Treatment of Myocardial Ischemia & Congestive Heart Failure

PHC 721

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Angina Pectoris: Chest Pain/Discomfort evoked by Myocardial Ischemia

- Exertional (Stable):

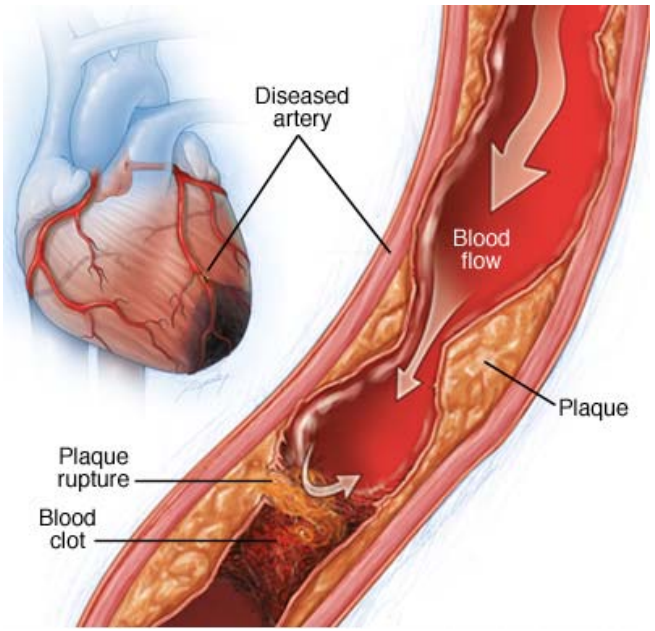
↑ O_2 demand, ↓ coronary blood flow (plaque)

- Unstable:

Acute, unexpected: ↑↑↑ risk of myocardial infarction

Dental Implications:

Inhalation anesthetics (e.g., Isoflurane) lead to systemic vasodilation and the resulting decrease in coronary blood flow ("coronary steal"). In patients with Angina Pectoris, coronary vessels distal to the plaque are maximally dilated, i.e. unable to compensate for the decreased blood flow by vasodilation ⇒ ↑ **risk of Myocardial Infarction**.



- Variant (aka Prinzmetal's):

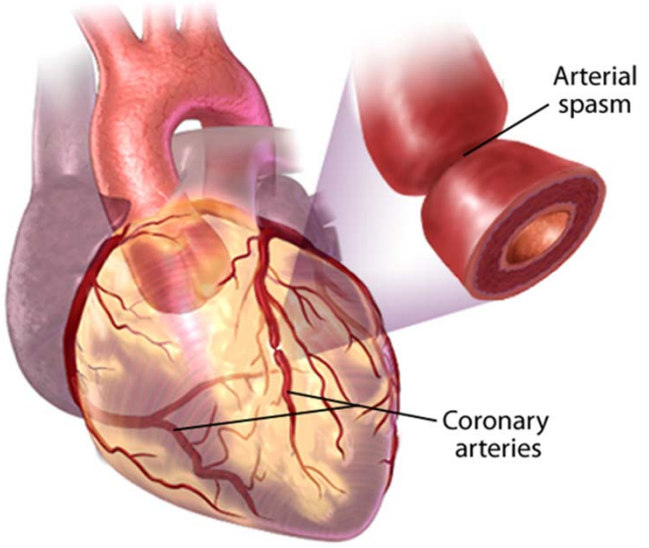
At rest (often at night), coronary artery spasm

- Microvascular:

Microvascular disease, vasospasms in microvessels

- Atypical:

Atypical and vague symptoms (chest discomfort rather than pain, back pain, nausea, etc.). More frequent in women.



