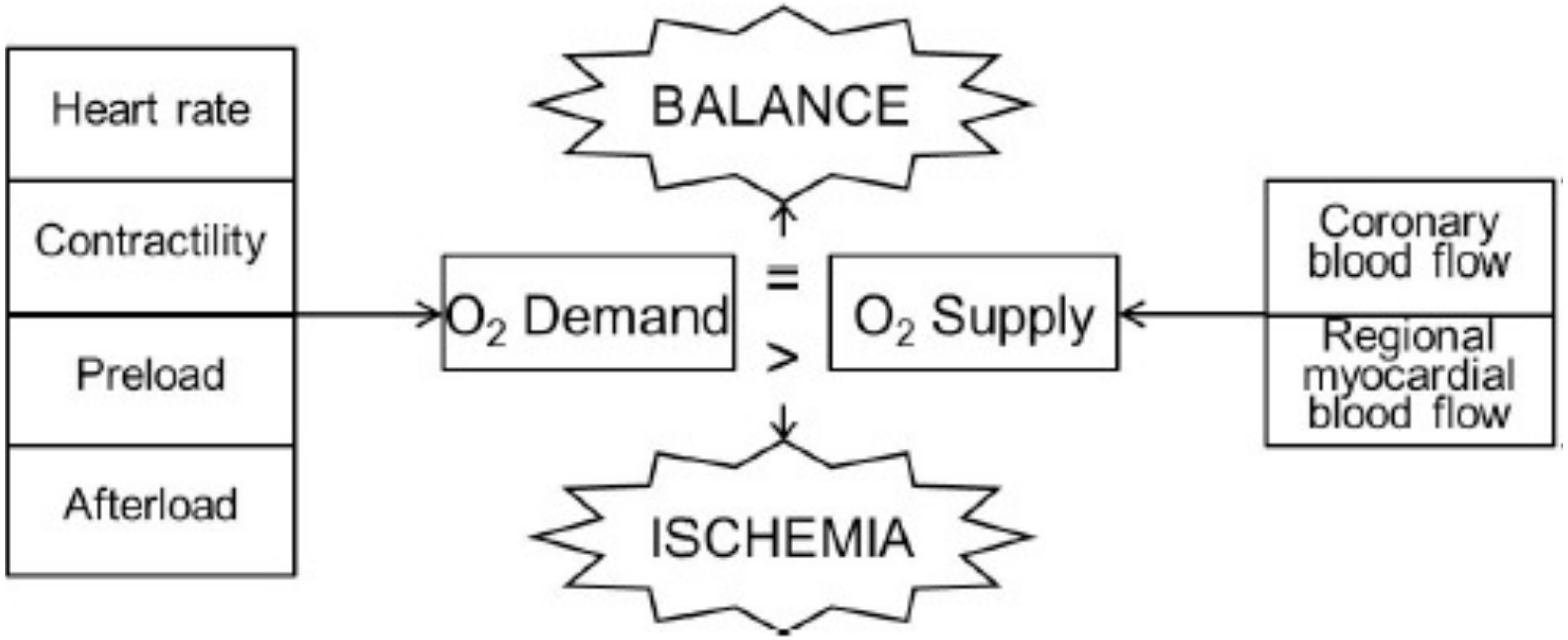
ACTIVE LEARNING

List the determinants of oxygen demand.

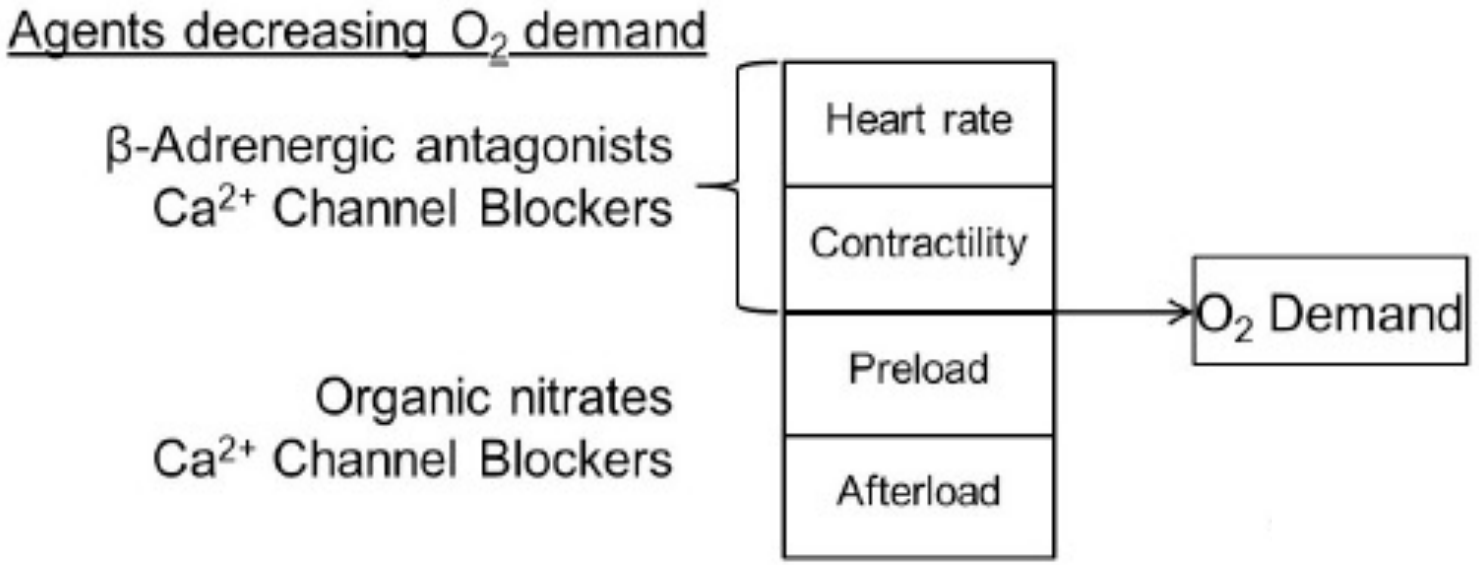
Now list the determinants of oxygen supply.

