Pharmacology of the heart
(congestive heart failure, ischemic heart disease)

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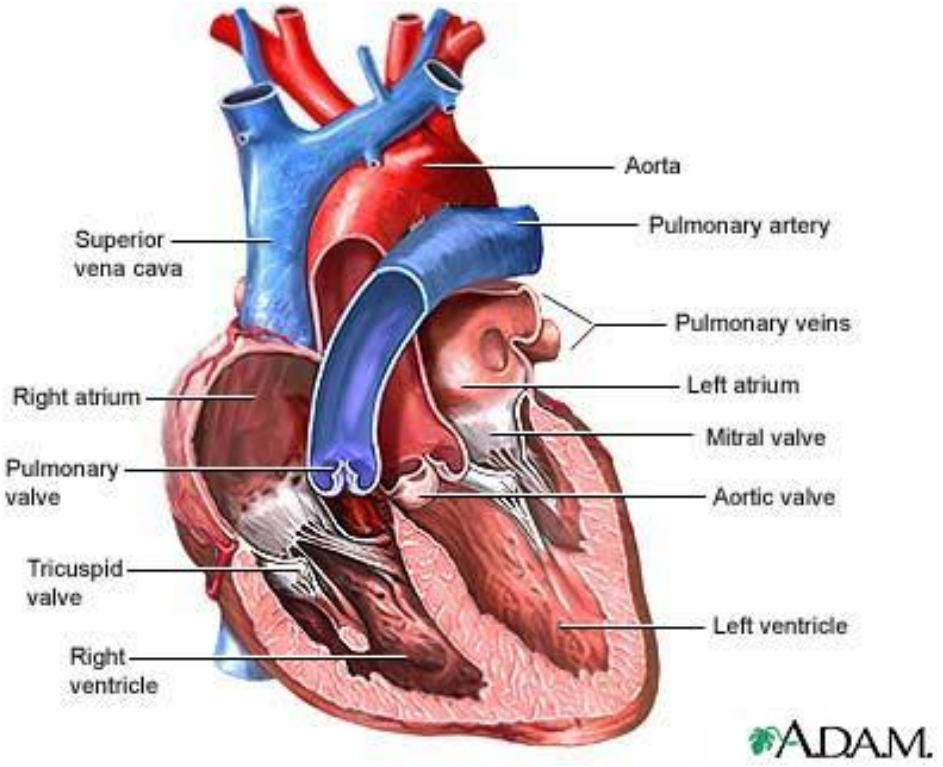
Cardiac output (CO)

- Frequency (HR)
- Contractility
- Preload
- Afterload



Congestive heart disease

- Definition!
- acute vs. chronic
- Left ventricular failure vs. Right ventricular failure
- Systolic:
  - myocarditis
  - arrhythmia
  - myocardial infarct
  - cardiomyopathia (dilatative)
  - stenosis of aortae, hypertension
- Diastolic:
  - pericardial tamponade
  - cardiomyopathia (restrictive)
- Combination

Symptoms

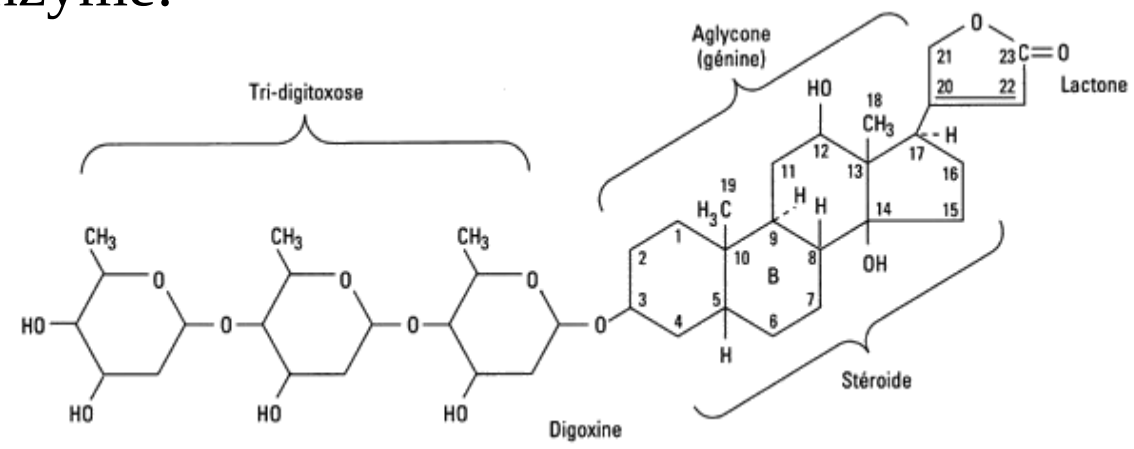
- Forward failure:
  - (LVF)
    - confusion
    - hypotension
    - dizziness
    - ischaemic heart disease
  - (RVF)
    - cyanosis, (dyspnoe)
- Backward failure:
  - (LVF)
    - Dyspnoe (PND, Asthma cardiale, Pulmonary edema)
  - (RVF)
    - hepato-splenomegalia
    - dilated jugular veins
    - diuresis ↑
    - acral edema

