



**UZ  
LEUVEN**



# Cardiovascular Active Medications

Co's les 2023-2024

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# Cardiovascular Active Medications

- Many drugs are used to manage hemodynamic before, during and after any operation
- Drug errors → accidental injury to patients especially critically ill
- Use familiar drugs or read the drug information before using the one you don't know



# Cardiovascular Active Medications

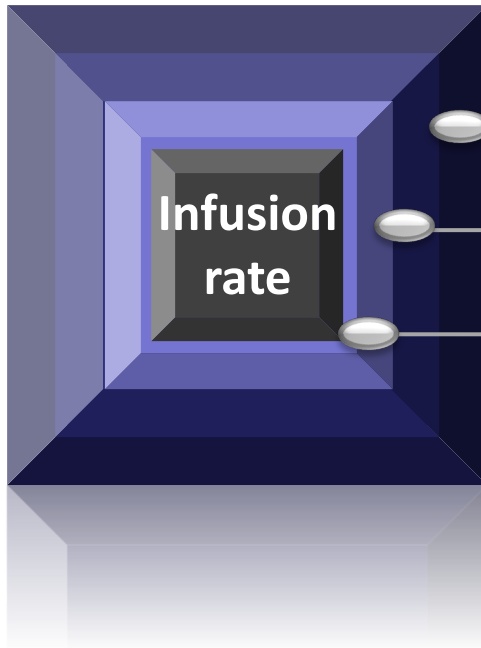
## Drug dose calculations

- Not all drugs labeled in a uniformed manner
- Drugs labeled **Z%** contains **Z gram/dL**  $\equiv$  **Zx10 mg/mL**
- Concentration given as a ratio e.g bupivacaine 0.25% + epinephrine 1:200.000 means 5 $\mu$ g epinephrine for each ml.



# Cardiovascular Active Medications

## Calculating infusion rate



Dose rate ( $\mu\text{g}/\text{min}$ ) e.g. noradrenaline  $0.1\mu\text{g}/\text{kg}/\text{min}$

Concentration e.g. noradrenaline  $4\text{mg} / 40 \text{ ml NaCl } 0.9\%$

Volume rate ( $\text{ml}/\text{hour}$ ) = dose rate / concentration

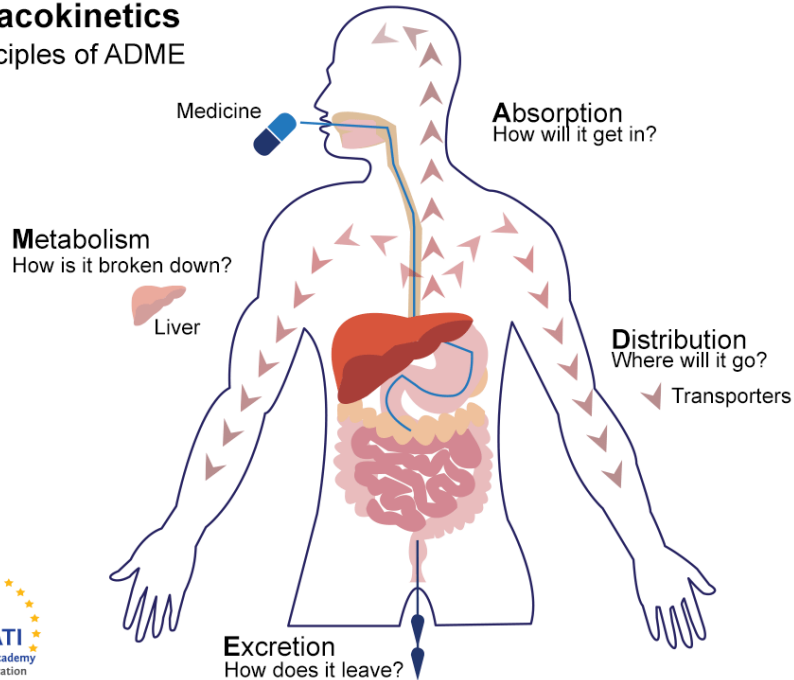


# Cardiovascular Active Medications

## Pharmacokinetics: what the body does for the drug

### Pharmacokinetics

The principles of ADME

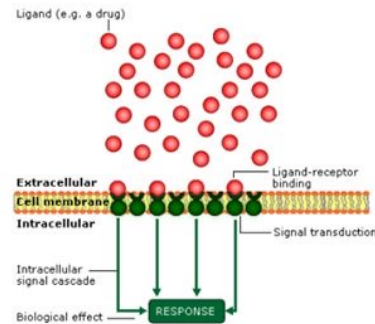


# Cardiovascular Active Medications

**Pharmacodynamics:** what the drug does for the body

## What is pharmacodynamics?

- “What a drug does to the body”
- Drugs act by binding to receptors
  - They then cause either **activation** or **inhibition** of a regular body process to give a biological response
- What do you need to know?
  - A little bit about the different types of receptor
  - Different ways which drugs can affect receptors
  - A little bit about pharmacological terminology



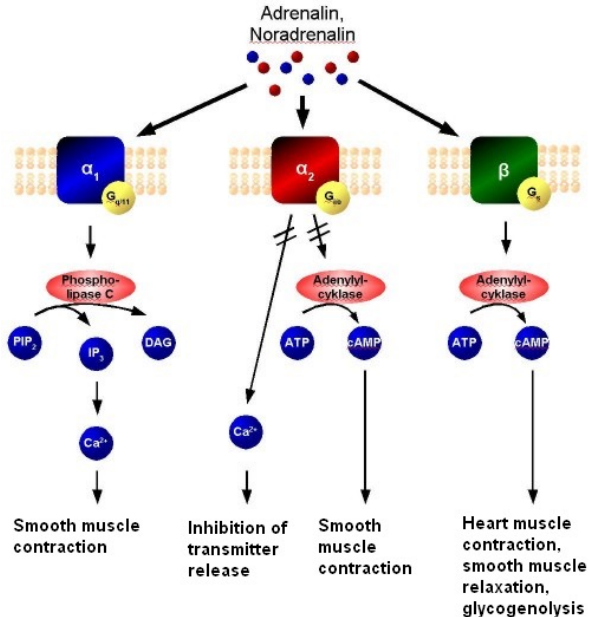
Receptors are usually glycoproteins located in cell membranes that bind smaller molecules (ligands), including drugs. This binding initiates a series of biochemical reactions inside the cell (signal transduction), often involving the generation of ‘secondary messengers’, and culminating in a biological response.



# Cardiovascular Active Medications

## Drug – receptors interaction

Adrenergic receptors : are G protein-coupled receptors; targets for catecholamine



# Cardiovascular Active Medications

## Drug – receptors interaction

### Adrenergic receptors

### $\beta$ -receptor effects

Inotropy	<i>inos</i>	force
Chronotropy	<i>kronos</i>	rate
Dromotropy	<i>dromos</i>	conduction
Bathmotropy	<i>bathmos</i>	ectopy tachyarrhythmia

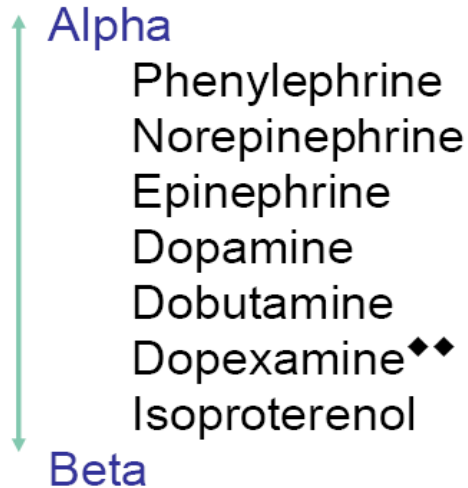




# Cardiovascular Active Medications

## ACTIONS OF ADRENERGIC AGONISTS

### CATECHOLAMINES: SELECTIVITY OF SYMPATHOMIMETIC DRUGS



♦♦Not currently approved by the FDA for use in the United States.

Bailey JM, et al. *Adult Cardiac Surgery*. 1997:225-254.  
Levy JH. *J Cardiothorac Vasc Anesth*. 1993;7(suppl):46-51.