How might you use pharmaceuticals to augment these determinants in the management of myocardial ischemia?

PATHOPHYSIOLOGY OF ANGINA



PHARMACOLOGIC MODIFICATION



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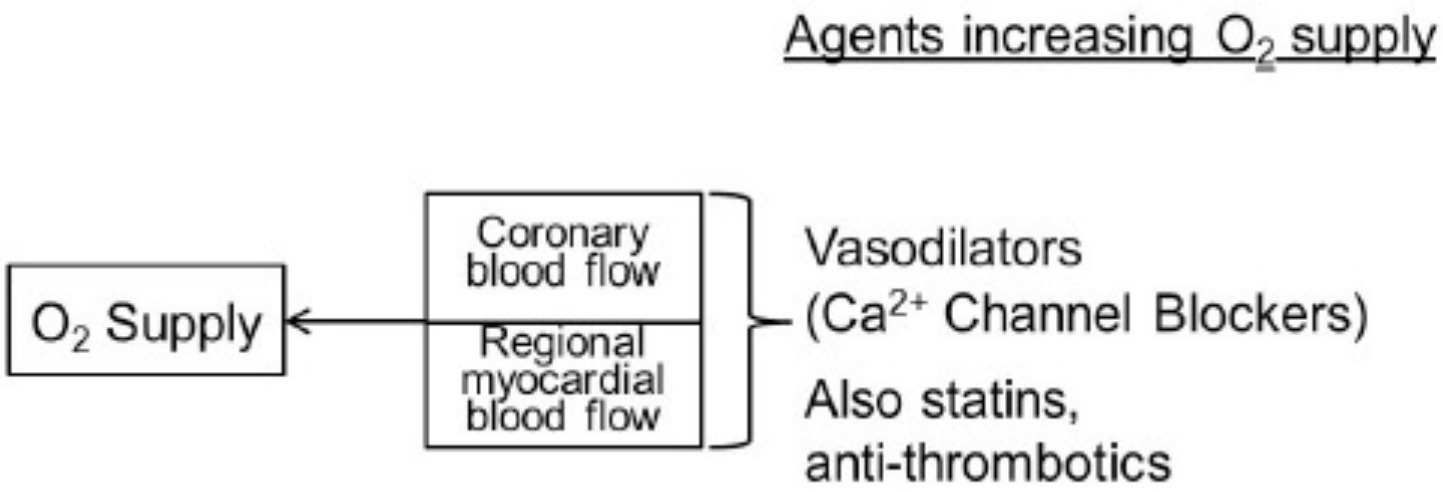

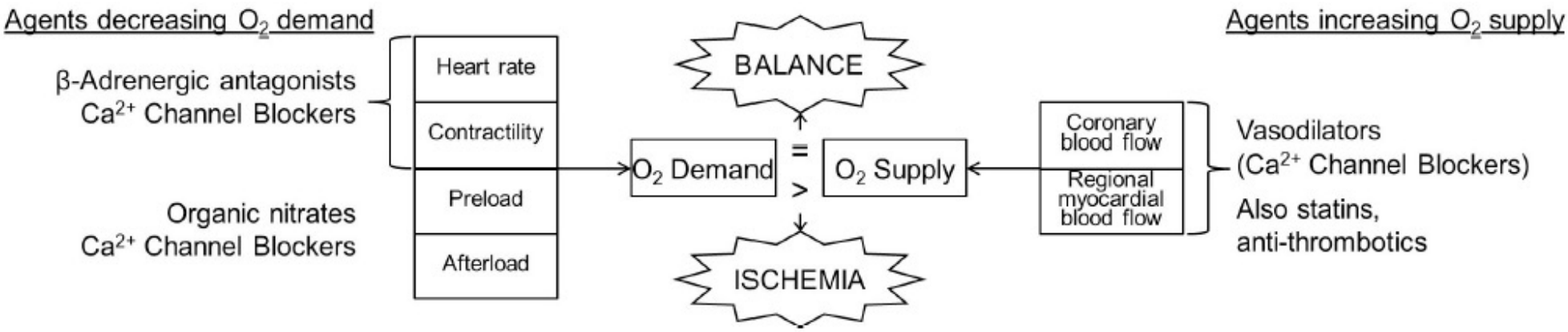
Agents decreasing O_2 demand
β-Adrenergic antagonists
Ca^{2+} Channel Blockers
Organic nitrates
Ca^{2+} Channel Blockers
Heart rate
Contractility
Preload
Afterload
BALANCE
O_2 Demand
=
>
O_2 Supply
ISCHEMIA
Coronary blood flow
Regional myocardial blood flow
Agents increasing O_2 supply
Vasodilators
(Ca^{2+} Channel Blockers)
Also statins,
anti-thrombotics

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CALCIUM CHANNEL BLOCKERS

What do you recall about calcium channel blockers?

When poll is active, respond at **pollev.com/skyem**

I am confident regarding the pharmacology of calcium channel blockers.