Therapeutical ways

- Contractility ↑:
  - positive inotropic drugs: cardiac glycosides, bipiridines, Ca^{2+} sensitizers,
- Preload ↓:
  - diuretics: furosemide
  - nitric oxide
- Afterload ↓:
  - diuretics: thiazides
  - antihypertensive agents
- Frequency: -

Cardiac glycosides

- History
  - ancient Egypt,
  - 18th century William Withering
- digoxin, digitoxin
- Digitalis lanata, Digitalis purpurea, Strophantus species
- active after drying, enzyme: digipurpidase
- Structure
  - steroid ring
  - 3C – digitoxose
  - 17C – lactone ring



Cardiac glycosides

- Mechanism of action:
  - blocking Na^+/K^+ ATPase in cardial myocytes
  - Na^+/Ca^{2+} exchange
  - i.c. $Ca^{2+} \uparrow \rightarrow$ CICR

- Cardial effects:
  - (+) inotropic → contractility ↑
  - (-) chronotropic → HR ↓
  - (-) dromotropic → AV block!

  sensitizing atrial area to the effect of Ach

  - arrhythmic effect (esp. in ventricles) (ES, bigeminia,VT, VF!)

    → Late after depolarisation – LAD (etiology of arrhytmias)

Cardiac glycosides

- Vessels
  - i.c. Ca 2+ → vasoconstriction – blood pressure↑
- GIT
  - i.c. Ca 2+ → vomitus, diarrhea, colica abd.
- CNS
  - hallucinations, visual disturbances
  - convulsions
  - dizziness

Cardiac glycosides

Pharmacokinetics:

	digoxine	digitoxine
Oral availability (percentage of absorbed)	75	>90
PPB	20-40	>90
Metabolized by	kidney	liver

Cardiac glycosides

- Therapeutical indications:
  - congestive heart disease
  - atrial flutter → atrial fibrillation
  - arrhytmias (SVES, SVT)

- Digitalis intoxication
  - TI ↓, therapeutic dose, toxic dose
  - provoked by hypercalcemia, hypokalemia, CRF, IHD
  - bradycardia, block, bigeminia, ST alterations (depression),
  - Th.: atropin!, K+, lidocaine, amidarone, AB

Cardiac glycosides

- Digoxin
  - cumulative dose: 1mg/day 2 days long
  - maintenance dose: 0,25mg-0,5mg/day

- Digitoxin:
  - cumulative dose: 1mg/day
  - maintenance dose: 0,1 mg/day

Phosphodiesterase inhibitors

- Mechanism of action: blocking PDE, cAMP↑
- Type of PDEs:
  - PDE I: brain, inhibited by vinpocetin (Cavinton®)
  - PDE III: heart, vessels (inodilatators)
  - PDE IV: retina, inhibiting→blue vision
  - PDE V: corpus cavernosum, inhibited by sildenafil, tadalafil

- PDE III inhibition:
  - heart: cAMP↑→PKA→Ca2+ channels-P→Ca2+↑→CICR
  - vessels: cAMP↑→MLCK-P, K+channels-P, K+↑→vasodilation

Phosphodiesterase inhibitors

- Bipiridines
  - amrinone, milrinone
    - CAST: thrombocytopenia, morbidity, mortality↑
  - vesnarinone
    - VEST: mortality↑

Positive inotropic drugs

- Ca^{2+} senzitizers:
  - pimobendane, levosimendane
  - mechanism of action:
    - increase the binding rate of Ca^{2+} to troponin C
    - senzitizing myofibrilles to Ca^{2+}