# Cardiovascular Active Medications

## ACTIONS OF ADRENERGIC AGONISTS

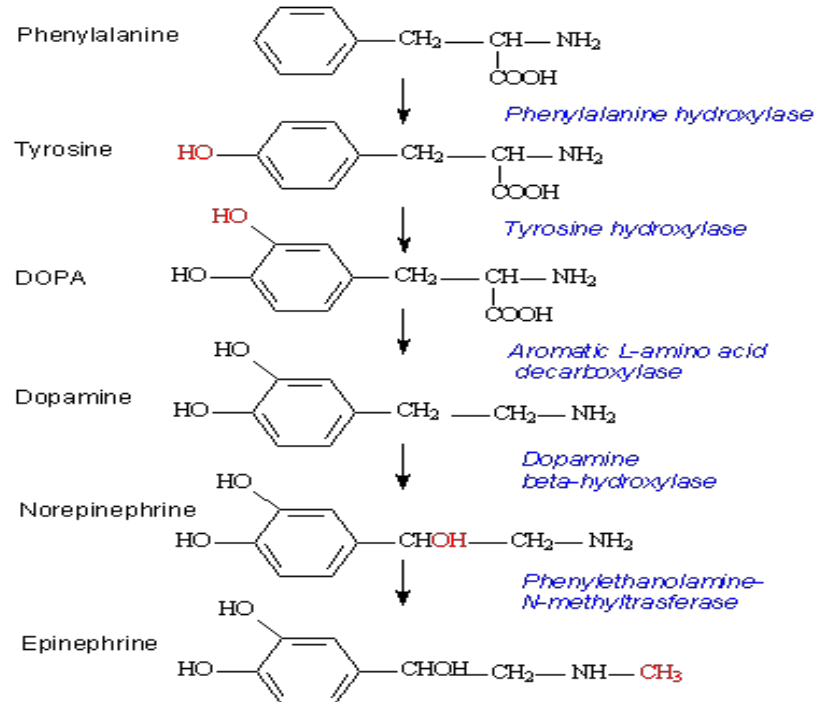
■ SYMPATHO-MIMETICS	I ■ RECEPTORS						■ DOSE DEPENDENCE ( $\alpha$ , $\beta$ , or DA)
	■ $\alpha_1$	■ $\alpha_2$	■ $\beta_1$	■ $\beta_2$	■ DA <sub>1</sub>	■ DA <sub>2</sub>	
Phenylephrine	+++++	?	±	0	0		++
Norepinephrine	+++++	+++++	+++	0	0		+++
Epinephrine	+++++	+++	+++++	++	0		+++++
Ephedrine	++	?	+++	++	0		++
Dopamine	+ to +++++	?	+++++	++	+++	?	+++++
Dobutamine	0 to +	?	+++++	++	0		++
Isoproterenol	0	0	+++++	+++++	0		0

DA, dopamine.



# Cardiovascular Active Medications

## Synthesis of endogenous catecholamines



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



- Phenylephrine
- Vasopressin
- Norepinephrine
- Epinephrine
- Dopamine
- Ephedrine

# Cardiovascular Active Medications

## Phenylephrine ( Neo-Synephrine)

- Is mainly  $\alpha$  drug
- Cause vasoconstriction arteriole & less venous
- Short duration ( < 5 min)
- Dose: Iv bolus 1 - 10  $\mu\text{g}/\text{kg}$  (40 -100  $\mu\text{g}$ ), Or Iv infusion 0.5 – 10  $\mu\text{g}/\text{kg}/\text{min}$  (10-100  $\mu\text{g}/\text{min}$ )



# Cardiovascular Active Medications

## Phenylephrine ( Neo-Synephrine) indications

- In hypotension due to  $\downarrow$  SVR.
- In SVT (reflex vagal stimulation).
- Reverse right-to-left shunt during cyanotic spells in TVF.
- Temporary therapy of hypovolemia till blood volume is restored



# Cardiovascular Active Medications

## Phenylephrine ( Neo-Synephrine) disadvantages

- May ↓ CO due to ↑ afterload.
- May ↑ PVR.
- May ↓ renal & mesenteric perfusion.
- Reflex bradycardia.
- Rarely may induce CAS or spasm of the graft.
- Effect on CO is controversial (may ↑ and ↑ SV)



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



Phenylephrine

Vasopressin

Norepinephrine

Epinephrine

Dopamine

Ephedrine



# Cardiovascular Active Medications

## Vasopressin (pitressin)

- Endogenous ADH in high concentration.
- → peripheral vasoconstriction.
- Activation of smooth muscle V1 receptors.
- No actions on  $\beta$ -adrenergic receptors.
- Vasopressin causes cerebrovascular dilation.



# Cardiovascular Active Medications

## Vasopressin (pitressin) indications

- Septic shock or vasoplegic syndrome .
- In sever hemorrhagic shock
- 20-40 U Iv in cardiac arrest when epinephrine not effective
- May maintain SVR in severe acidosis, sepsis, or after CPB



# Cardiovascular Active Medications

## Vasopressin (pitressin) disadvantages

- Arrhythmia, ↓ CO & myocardial ischemia.
- Sever peripheral vasoconstriction & gangrene.
- Bronchoconstriction.



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



Phenylephrine

Vasopressin

Norepinephrine

Epinephrine

Dopamine

Ephedrine

# Cardiovascular Active Medications

## Norepinephrine (Noradrenaline or Levophed)

- Is a postganglionic sympathetic neurotransmitter.
- Released from adrenal medulla en CNS neurons.
- Direct  $\alpha_1$ ,  $\alpha_2$  &  $\beta_1$  agonist.
- Limited  $\beta_2$  effect in vivo.



# Cardiovascular Active Medications

## Norepinephrine indications

- Septic shock or vasoplegic after CPB
- In sever hemorrhagic shock.
- AS with low SVR.
- When phenylephrine is ineffective
- Must be given as IV infusion between  $0.05\text{-}0.3 \mu\text{g/kg/min}$



# Cardiovascular Active Medications

## Norepinephrine side effect

- Reduce organ perfusion ( kidney, bowel, etc.)
- In high doses produce myocardial ischemia & possibly CAS.
- Arrhythmias.
- Risk of skin necrosis if SC extravasation occur.



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



Phenylephrine

Vasopressin

Norepinephrine

Epinephrine

Dopamine

Ephedrine



# Cardiovascular Active Medications

## Epinephrine (adrenaline)

- Produced by adrenal medulla.
- Direct agonist at  $\alpha$  &  $\beta$  receptors.
- $\uparrow$  contractility & HR.
- SVR is dose dependent.



# Cardiovascular Active Medications

## Epinephrine (adrenaline)

- Lusitropic effect ( $\beta_1$ ) enhances rate of ventr. relaxation.
- It is an effective bronchodilator & mast cell stabilizer.
- If BP  $\uparrow$  , tachycardia may  $\downarrow$  due to reflex vagal stimulation.
- CO may  $\downarrow$  in very high doses.



# Cardiovascular Active Medications

## Epinephrine (adrenaline) indications

- In a systole or VF. dose 0.5-1mg IV/IO acces
- In anaphylactic shock
- In bronchospasm ( mild to moderate reaction dose :SC 10  $\mu\text{g}/\text{kg}$  or IV 0.03 $\mu\text{g}/\text{kg}$  bolus
- Weaning from CPB if CO low. dose 0.01-0.3 $\mu\text{g}/\text{kg}/\text{min}$



# Cardiovascular Active Medications

## Epinephrine (adrenaline) indications

- Produce a bloodless field in dentistry & otolaryngology.
- Prolong the action of LA.
- When no respond to ephedrine or phenylephrine after LRA.



# Cardiovascular Active Medications

## Epinephrine (adrenaline) disadvantages

- Arrhythmias.
- Organ ischemia if used in high doses (kidney)
- Myocardial ischemia due to tachycardia & + ve inotropy
- Elevation of plasma glucose & lactate.
- Extravasation cause necrosis



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



Phenylephrine

Vasopressin

Norepinephrine

Epinephrine

Dopamine

Ephedrine

# Cardiovascular Active Medications

## Dopamine (Dynatra)

- Stimulate both adrenergic & DA receptors.
- Low dose DA → renal & mesenteric vasodilatation.
- Moderate dose mainly DA &  $\beta_1$  receptors → contractility & renal vasodilatation.
- High doses  $\alpha_1$  receptors → peripheral vasoconstriction.



# Cardiovascular Active Medications

## Dopamine (Dynatra) doses

- IV infuse via central line
- Low dose 1-5  $\mu\text{g}/\text{kg}/\text{min}$
- Intermediate dose 5- 15  $\mu\text{g}/\text{kg}/\text{min}$
- High dose  $> 15 \mu\text{g}/\text{kg}/\text{min}$





# Cardiovascular Active Medications

## Dopamine (Dynatra) effect

- Renal effects
- Effects on splanchnic perfusion
- Effects on gastrointestinal motility
- Endocrine and immunological effects
- Intra-operative use (cardiogenic shock, weaning CPB)



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



Phenylephrine

Vasopressin

Norepinephrine

Epinephrine

Dopamine

Ephedrine

# Cardiovascular Active Medications

## Ephedrine

- Is a plant- derived alkaloid with sympathomimetic effects.
- Has direct & indirect mechanism of action.
- Mild direct  $\alpha$ ,  $\beta_1$  &  $\beta_2$  - agonist.
- Indirect through noradrenaline release from neurons.