HISTORICAL PERSPECTIVE

Verapamil, a calcium channel blocker, was the result of attempting active analogs of papaverine

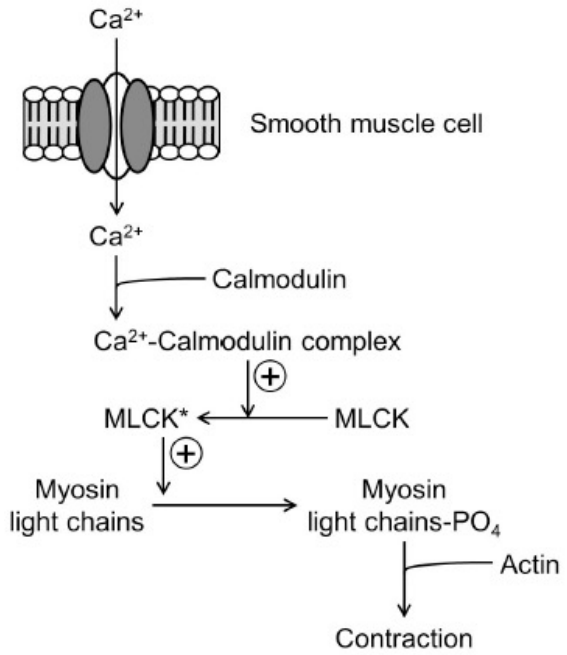
Papaverine is a vasodilator alkaloid found in the opium poppy

CALCIUM AND SMOOTH MUSCLE CONTRACTION

Smooth muscle contraction triggered by influx of calcium through transmembrane calcium channels

Calcium combines with calmodulin → forms complex that converts myosin light-chain kinase its active form (MCLK*)

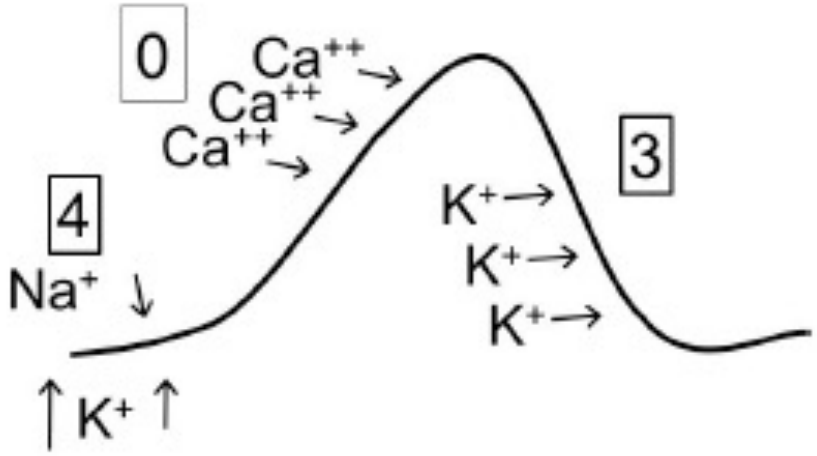
MCLK* phosphorylates myosin light chains → myosin interactions with actin → contraction



CARDIAC CONTRACTILITY & RATE

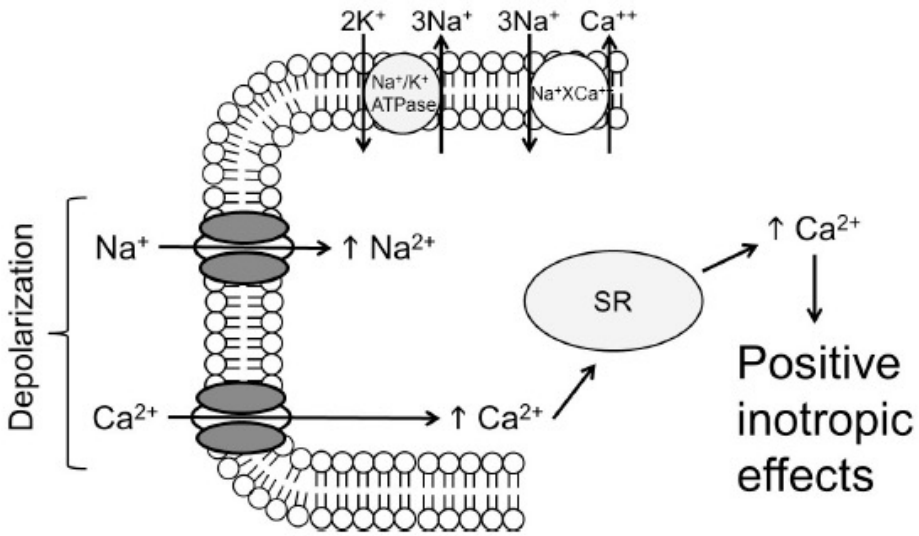
Cardiac muscle is highly dependent on calcium influx during each action potential for normal function

Impulse generation in the sinoatrial node and conduction in the atrioventricular node, inward flow of Na (phase 4) results in depolarization to threshold potential opening voltage-gated Ca2+ channels (phase 0).

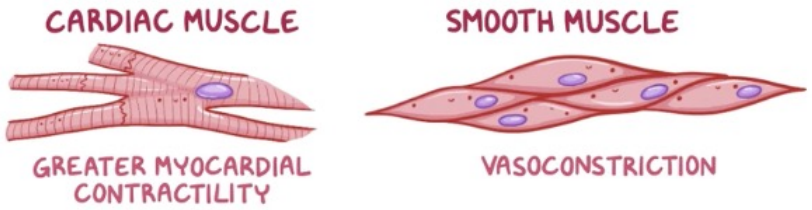


CARDIAC CONTRACTILITY & RATE

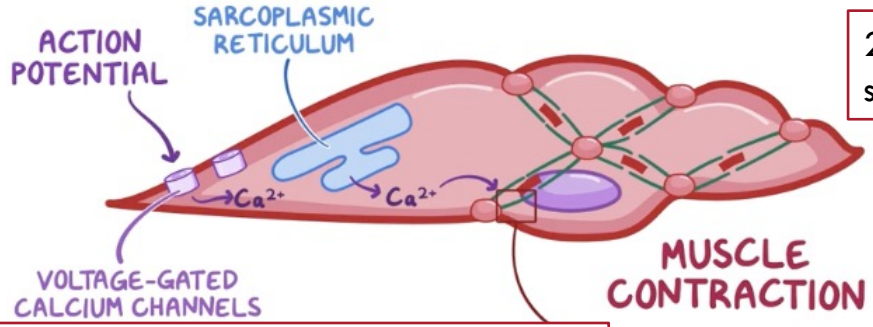
Excitation-contraction coupling in all cardiac cells requires calcium influx