Myocardial Ischemia: O_2 Supply < O_2 Demand

Treatment of Myocardial Ischemia

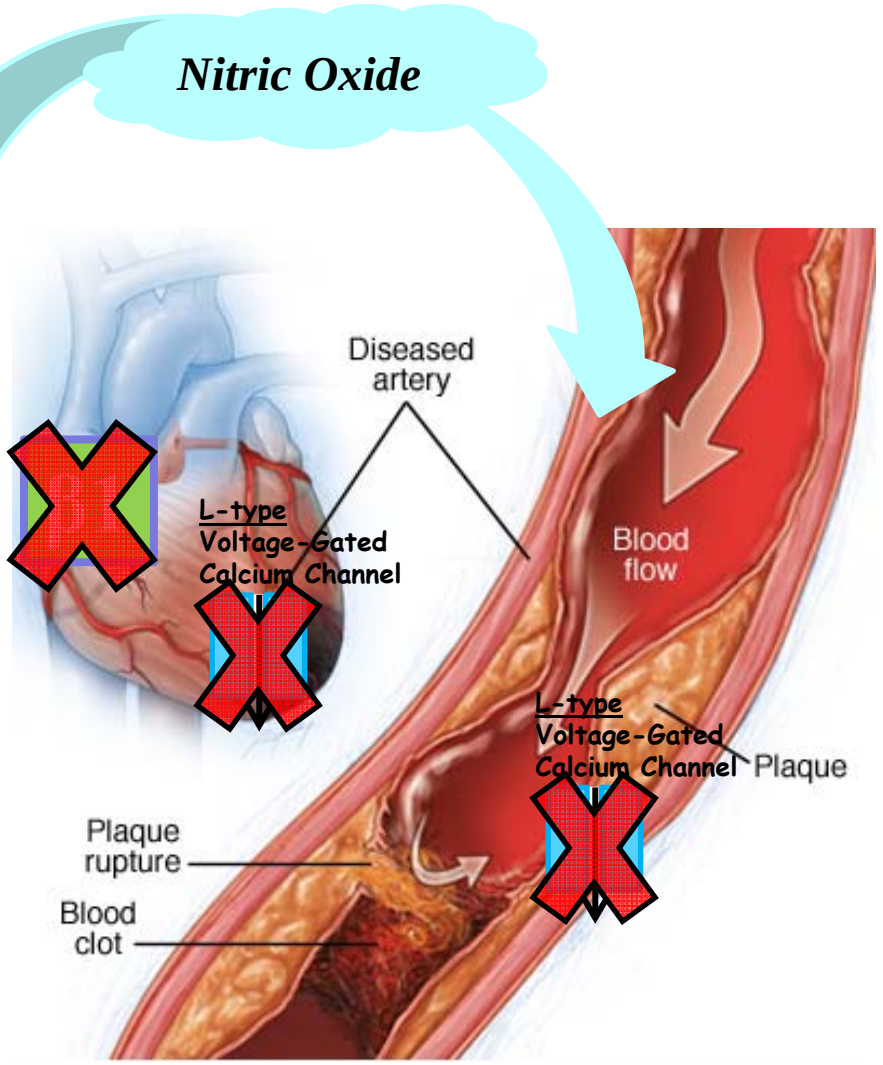
Myocardial Ischemia: O_2 Supply < O_2 Demand

Pharmacological Intervention: ↑ O_2 Supply & ↓ O_2 Demand

- Organic Nitrates:
  Glyceryl trinitrate *(Nitroglycerin)*
  Isosorbide dinitrate

- β-adrenergic Antagonists (beta-blockers):
  Propranolol, ***Bisoprolol***
  Labetalol

- Ca^{2+} channel Antagonists:
  Verapamil,
  Dihydropyridines (Nifedipine, Amlodipine)



Nitrovasodilators: Organic Nitrates

Mechanism of Action:

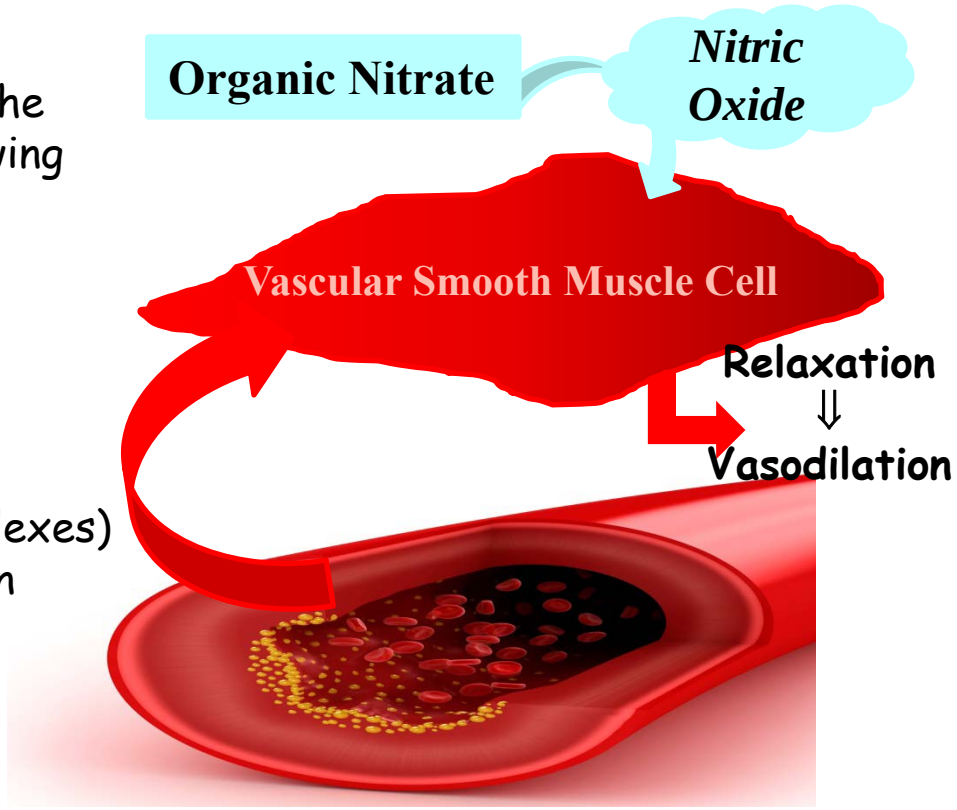
- Release of nitric oxide (NO) ⇒ ↑cyclic GMP ⇒ ↑ Protein Kinase G (PKG) and other kinases ⇒ ↑ Phosphatases ⇒ Dephosphorylation of the Myosin Light Chain & ↓ cytosolic Ca^{2+} ⇒ Vascular Smooth M. Relaxation ⇒Vasodilation ⇒ ↑ Venous Capacitance (↓ venous return/pre-load) & ↓ Peripheral Vascular Resistance (↓ after-load) ⇒ ↓ Cardiac O_2 demand & ↑ regional blood flow (e.g., restoration of blood flow near endocardium)
- Relaxation of smooth muscle in the respiratory, GI, biliary tracts ⇒ relief of biliary, esophageal spasm

Indications:

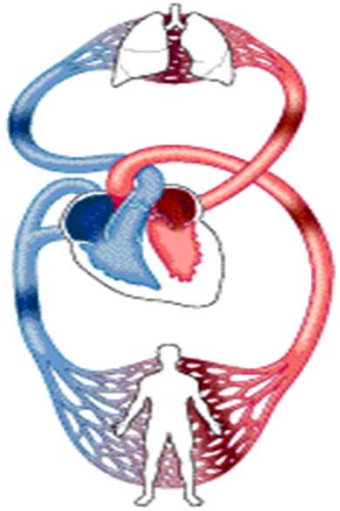
- Exertional Angina (sublingual application at the time of the attack; tolerance develops following continuous exposure)
- Acute Myocardial Infarction (except patients with hypotension)

Side effects:

- Severe Hypotension:
  - in autonomic dysfunction (impaired baroreflexes)
  - in patients treated for erectile dysfunction with phosphodiesterase 5 (PDE 5) inhibitors (e.g., Sildenafil-Viagra; Tadalafil-Cialis).
- Headache, often severe



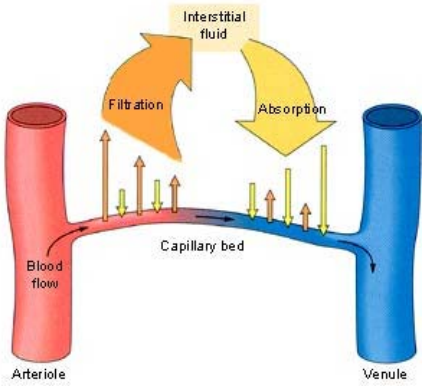
Congestive Heart Failure



Heart Failure: the heart is unable to pump the amount of blood that is adequate for the needs of the tissues

Congestion: volume overload (blood backs up in organs):
↑ hydrostatic pressure →↑ filtration → edema:
pulmonary edema, hydroperitoneum (ascites),
peripheral edema (swelling of feet, ankles, etc)

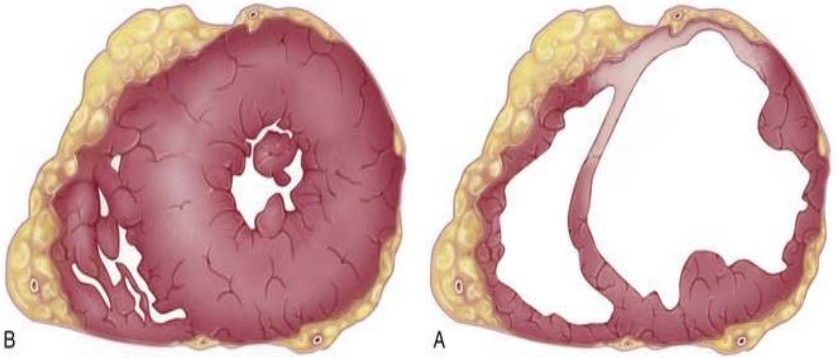
- Acute (in myocardial infarction, arrhythmia, etc.) – risk of sudden death!
- Chronic (in coronary artery disease, cardiac valve disease, etc.)



- Right ventricle only (Cor Pulmonale) – less common
- Left ventricle or both ventricles – more common

- <u>Systolic dysfunction:</u>
↓ ventricular contraction → ↓ stroke volume → ↑ end-systolic ventricular volume → compensatory sympathetic activation and stimulation of the Renin-Angiotensin-Aldosterone System → ↑ peripheral vascular resistance, Na^+ and H_2O retention → ↑ end-diastolic volume (preload), ↑ O_2 demand → compensatory cardiac hypertrophy → eventually dilated cardiomyopathy

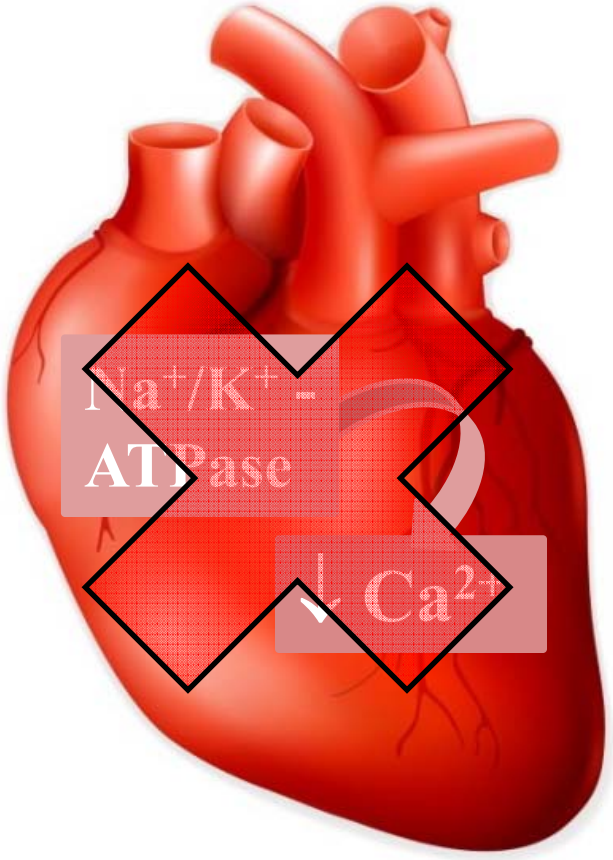
- <u>Diastolic dysfunction:</u>
↓ elasticity of the myocardium → ↓ filling during diastole → ↓ stroke volume