# Cardiovascular Active Medications

## Ephedrine

- Does not reduce blood flow to placenta; safe in pregnancy
- Its effect stays for 5 to 10 min
- No metabolism by MAO, renal elimination



# Cardiovascular Active Medications

## Ephedrine indications

- In hypotension due to low SVR or low CO
- In hypovolemia as a temporal therapy until volume restore
- In transient myocardial depression due to anesthetic overdose
- Improves uterine blood flow in obstetric due to increase BP



# Cardiovascular Active Medications

## Ephedrine disadvantages

- Tachyphylaxis: a rapidly decreasing response of ephedrine after administration of the initial doses
- Caution with MAO inhibitors and norepinephrine-dopamine reuptake inhibitors (NDRIs) due to excessive serum levels of norepinephrine lead to malignant hypertension
- Blunted effect when NE stores are depleted



# Cardiovascular Active Medications

## Commonly used drugs with vasopressors effect



Phenylephrine

Vasopressin

Norepinephrine

Epinephrine

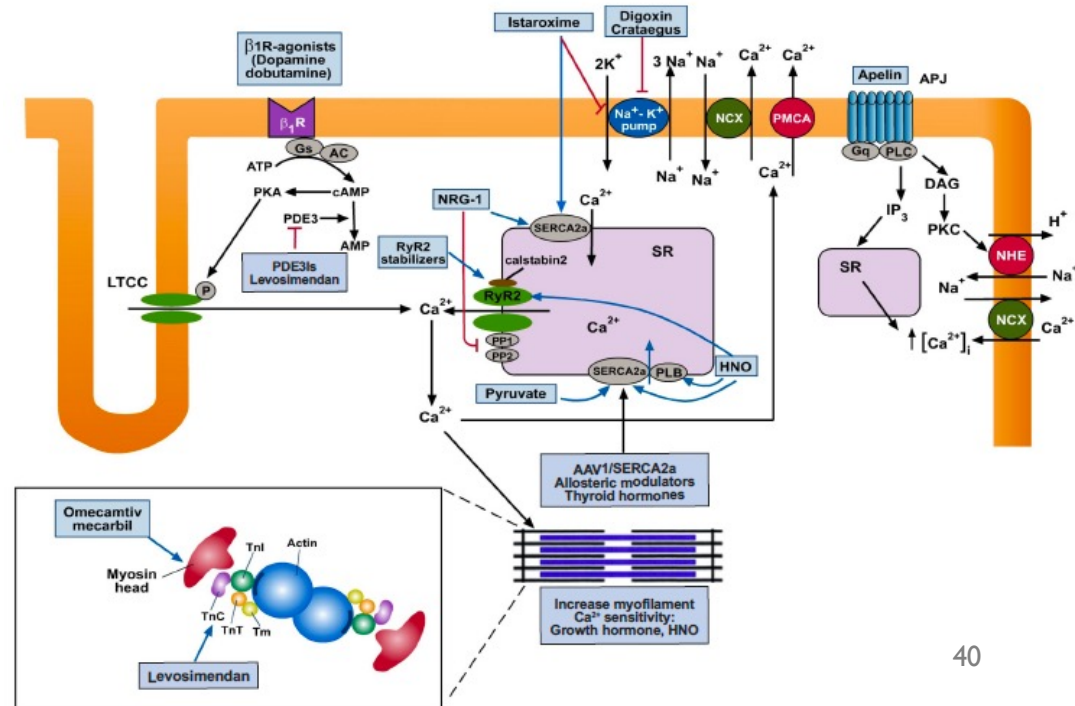
Dopamine

Ephedrine

# Cardiovascular Active Medications

Commonly used drugs with positive inotropic effect

1. Isoproterenol
2. Epinephrine
3. Dobutamine
4. PDE III inhibitors
5. Dopamine
6. Ephedrine
7. Calcium
8. Digoxine
9. T3 hormone
10. Glucagon





# Cardiovascular Active Medications

## The positive inotropic medications

- Chronic use of oral inotropic agents in ambulatory patients, with the exception of digoxin, remains unproven.
- Inotropic therapy is of potential value in patients with decreased cardiac contractility.
- Heart failure due to diastolic dysfunction or mitral stenosis do not need inotropic support.

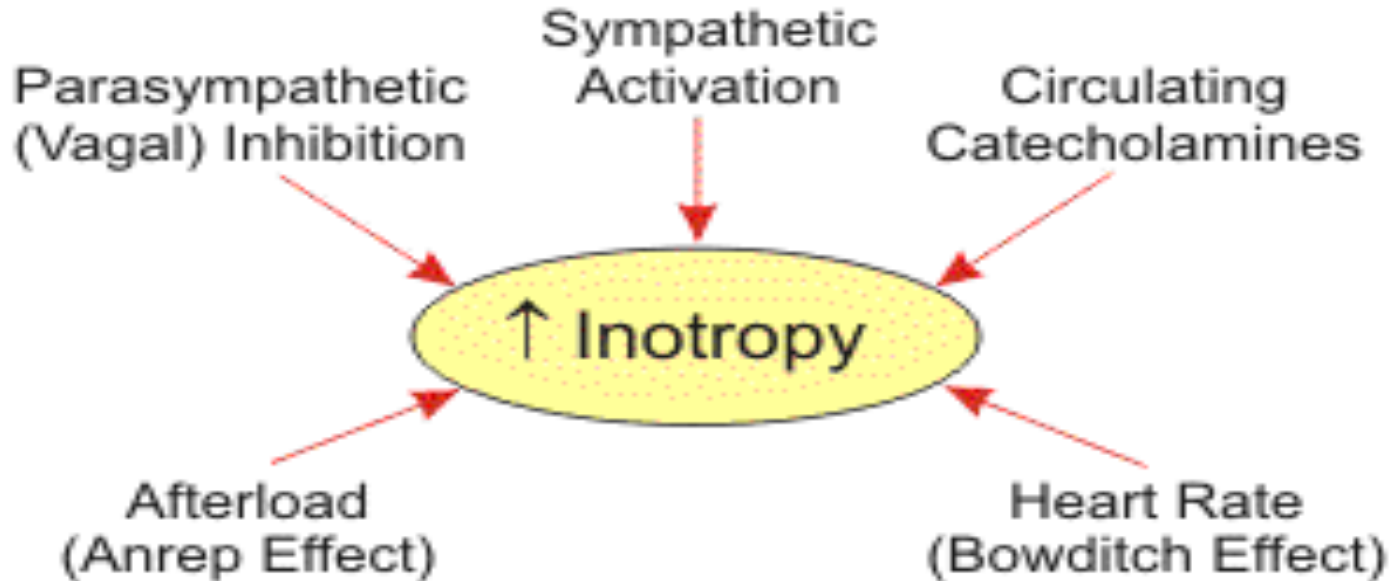
# Cardiovascular Active Medications

## Factors Regulating Inotropy

- Sympathetic nerves
- Parasympathetic have a significant –ve inotropic
- Circulating epinephrine augment sympathetic adrenergic effects.
- Sudden **↑** in **afterload** cause a small **↑**inotropy (*Anrep effect*).
- An **↑**in **HR** also stimulates inotropy (*Bowditch effect*)