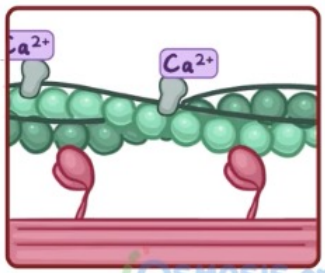
CALCIUM: CARDIAC & SMOOTH MUSCLE



Both depend on Ca



2. The extracellular Ca→ release of intracellular Ca ions stored in the sarcoplasmic reticulum.



1. Voltage-gated Ca channels in the membrane of the muscle cell open when they receive an action potential → Ca ions flow into cell from the extracellular space.

3. Ca ions then bind to troponin regulatory proteins, which change shape and release the thin filaments in the muscle fiber. This allows the thin filament to bind to the thick filament, eventually leading to muscle contraction.

CALCIUM CHANNEL BLOCKER MECHANISM OF ACTION

Block voltage-gated L-type calcium channels

- Calcium channels most important in cardiac and smooth muscle

Bind alpha-1 subunit of L-type calcium channels from inner side of membrane

- Reduce calcium influx through channel

CALCIUM CHANNEL BLOCKER MECHANISM OF ACTION

Decrease cardiac oxygen demand by **reducing afterload**

- Blocking calcium channels relaxes arterial smooth muscle → ↓ afterload
- Less effect on venous beds → do not affect preload significantly

Also **reduce cardiac contractility and rate**

CALCIUM CHANNEL BLOCKER MECHANISM OF ACTION

Dihydropyridines (nifedipine, amlodipine)

- Greater degree of peripheral vasodilation → baroreflex-mediated increase in sympathetic tone to overcome negative inotropic effect of drug
- **"Di**hydropyridines **di**late"

Nondihydropyridines (diltiazem, verapamil)

- Depress rate of sinus node pacemaker and slow AV conduction

ACTIVE LEARNING

Based on their mechanism of action, which subclass of calcium channel blockers – dihydropyridines or nondihydropyridines – would be most efficacious in the management of arrhythmias? Defend your answer.

When poll is active, respond at **pollev.com/skyem**

Based on their mechanism of action, which subclass of calcium channel blockers – dihydropyridines or nondihydropyridines – would be most efficacious in the management of arrhythmias?

CALCIUM CHANNEL BLOCKERS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Dihydropyridines Amlodipine Nifedipine	Cautions: Hepatic impairment Heart failure (lack of benefit)	Cardiac depression **Peripheral edema** **Flushing** **Dizziness** Gingival hyperplasia	Increases simvastatin and atorvastatin levels, cyclosporine levels
Non-dihydropyridines Diltiazem Verapamil	Sinus bradycardia AV block Acute MI Pulmonary	Hyperprolactinemia (verapamil) **Constipation** Gingival hyperplasia Higher doses: Cardiac depression, hypotension, AV block	Inhibitors of CYP3A4 Verapamil increases simvastatin and atorvastatin levels Users of β-blockers more sensitive to cardiac depression Verapamil may increase digoxin levels

CLINICAL USE

Dihydropyridines

Hypertension

Angina

Raynaud phenomenon

Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm)

Non-dihydropyridines (diltiazem, verapamil)

Hypertension

Angina

Atrial fibrillation/flutter

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NITRATES

ACTIVE LEARNING

Describe the role of nitric oxide in smooth muscle relaxation.

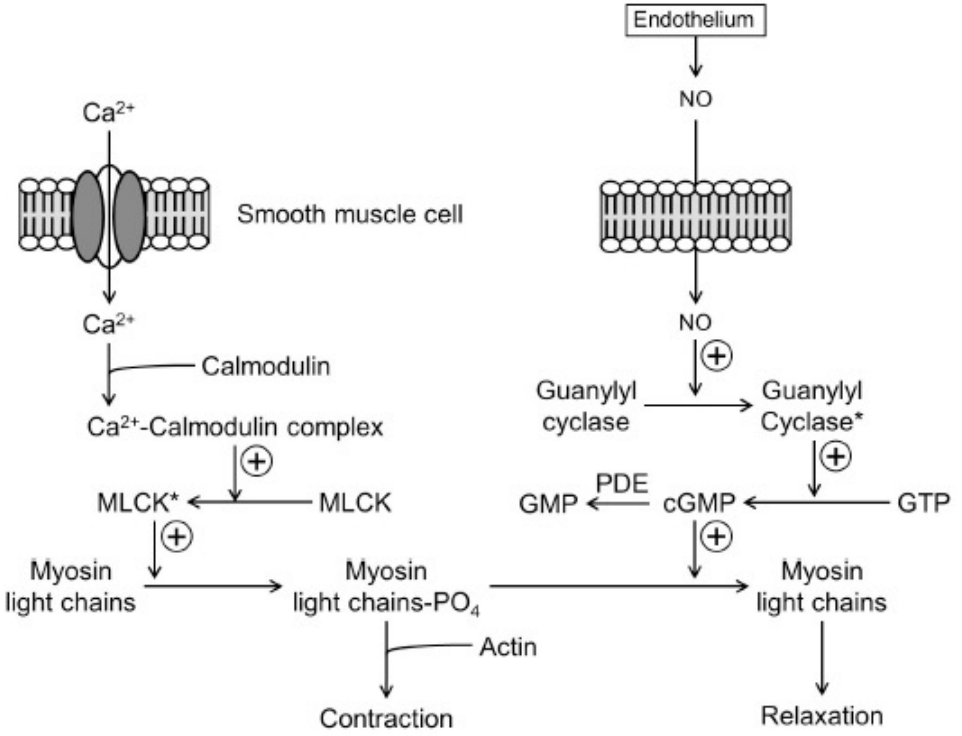
NITRIC OXIDE (NO) & SMOOTH MUSCLE RELAXATION