- Direct sympathomimetic drugs:
  - Dopamine:
    - 1-3 μg/kg/min - D_1, D_2 receptors – renal! art.aff., GFR↑, RBF↑
    - 3-5 μg/kg/min - β_1,β_2 – cardial! cardiogen shock
    - post AMI
    - 5-10 μg/tskg/min - α_1 vessels! RR↑

  - Dobutamine:
    - 5-20 μg/tskg/min - β_1,β_2 – heart! cardiogen shock

Ischaemic heart disease

coronary stenosis

↓

O_2 demand ≠ O_2 supply

↓

contractility disorders

↓

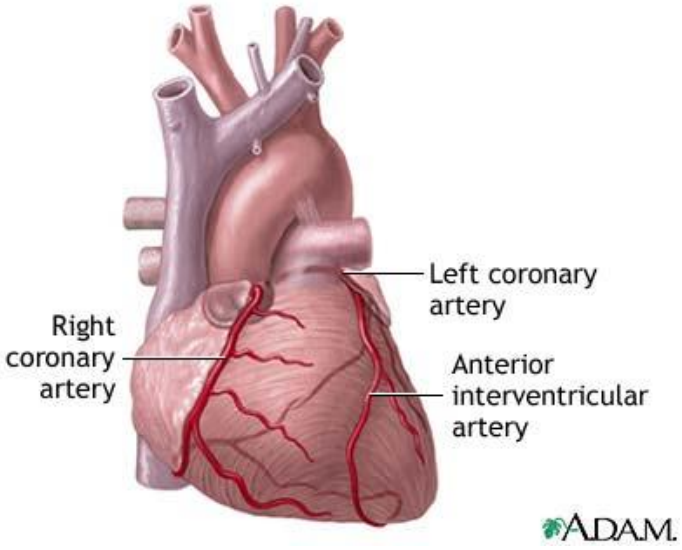
EDV↑

↓

EDP↑

↓

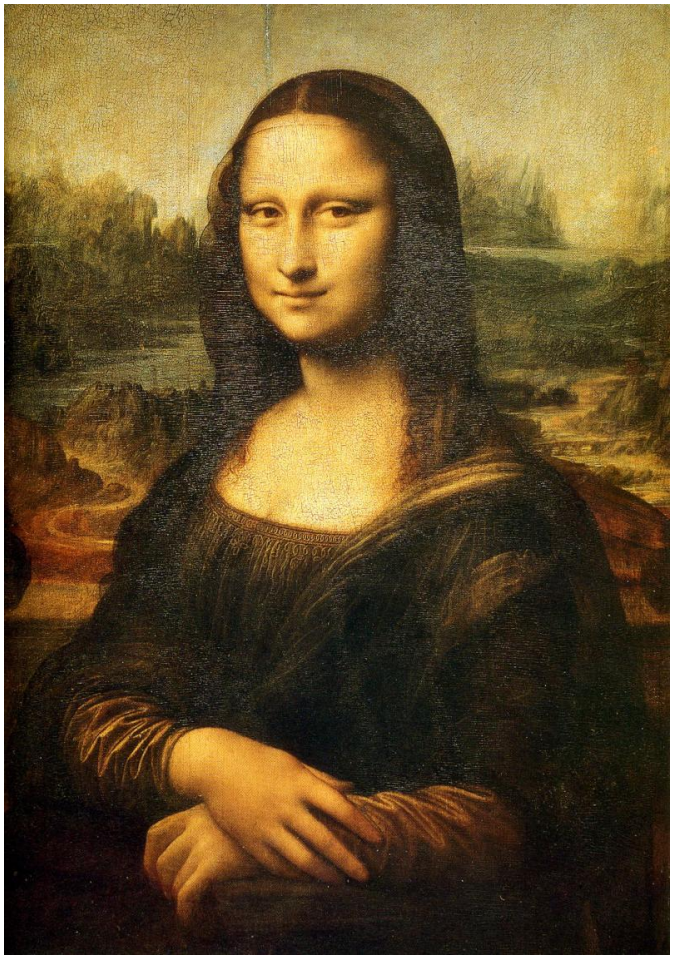
extravascular coronary resistance



Ischaemic heart disease

- Clinical types:
  - stable AP
  - unstable AP (preinfarct st.) → ACS
  - AMI → ACS
- Diagnosis:
  - chest pain!, dyspnoe, dizziness, nausea, weakness
  - ECG
  - necroenzymes (troponin, LDL, etc.)