# Cardiovascular Active Medications

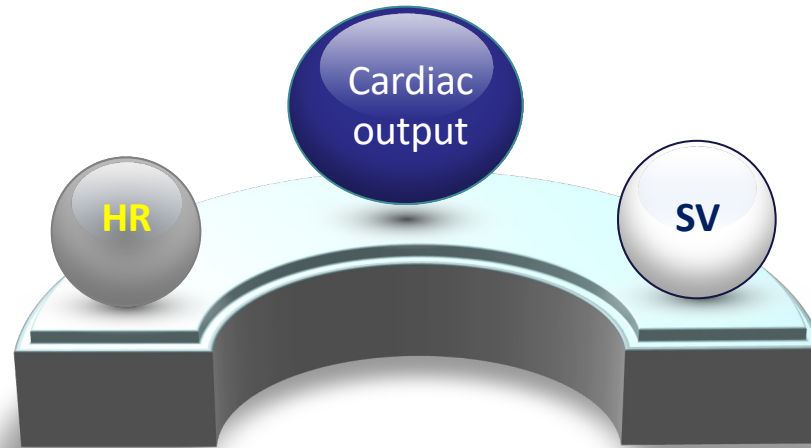
## Factors Regulating Inotropy



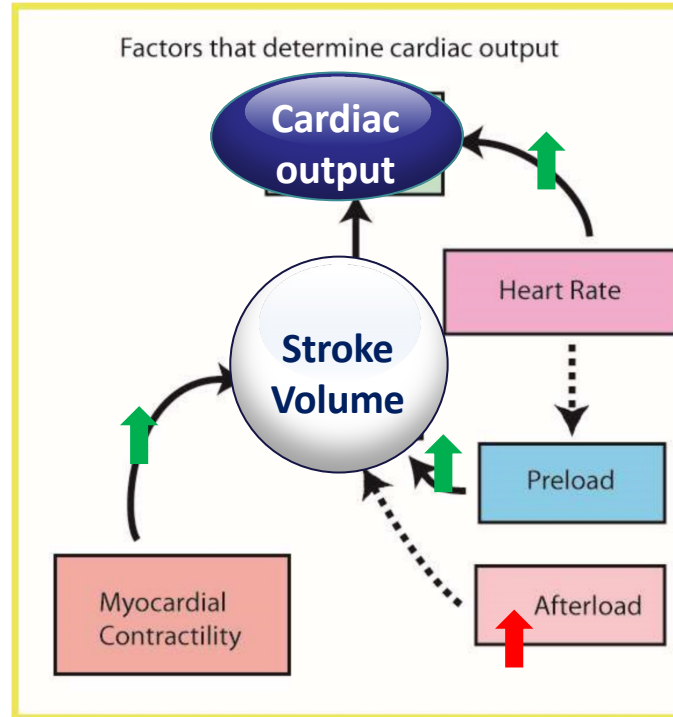
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# Cardiovascular Active Medications

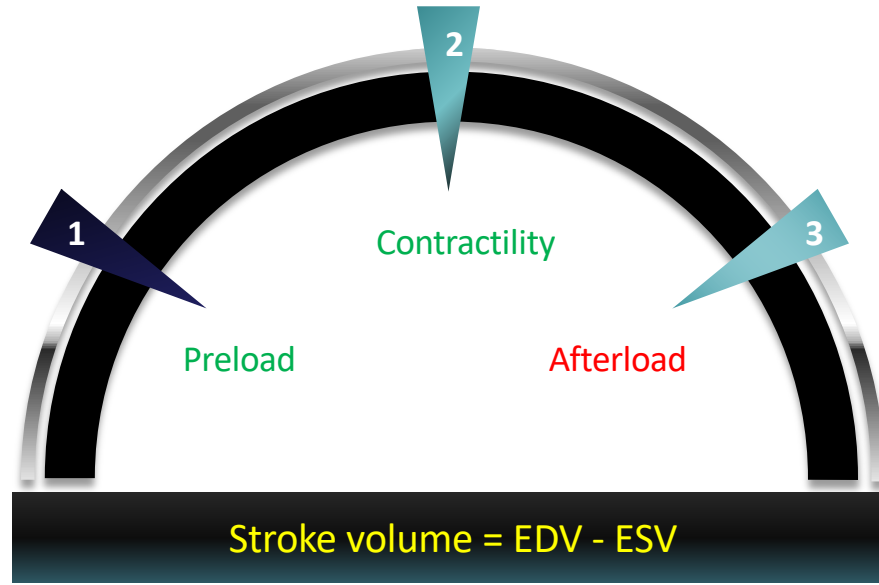
- When the cardiac index is ( $>2.6$  L/min/m<sup>2</sup>) but the blood pressure is low.
- → phenylephrine/ norepinephrine. Vasopressin if both not effective.



# Cardiovascular Active Medications

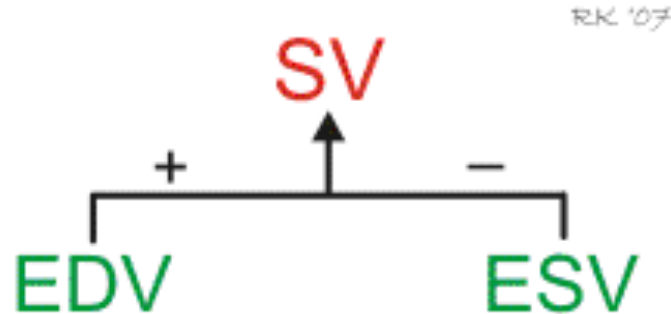


# Cardiovascular Active Medications



# Cardiovascular Active Medications

Regulation of Stroke Volume (SV) = EDV - ESV



↑ Preload → ↑ SV (↑ EDV)

↑ Afterload → ↓ SV (↑ ESV)

↑ Inotropy → ↑ SV (↓ ESV)

# Cardiovascular Active Medications

## Mechanisms of Positive Inotropic Effects

### A. INCREASED MYOPLASMIC $Ca^{++}$ CONCENTRATION

#### 1. Increase in intracellular cAMP level

- stimulation of adenylate-cyclase
  - receptor-mediated stimulation
  - direct stimulation
- phosphodiesterase inhibition

#### 2. cAMP independent activation of $Ca^{++}$ channels

- alpha-adrenergic agents
- Ca-agonists

#### 3. Increase in myoplasmic $Na^{+}$ concentration

- inhibition of  $Na^{+}/K^{+}$  ATP-ase
- prolongation of the open state of  $Na^{+}$  channels