NO released from endothelium activates soluble form of guanylyl cyclase → ↑ intracellular levels of cyclic GMP (cGMP)

cGMP promotes dephosphorylation of myosin light chain and ↓ of cytosolic calcium → relaxation of smooth muscle cells

Vascular smooth muscle relaxation → vasodilation

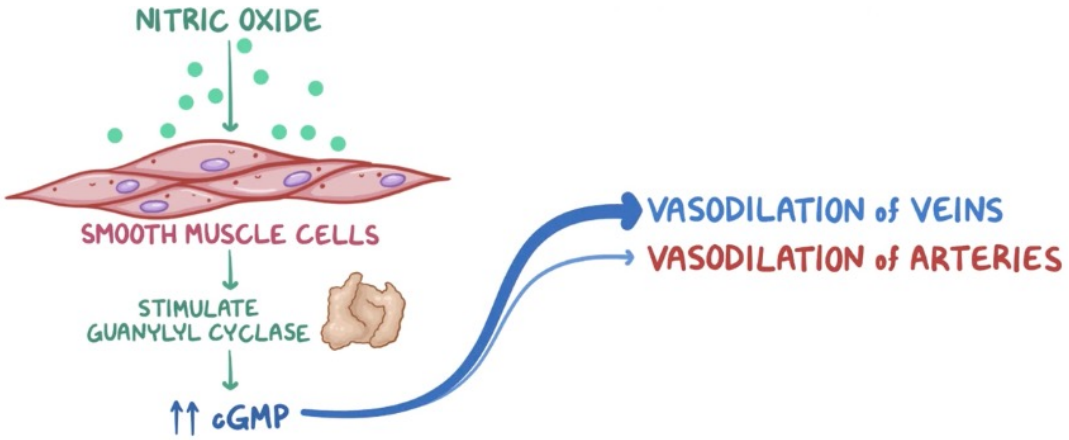
NO-mediated guanylyl cyclase activation → inhibition of platelet aggregation



NITRATE MECHANISM OF ACTION

Prodrugs of NO

Liberated NO acts to relax vascular smooth muscle and cause vasodilation



ANTIANGINAL MEDICATIONS
"NITRATES"

VASODILATION of SMALL VEINS & VENULES → ↓↓ PRELOAD → VOLUME of BLOOD the HEART must EJECT w/ each CONTRACTION

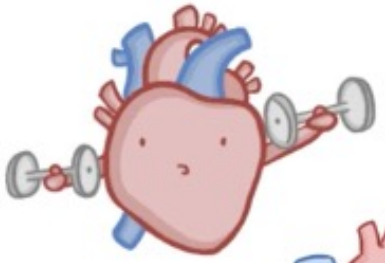
VASODILATION of SMALL ARTERIES & ARTERIOLES → ↓↓ AFTERLOAD → PRESSURE the HEART must WORK AGAINST to EJECT the BLOOD