Pharmacological management of AMI



Ischaemic heart disease

- Therapeutical applications:
  - O_2
  - nitric oxide
  - NSAID (aspirin)
  - maior analgetics (morphine, etc.)
  - atropine (if necessary..)
  - antiarrhytmic drugs (metoprolol, lidocaine)
  - anticoagulant drugs
  - thrombolytics
  - Ca^{2+} channel blocking drugs
  - ACE inhibitors
  - Positive inotropic drugs (CAVE: digoxin)
  - K+, Mg2+

Nitric oxide

Mechanism of action:

L-Arg ⟶ L- Citrulline + NO

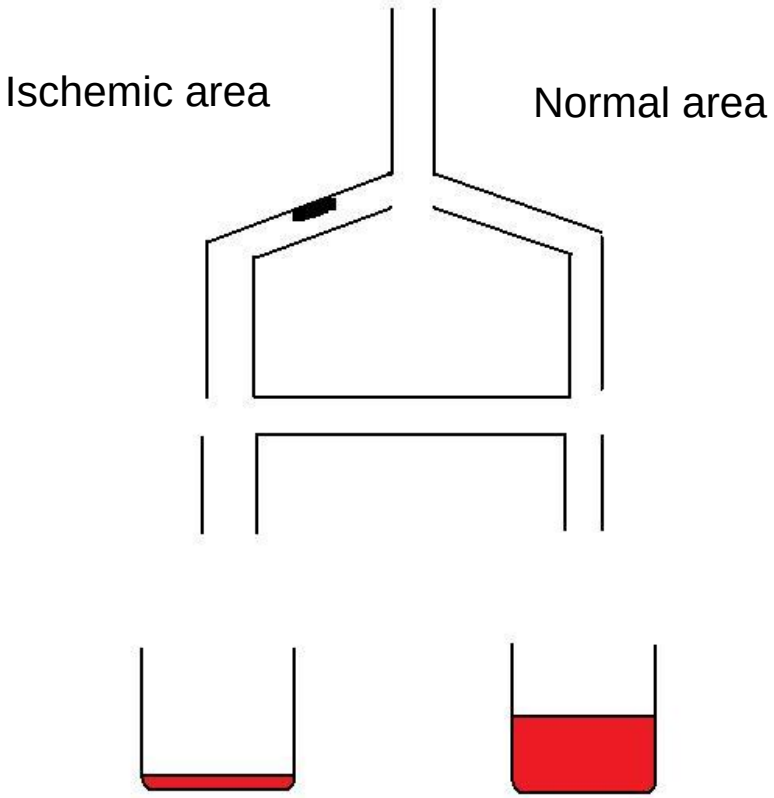
NO: sGC act. → cGMP↑ → PKG→ Ca2+↓
→(art./ven.) vasodilation → BP↓

enzymatic NO donors: nitroglycerin, ISMN, ISDN
non enzymatic NO donors: Na-nitroprusside

Coronary steal effect:

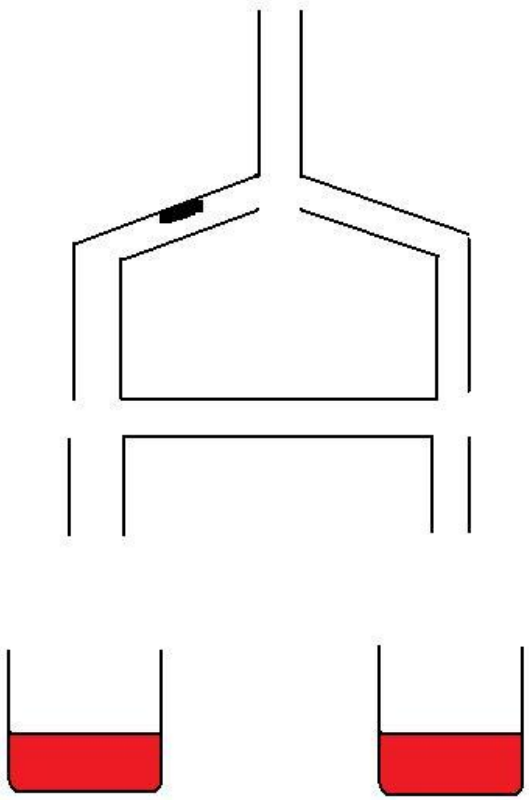
- conductive arteries (enzymatic NO donors)
- resistant arteries - collaterals (arterioles, D<100 um)

Coronary steal effect



Coronary steal effect

enzymatic NO donors



non enzymatic NO donors