#### 4. Direct inhibition of $Na^{+}/Ca^{++}$ exchange

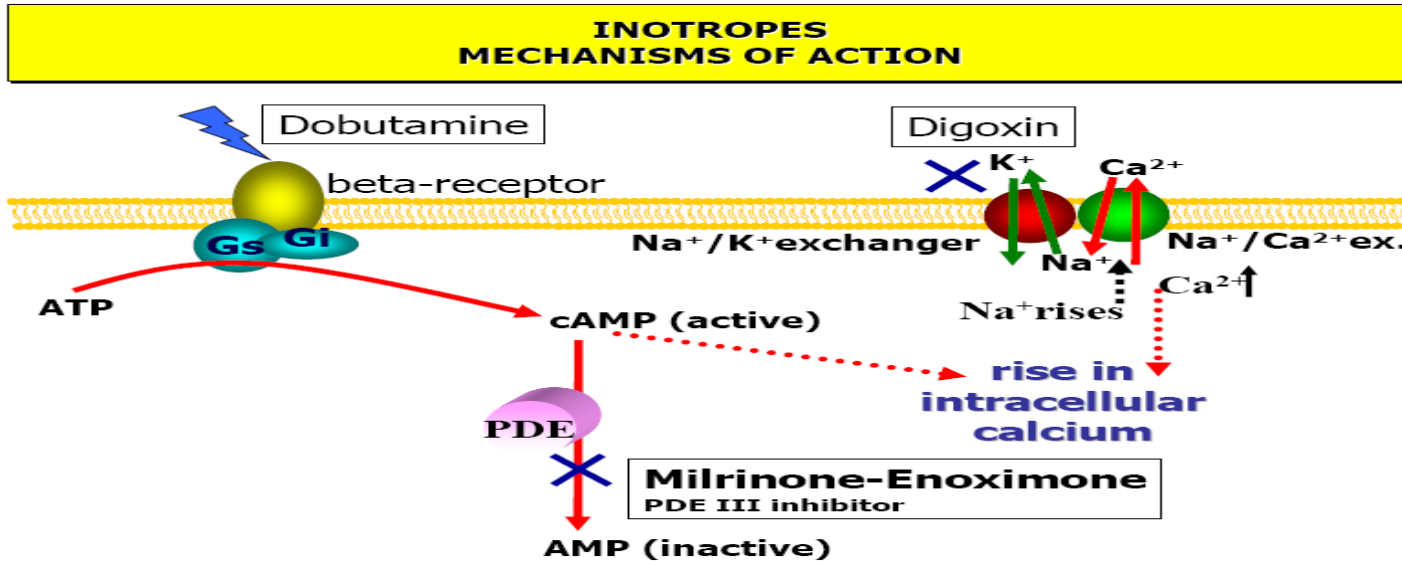
#### 5. Inhibition of $K^{+}$ channels

### B. INCREASED $Ca^{++}$ SENSIVITY OF CONTRACTILE PROTEINS



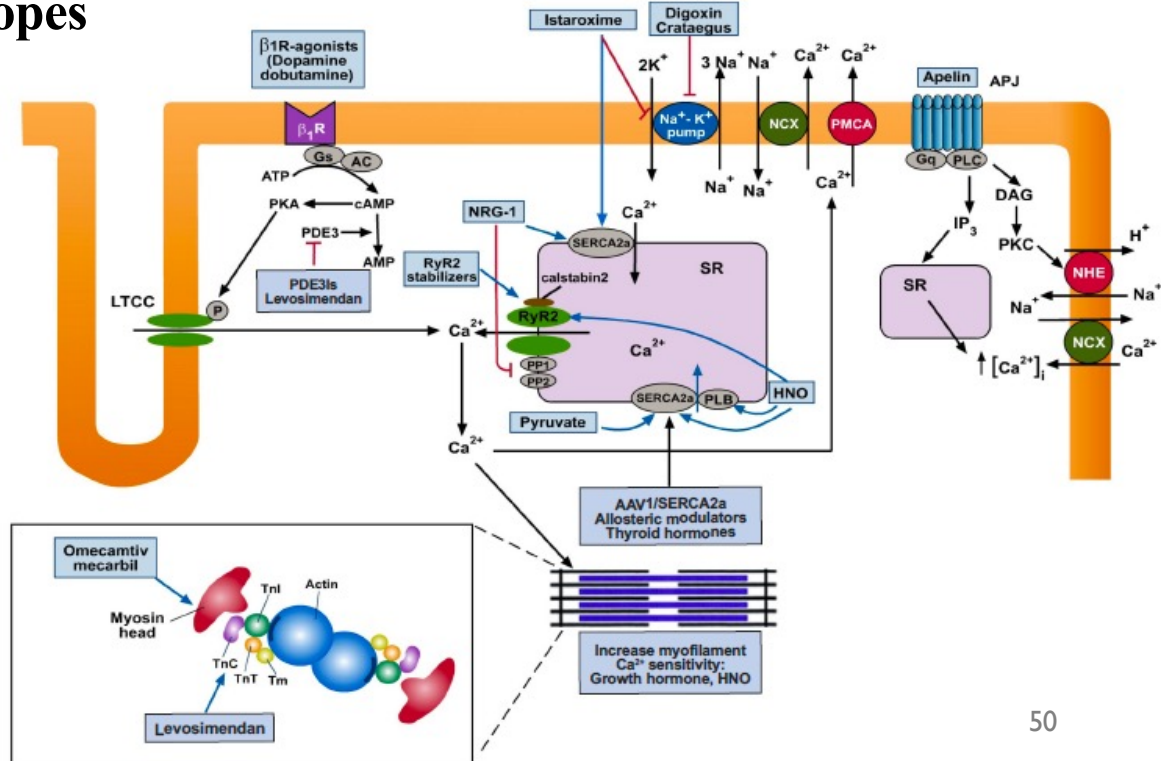
# Cardiovascular Active Medications

## Mechanisms of action of Inotropes



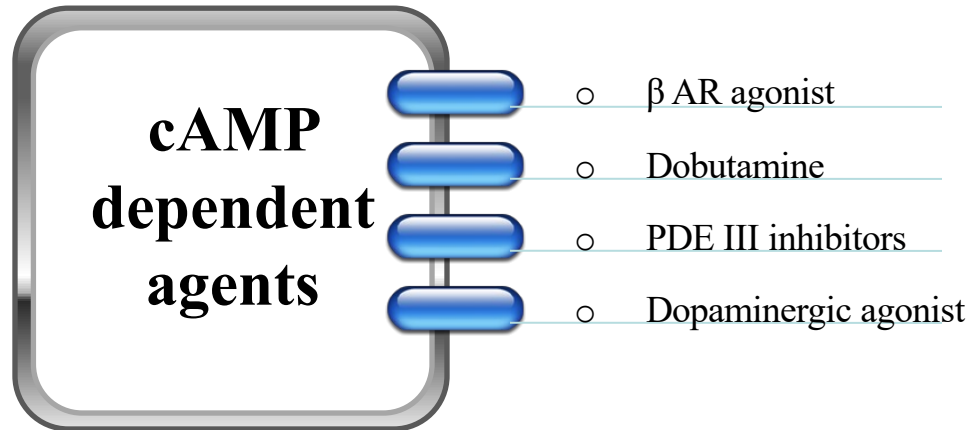
# Cardiovascular Active Medications

## Mechanisms of action of Inotropes



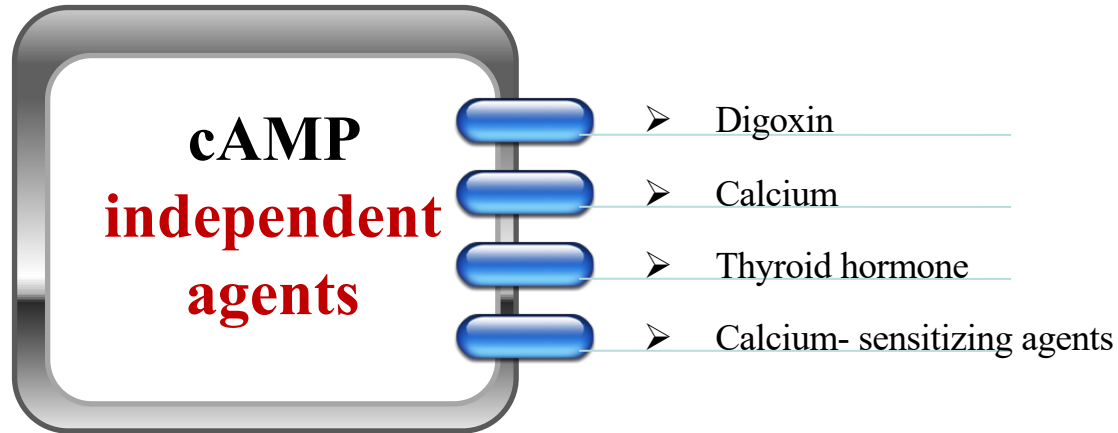
# Cardiovascular Active Medications

## The positive inotropic agents classification



# Cardiovascular Active Medications

## The positive inotropic agents classification



# Cardiovascular Active Medications

## cAMP –dependent agents

### Isoproterenol



- Pure Beta agonist.
- Increase contractility but ↓ SVR and diastolic BP
- So O<sub>2</sub> Demand ↑ while O<sub>2</sub> supply ↓ ( poor inotropic choice)
- Can ↓ the PVR in some patients with Pulm HT.

# Cardiovascular Active Medications

## Isoproterenol (Isuprel) uses



- In severe bradycardia when atropine not work
- In cases with third-degree heart block till PM can be placed
- Due to the  $\beta_2$  effect ,  $\downarrow$  PVR, used in some cases of mitral disease
- 0.2 mg /ml ampule @ 1-20  $\mu$ / min titrated to heart rate

# Cardiovascular Active Medications

## cAMP –dependent agents

### Dobutamine

- Relatively selective  $\beta$  agonist
- $\uparrow$  CO by increasing myocardial contractility
- Slightly  $\downarrow$  SVR and Slightly  $\uparrow$  HR
- Improve Cor BF, a good choice of inotrope in CHF & IHD
- Dose between 2 – 20  $\mu$ /kg/min



# Cardiovascular Active Medications

## cAMP –dependent agents

### PDE III inhibitors

- ↓ cyclic AMP degradation
- ↑ cyclic AMP concentration → enhanced  $\text{Ca}^{+2}$  influx into the cell
  
- Rise in cell  $\text{Ca}^{+2}$  → ↑ contractility
- Systemic arterial & venous dilation via inhibition of peripheral PD.



# Cardiovascular Active Medications

## PDE III inhibitors

### ENOXIMONE (Perfan)

- IV loading dose of 0.5 mg/kg
- IV continuous infusion of 5  $\mu$ g/kg/min
- $\uparrow$  in cardiac index may be delayed for 1 hour
- An IV loading bolus of more than 0.5 mg/kg may not provide much more hemodynamic benefit.