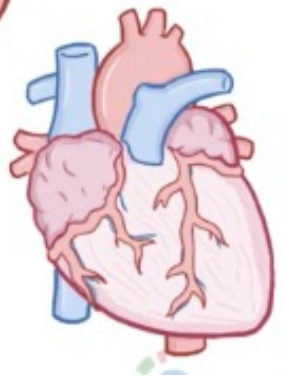
↓↓ SYSTEMIC VASCULAR RESISTANCE

↓↓ AMOUNT of WORK the HEART has to DO

↓↓ OXYGEN CONSUMPTION

↑↑ OXYGEN DELIVERY to HEART TISSUE



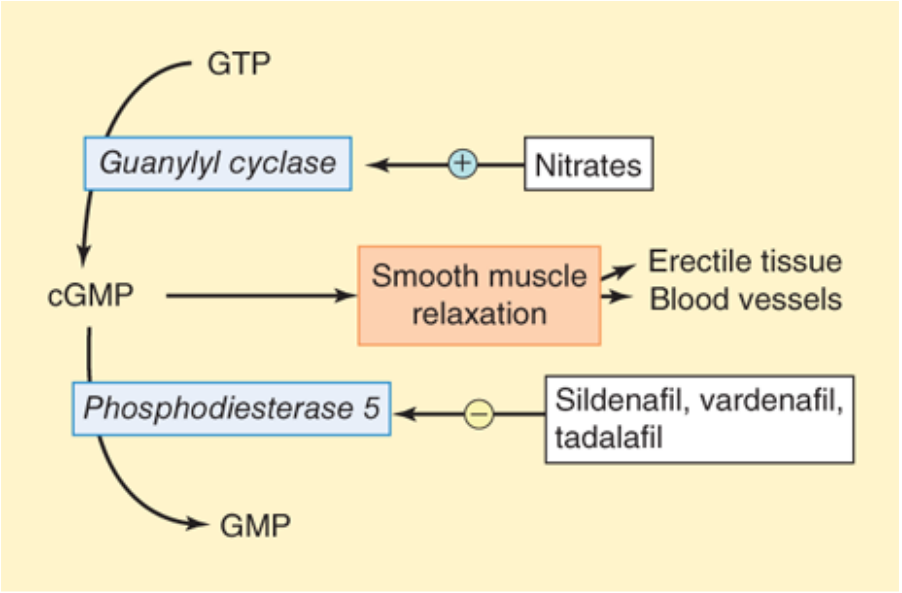


NITRATES

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Nitroglycerin Isosorbide dinitrate Isosorbide mononitrate	Intracranial pressure elevation (dilate cerebral veins → ↑ intracranial pressure) Right ventricular infarction Hypertrophic cardiomyopathy **PDE5 inhibitors use**	Flushing Headache (meningeal artery vasodilation) Orthostatic hypotension (venodilator effect) Reflex tachycardia (can be treated with beta-blockers) "Monday disease" Tolerance may develop	**Avoid with PDE5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra)**

CINEMATIC REMINDER

https://www.youtube.com/watch?v=viK121c8iZI



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

CLINICAL USE & PK

Clinical Use

Angina

Acute coronary syndromes

Pulmonary edema

PK

Sublingual route preferred for rapid use

Oral route preferred for longer duration of action

Also available as patch, ointment, buccal

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BETA-BLOCKERS

ACTIVE LEARNING

Write down what you remember about beta-adrenergic receptors.

- Types
- Locations
- Actions

BETA-ADRENERGIC RECEPTORS

Sympathetic nervous system

Adrenergic receptors

- Alpha
- Beta
  - Located on most types of smooth muscle, cardiac muscle

Norepinephrine is physiologic ligand/transmitter

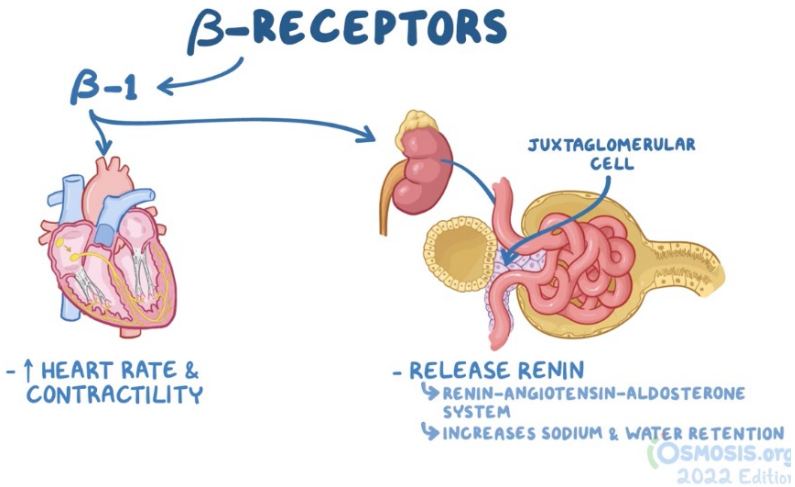
BETA RECEPTORS

Receptor	Location	G Protein Class	Effector/Signaling Pathway	Major Functions
Beta$_1$ (β_1)	Cardiac muscle, juxtaglomerular apparatus	G_s	Increased adenylyl cyclase → increased cAMP	↑ Heart rate, ↑ force; ↑ renin release
Beta$_2$ (β_2)	Smooth muscle, liver, heart	G_s	Increased adenylyl cyclase → increased cAMP	Relax smooth muscle; ↑ glycogenolysis; ↑ heart rate, force
Beta$_3$ (β_3)	Adipose cells	G_s	Increased adenylyl cyclase → increased cAMP	↑ Lipolysis

ACTIVE LEARNING

Complete the following table with how you would expect beta-1 and beta-2 receptors agonists and antagonists to impact the heart and lungs.

	Heart	Lungs
Beta-1 Receptor AGONIST		
Beta-1 Receptor ANTAGONIST		
Beta-2 Receptor AGONIST		
Beta-2 Receptor ANTAGONIST		


β-RECEPTORS
β-1
JUXTAGLOMERULAR CELL
- ↑ HEART RATE & CONTRACTILITY
- RELEASE RENIN
↳ RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM
↳ INCREASES SODIUM & WATER RETENTION
OSMOSIS.org
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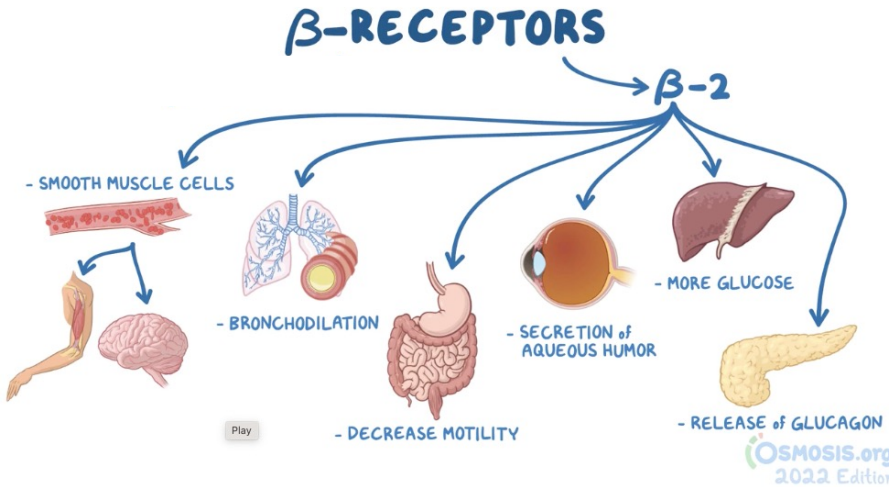