Pharmacotherapy of Congestive Heart Failure

Issues: ↑ Preload, ↑ Afterload, ↓ Myocardial Contractility, Pathological Remodeling

Interventions: ↓ EFV, ↓ BP, ↑ Contractility, ↓ O_2 demand, ↓ Ventricular stiffness



- Cardiac Glycosides: ***Digoxin***

- Dopaminergic Agonist: ***Dopamine***

- Diuretics:
Furosemide, Hydrochlorothiazide, Spironolactone

- **RAA-SYSTEM INHIBITORS:**
- Angiotensin-Converting Enzyme (ACE) Inhibitors:
Captopril, ***Enalapril***, *Ramipril*
- Angiotensin II Receptor (AT_1) Antagonists:
Losartan, *Valsartan*
- Direct Renin Inhibitors:
Aliskiren

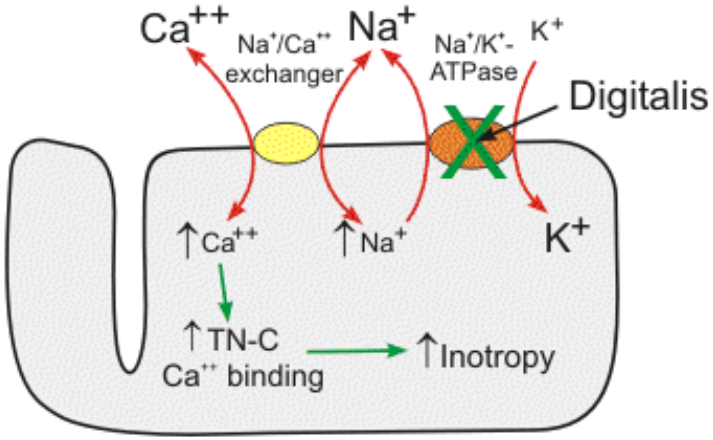
- β-adrenergic Antagonists (beta-blockers):
Propranolol, ***Bisoprolol***
Labetalol

Vasodilators:
Hydralazine, Sodium Nitroprusside, Organic Nitrates (Nitroglycerin, Isosorbide dinitrate)

Cardiac Glycosides: *Digoxin*

Mechanism of Action:

Cardiomyocytes: Inhibition of sarcolemmal Na^+/K^+-ATPase $\Rightarrow\uparrow$cytosolic $Na^+ \Rightarrow$ $\downarrow$ transmembrane Na^+ gradient $\Rightarrow \downarrow Ca^{2+}$ efflux $\Rightarrow \uparrow Ca^{2+}$ accumulation in the sarcoplasmic reticulum $\Rightarrow \uparrow$releasable $Ca^{2+} \Rightarrow \uparrow$ cardiac contractility



Indications:

Congestive Heart Failure, but limited to patients
who do not improve on ACE inhibitors and beta-blockers at maximal doses.

Side effects:

- Ventricular Arrhythmias (life-threatening!) when overdosed (e.g., inhibition of P-glycoprotein transporter activity by Verapamil $\Rightarrow \downarrow$ renal tubular elimination)
- Elevated extracellular potassium reduces Digoxin binding to Na^+/K^+-ATPase $\Rightarrow\downarrow$effectiveness