# Cardiovascular Active Medications

## PDE III inhibitors

### MILIRINONE (Corotrope)

- Loading dose: 50  $\mu\text{g}/\text{kg}$  (over  $\geq 10$  min)
- Maintenance infusion of 0.5  $\mu\text{g}/\text{kg}/\text{min}$
- Elimination half life: 50-60 min
- Achieves therapeutic plasma concentrations of  $> 100$  ng/ml



# Cardiovascular Active Medications

## PDE III inhibitors

### Milrinone in Renal Failure

Creatinine clearance	Infusion Rate
50 mL/min	0,43 $\mu\text{g/kg/min}$
40 mL/min	0,38 $\mu\text{g/kg/min}$
30 mL/min	0,33 $\mu\text{g/kg/min}$
20 mL/min	0,28 $\mu\text{g/kg/min}$
10 mL/min	0,23 $\mu\text{g/kg/min}$
5 mL/min	0,20 $\mu\text{g/kg/min}$



# Cardiovascular Active Medications

## PDE III inhibitors

### Side effects

- Excessive ↓ in BP
- Thrombocytopenia
- Dysrhythmias

# Cardiovascular Active Medications

**cAMP –dependent agents**

**Dopaminergic drugs**

Dopamine (Dynatra) in low and intermediate doses

# Cardiovascular Active Medications

## *cAMP –independent agents*

### Digoxin

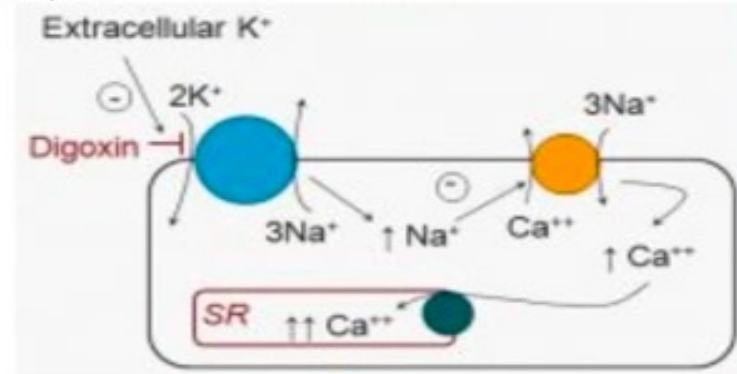
- Cardiac Glycoside, Antiarrhythmic Agent Class IV
- ECG 6 h after each dose
- Rx of congestive heart failure
- Regulates ventricular rate in tachyarrhythmia such as AF, Aflutter and SVT

# Cardiovascular Active Medications

## Digoxin

### Mechanism of action

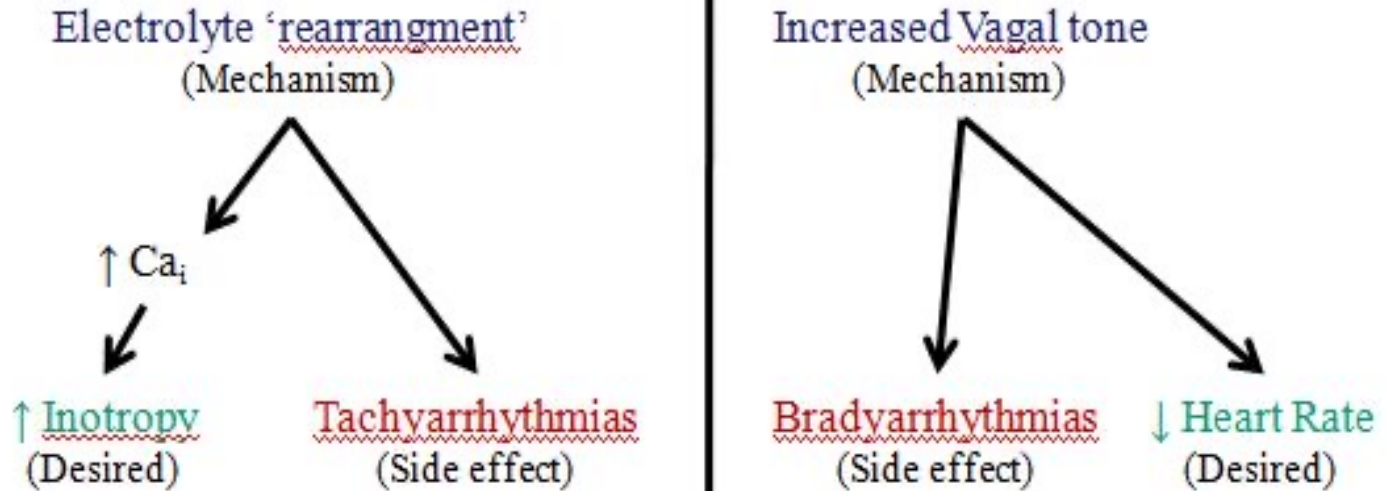
- Reversibly inhibits the Na-K-ATPase pump in myocytes
  - Reduces transport of Na from intracellular to extracellular space
  - Increased Intracellular sodium  
→ inhibits Na-Ca exchange  
→ **increased intracellular Ca**
- Causes **increased contractility** and improved LV systolic function
  - **Excessive intracellular calcium**  
→ **premature contractions** and trigger arrhythmias
- Also **increases vagal tone**
  - Slows firing of the SA node
  - Prolongs conduction of the AV node



# Cardiovascular Active Medications

## Digoxin

### Digoxin mechanisms of action





# Cardiovascular Active Medications

## Digoxin side effects

- VES bigemine or trigemenie, bradycardia or irregular HR
- Bloody or black, terry stool
- Blurred vision or yellow vision
- Confusion, hallucination, feeling weak , headache & dizziness

# Cardiovascular Active Medications

## Digoxin

### Total digitalizing dose TDD:

- Adult TDD 8-12  $\mu\text{g}/\text{kg}$  IV or IM.
- Infant TDD 20-30  $\mu\text{g}/\text{kg}$  IV or IM.
  
- Give 1/2 of the (TDD) in the initial dose.
- Give 1/4 of the TDD in each of 2 subsequent doses at 6-8h.
  
- Caution when used with B-blockers or Ca-blockers

# Cardiovascular Active Medications

## *cAMP –independent agents*

### CALCIUM

- $\text{Ca}^{+2} < 0.5$  mmoles/L cause depression of ventricular function
- Leading to low cardiac output and hypotension

### RATIONALE

- To overcome the effects of cardioplegia
- weaning from cardiopulmonary bypass
- Massive transfusion
- Intraoperative citrate loading in the presence of poor or absent (during the anhepatic phase) liver function



# Cardiovascular Active Medications

## CALCIUM

- Vasoconstrictor response when normal serum  $\text{Ca}^{+2}$  is present.
- May worsen residual myocardial ischemia.
- May produce coronary artery spasm.
- May induce pulmonary hypertension.



# Cardiovascular Active Medications

## CALCIUM

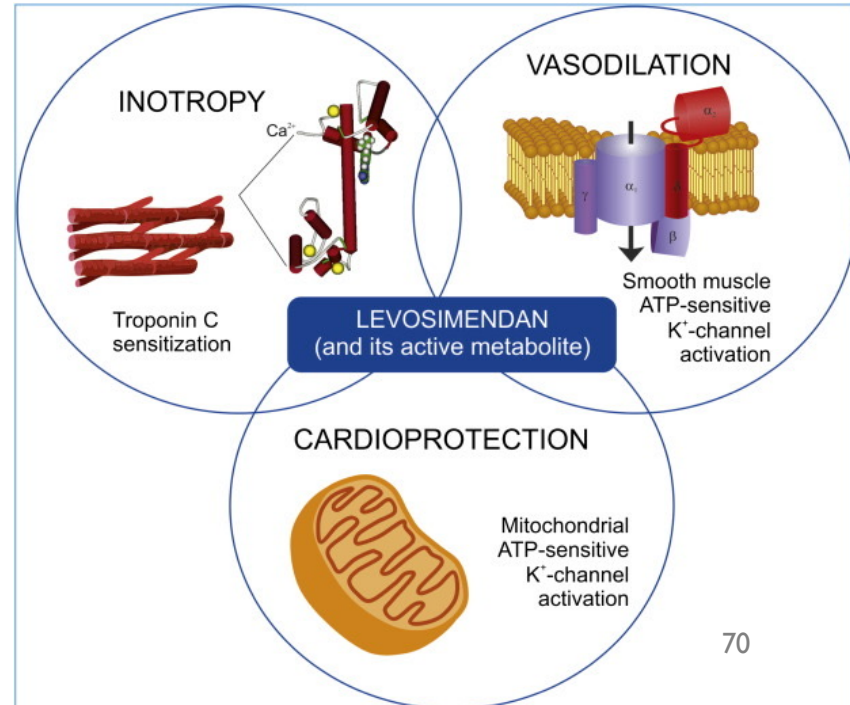
- Adverse effect on diastolic relaxation
- Doses in children 25 mg/kg slow IV
- Adult 500 mg tot 1 g calcium slow IV over 10-20 min