β-RECEPTORS
β-2
- SMOOTH MUSCLE CELLS
- BRONCHODILATION
- SECRETION of AQUEOUS HUMOR
- MORE GLUCOSE
Play
- DECREASE MOTILITY
- RELEASE of GLUCAGON
OSMOSIS.org
2022 Edition

ACTIVE LEARNING

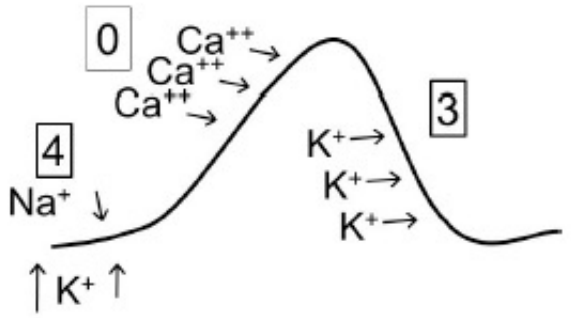
Complete the following table with how you would expect beta-1 and beta-2 receptors agonists and antagonists to impact the heart and lungs.

	Heart	Lungs
Beta-1 Receptor AGONIST	Increased contractility, HR	No effect
Beta-1 Receptor ANTAGONIST	Decreased contractility, HR	No effect
Beta-2 Receptor AGONIST	Increased contractility, HR	Bronchodilation
Beta-2 Receptor ANTAGONIST	Decreased contractility, HR	Bronchoconstriction

CARDIAC ACTIONS OF BETA-ADRENERGIC RECEPTOR ACTIVATION

Conduction and heart rate (chronotropy)

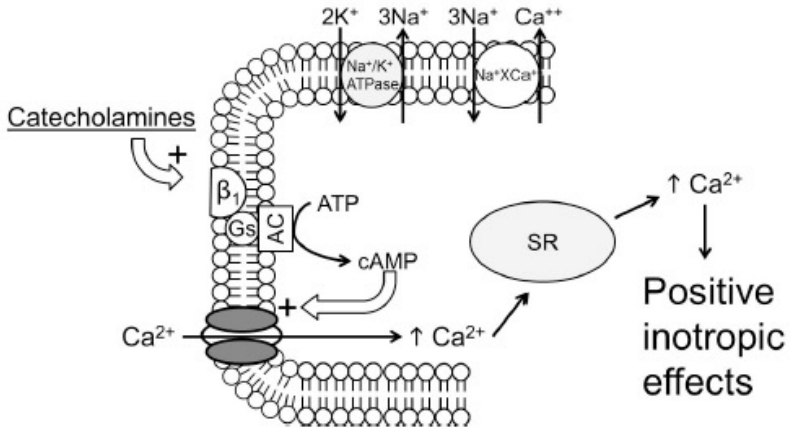
- Increased beta-1 receptor activation → opening of greater number of pacemaker channels → larger pacemaker current conducted through channels → faster phase 4 depolarization
- Opening of greater number of calcium channels → shifts threshold to more positive potentials



CARDIAC ACTIONS OF BETA-ADRENERGIC RECEPTOR ACTIVATION

Contractility (inotropy)

- Increased beta-1 receptor activation → ↑ cAMP → activation of cAMP-dependent protein kinase → phosphorylates L-type calcium channel increasing probability of channel opening and influx of calcium
- Increases force of myocardial contraction



BETA-BLOCKER MECHANISM OF ACTION

Beta-1 receptor ANTAGONISM decreases the slope of phase 4

- Decreases automaticity and heart rate

Beta-1 receptor ANTAGONISM prevents the activation of cAMP-dependent protein kinase and ultimately calcium influx

- Decreases inotropy

Reduces myocardial oxygen demand at rest and during exercise

BETA-BLOCKER MECHANISM OF ACTION

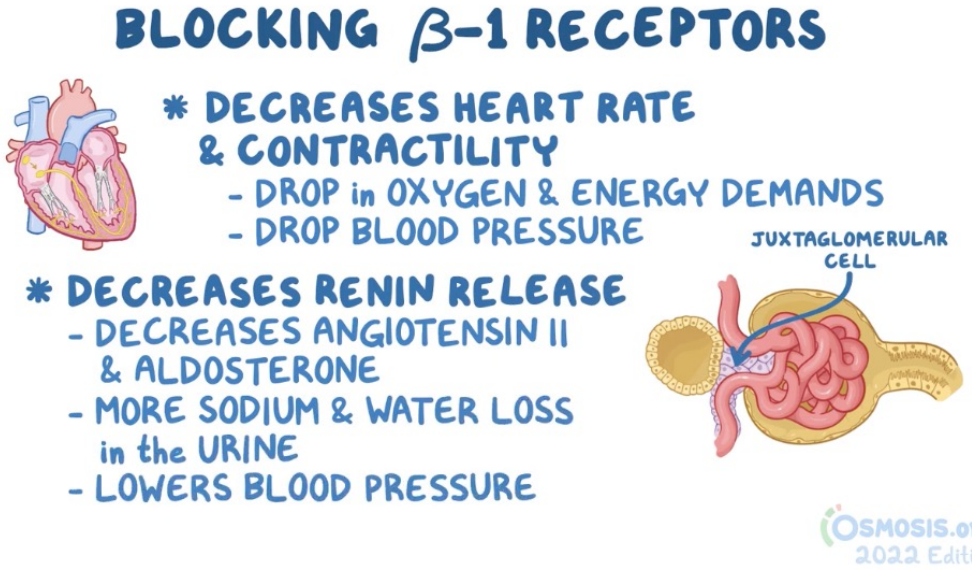
Effectiveness in angina attributed to ↓ in myocardial oxygen demand at rest and during exertion