# Cardiovascular Active Medications

## *cAMP –independent agents*

### Calcium- sensitizing agents (Levosimendan )



# Cardiovascular Active Medications

## *cAMP –independent agents*

### Levosimendan

- It has a selective phosphodiesterase (PDE)-III inhibitory action
- loading dose: 6-24mcg/kg over 10 min
- infusion for 24 hours of 0.05-0.2mcg/kg/min



# Cardiovascular Active Medications

## *cAMP –independent agents*

Levosimendan Mechanism	Physiologic Effect	Potential Benefits for Cardiac Surgery Patients
Calcium Sensitizer	Oxygen Sparing Increase in Cardiac Output <sup>(1,2)</sup>	Oxygen Efficient Increase in Post-Op Cardiac Reserve/Output
K-ATP Channel Activator- Mitochondria	Protects Cardiac Cells During Ischemia <sup>(3,4)</sup>	Reduced Peri-Op Myocardial Infarction
K-ATP Channel Activator- Vascular Smooth Muscles Cells	Improved microcirculatory blood flow <sup>(5,6)</sup>	Improved Post Op Organ Perfusion

**Improved  
Outcomes**



1. De Hert et al., 2007; 2. Eriksson et al., 2009; 3. Zangrillo et al., 2009;  
4. Tritapepe et al., 2009; 5. Bragadottir et al., 2013; 6. Baysal et al, 2014



# Cardiovascular Active Medications

## Levosimendan: INDICATIONS

- Acute heart failure
- Sepsis ?
- post resuscitation myocardial dysfunction
- perioperative optimization of cardiac patients with cardiomyopathy



# Cardiovascular Active Medications

## Levosimendan: ADVERSE EFFECTS

- hypotension
- headache
- Nausea and Vomiting
- Dysrhythmias



# Cardiovascular Active Medications

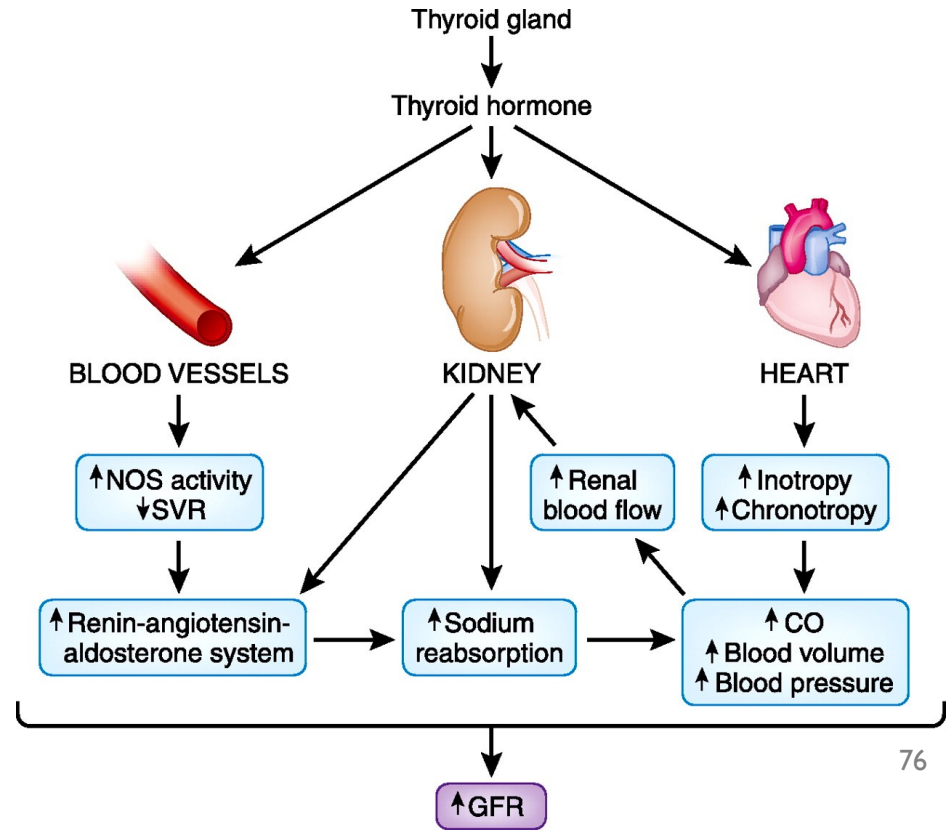
- **Levosimendan:** PHARMACOKINETICS
- Absorption – IV or PO
- Distribution – highly protein bound, peak concentrations reached after 2 days of treatment
- Metabolism – hepatic, active metabolite with  $t_{1/2}$  of 70 hours
- Elimination – dose adjust in renal insufficiency, eliminated in urine and faeces.



# Cardiovascular Active Medications

## Other +v inotropic

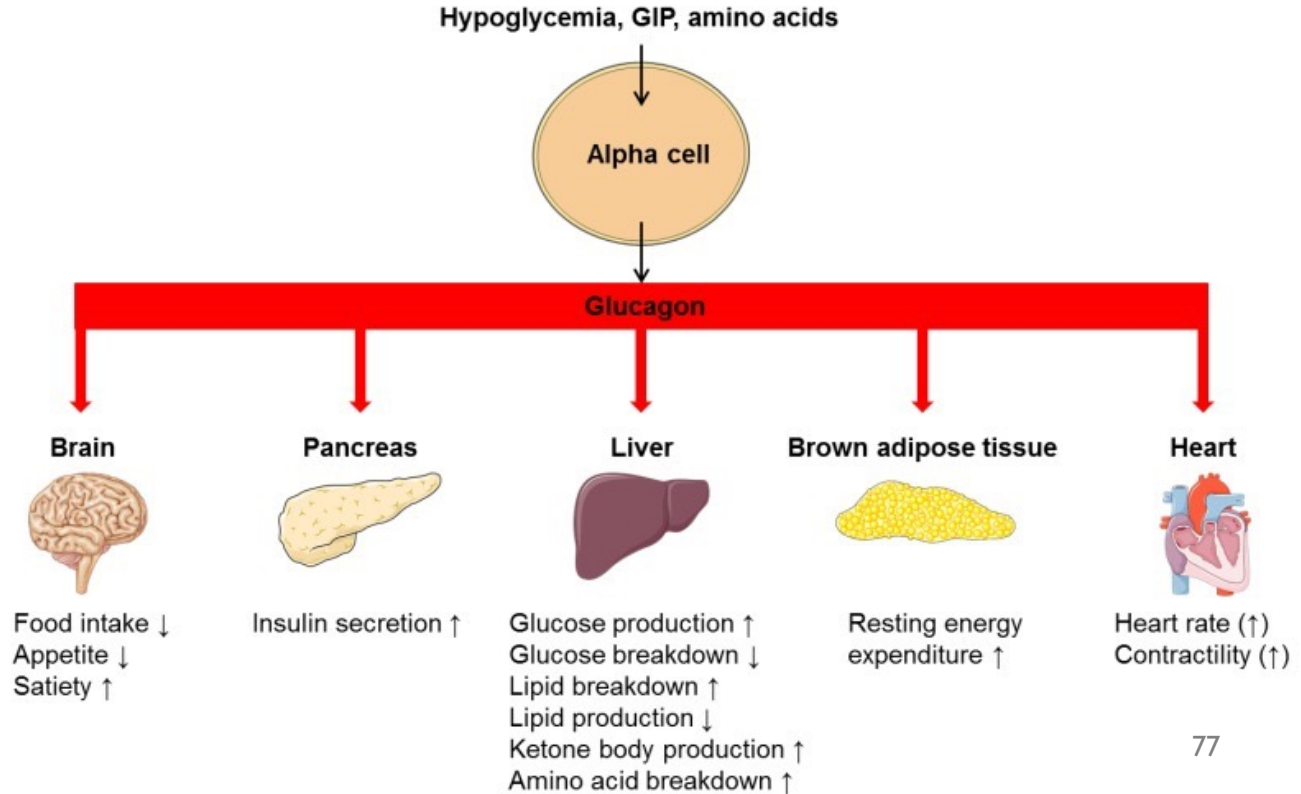
- Thyroid Hormone T3



# Cardiovascular Active Medications

Other +v inotropic

- Glucagon

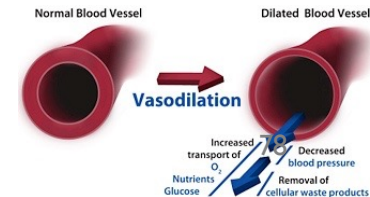


# Cardiovascular Active Medications

## Vasodilators

Classified by site of action

- ↓ SVR (arterial) like  $\text{Ca}^{+2}$  channel blocker
- ↓ both arterial and venous resistance like ACE inhibitors, nitroprusside, Angiotensin II receptor blockers etc.
- Venodilator: ↓ preload like Nitroglycerine relaxes venous smooth muscle with little effect on arteries