Negative chronotropic effect

Negative inotropic effect

Reduction in arterial blood pressure during exercise

May also ↑ myocardial perfusion due to augmented diastolic perfusion



BETA-BLOCKERS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Acebutolol Atenolol Carvedilol Esmolol Labetalol Metoprolol Nadolol Nebivolol Pindolol Propranolol Timolol ***-lol***	Asthma and other bronchospastic conditions (non-selective beta-blockers) Severe bradycardia AV blockage Bradycardia-tachycardia syndrome Severe unstable left ventricular failure Abrupt discontinuation	Fatigue Impaired exercise tolerance Insomnia Unpleasant dreams Worsening of claudication Erectile dysfunction Bradycardia May mask signs of hypoglycemia	Amiodarone (may induce cardiac arrest) Calcium channel blockers (bradycardia risk) Hypoglycemics (increased risk of hypoglycemia)

Boxed warning: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction (MI) have occurred.

BETA-BLOCKER SELECTIVITY

Drug	Selectivity
Acebutolol	β_1
Atenolol	β_1
Carvedilol[a]	Non-selective
Esmolol	β_1
Labetalol[a]	Non-selective
Metoprolol	β_1
Nadalol	Non-selective
Nebivolol[b]	B_1 at low doses
Pindolol	Non-selective
Propranolol	Non-selective
Timolol	Non-selective

[a]Also causes α-receptor blockade.

[b]Also causes vasodilation by causing release of nitric oxide from vascular endothelium.

CLINICAL USE

Angina

Heart failure with reduced ejection fraction

Hypertension

Myocardial infarction

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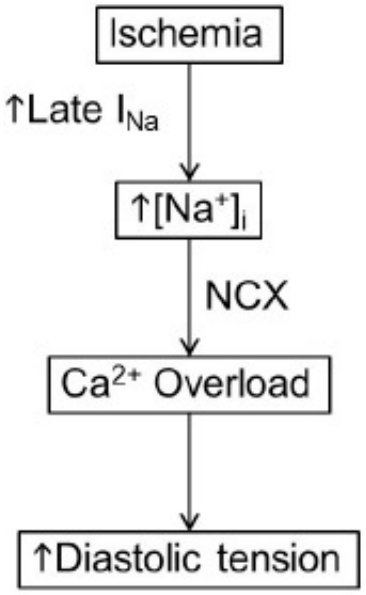
I_{NA} INHIBITORS

INTRACELLULAR SODIUM

Increases in intracellular sodium concentration, [Na2+]i, in ischemic cardiac myocytes cause calcium overload

- Via 3Na+-Ca2+ exchanger (NCX)
- Leads to contractile dysfunction and cellular injury

Late Na+ inward current (late I_{Na}) contributes to calcium overload



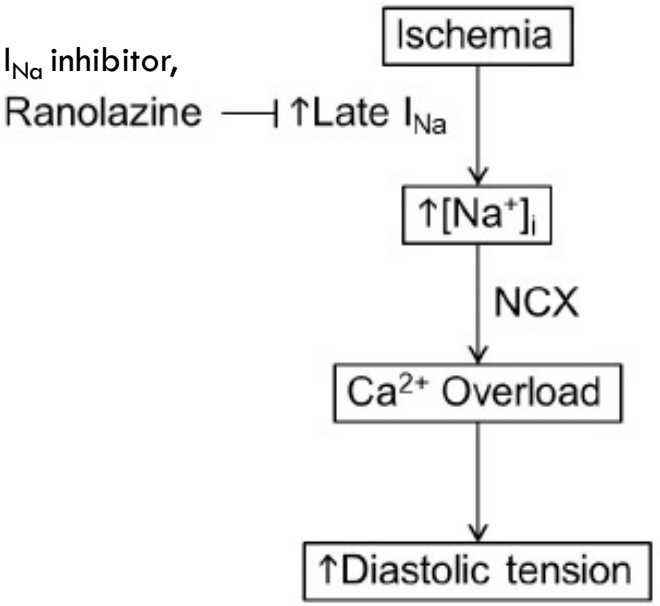
I_{NA} INHIBITOR MECHANISM OF ACTION

Inhibits enhanced late I_{Na}

- Prevents calcium overload
- Reduces diastolic tension, cardiac contractility, and work

Does not impact function of normal heart

- I_{na} is small current



I_{NA} INHIBITOR

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Ranolazine	Strong inhibitors of P450 enzymes Clinically significant hepatic impairment (increased plasma concentrations and QT prolongation)	Constipation Nausea Dizziness Headache QT prolongation	Drugs which are strong inhibitors of hepatic P450 enzymes (CYP3A4), e.g., ketoconazole, macrolide antibiotics, HIV protease inhibitors, grapefruit products or juice can increase plasma concentration of Ranolazine Diltiazem and verapamil are moderate inhibitors of P450 enzymes; the dose of ranolzine must be reduced when given concurrently with these drugs in treating CAD.

CLINICAL USE

Refractory exertional angina

ACUTE CORONARY SYNDROMES (ACS)

Initial

- Aspirin
- Heparin bolus + infusion
- Antiplatelet therapy (ticagrelor or clopidogrel)
- Morphine
- Oxygen
- Nitroglycerin
- STEMI
  - Percutaneous intervention OR thrombolytic (tenecteplase or other thrombolytic)

As Soon as Possible

- Beta-blocker
- Statin
- ACE inhibitor

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REFERENCE LIST

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ANY QUESTIONS?

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