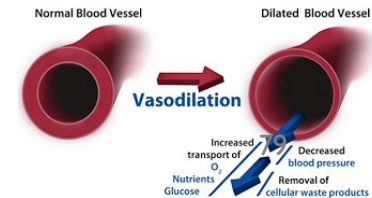


# Cardiovascular Active Medications

## Vasodilators

### Indication

- Hypertension
- Controlled hypotension anesthesia like nitroglycerine
- Myocardial ischemia like ACE inhibitor
- Pulmonary hypertension like Inhaled NO
- In cases of CHF and valvular regurgitation
- In nonrestrictive intra-cardiac shunt as in VSD

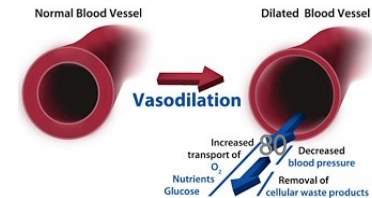


# Cardiovascular Active Medications

## Vasodilators

### Isosorbide dinitrate (cedocard)

- A venodilator, lesser effect on arterioles.
- Relaxation of the cor. A. → improving myoc. regional BF & myoc. O<sub>2</sub> demand.
- Dose 0.1-7 μ/kg/min
- Half-life is 1-3 min





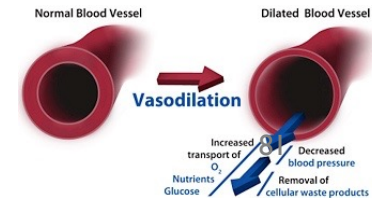
# Cardiovascular Active Medications

## Vasodilators

### Isosorbide dinitrate (cedocard)

### Effect on coronary circulation

- Coronary artery and arteriolar dilation (high dose)
- Spasm reversal or prevention
- Stenosis dilation
- ↑ collateral flow
- Improvement of regional subendocardial ischemia



# Cardiovascular Active Medications

## Vasodilators

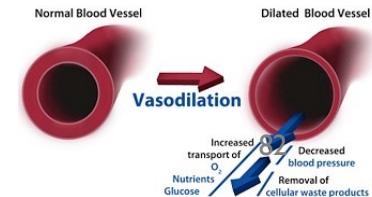
Isosorbide dinitrate (cedocard)

### Disadvantages

- ↓ BP may → ↓ CPP
- Reflex tachycardia & ↑ myoc contraction (dose related)
- Methemoglobinemia in high doses
- May increase ICP
- Inhibit HPV (monitor PO<sub>2</sub>)
- Tolerance in chronic use

$$CPP = DP - PCWP$$

CPP = Coronary Perfusion Pressure (mmHg)  
 DBP = Diastolic Blood Pressure (mmHg)  
 PCWP = Pulmonary Capillary Wedge Pressure (mmHg)  
 \*\*PCWP is also referred to as PAoP (Pulmonary artery occlusive pressure).

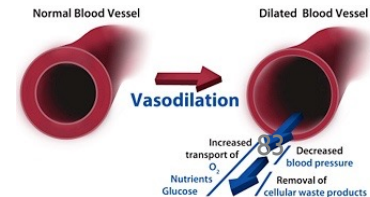


# Cardiovascular Active Medications

## Vasodilators

### Inhaled Nitric Oxide iNO

- Selective Pulmonary vasodilator
- ↓ intrapulmonary shunt and improves V/Q matching
- Rapidly inactivated by Hb in pulmonary capillaries, less or no systemic side effects (e.g. hypotension)
- Withdrawal may lead to Pulm. Htn.

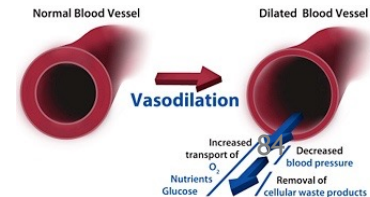


# Cardiovascular Active Medications

## Vasodilators

### Inhaled Nitric Oxide

- Potential for use in ARDS and Pulm. Htn.
- Methemoglobinemia (metHb >1%) can occur
- Special monitoring equipment required & Expensive
- Dose: 0.5-60 ppm in inhaled gas



# Cardiovascular Active Medications

## Vasodilators

### Urapidil (Ebrantil)

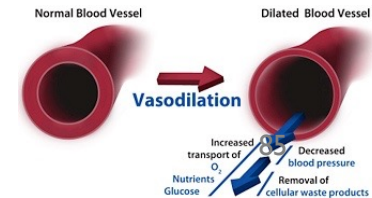
- Central sympathetic and peripheral  $\alpha_1$  antagonist & serotonin agonist.
- Cause reduction in syst. as well as diast. BP

### Indication

Hypertensive crises

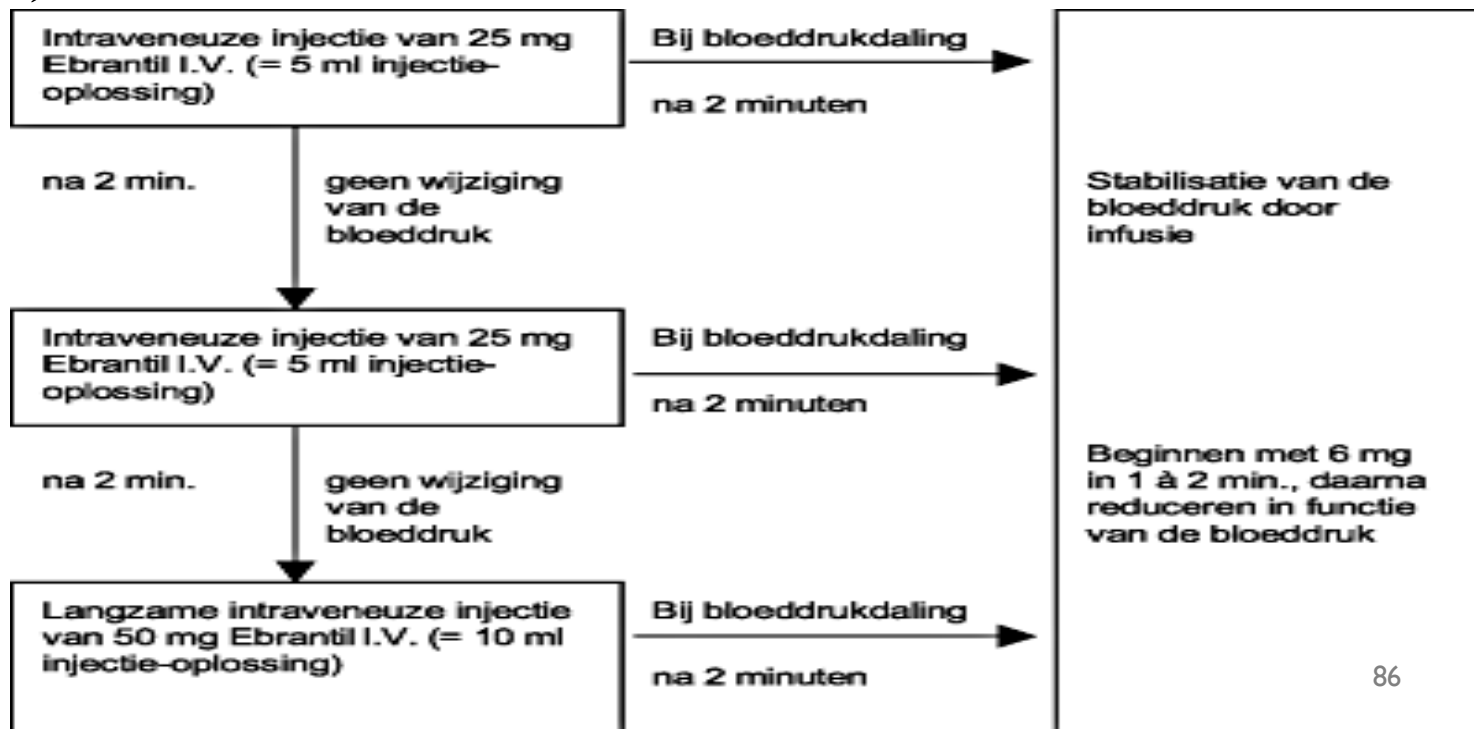
Malignant & therapy resistance Htn

Controlled hypotension anesthesia



# Cardiovascular Active Medications

## Urapidil (Ebrantil)



# Cardiovascular Active Medications

## Vasodilators

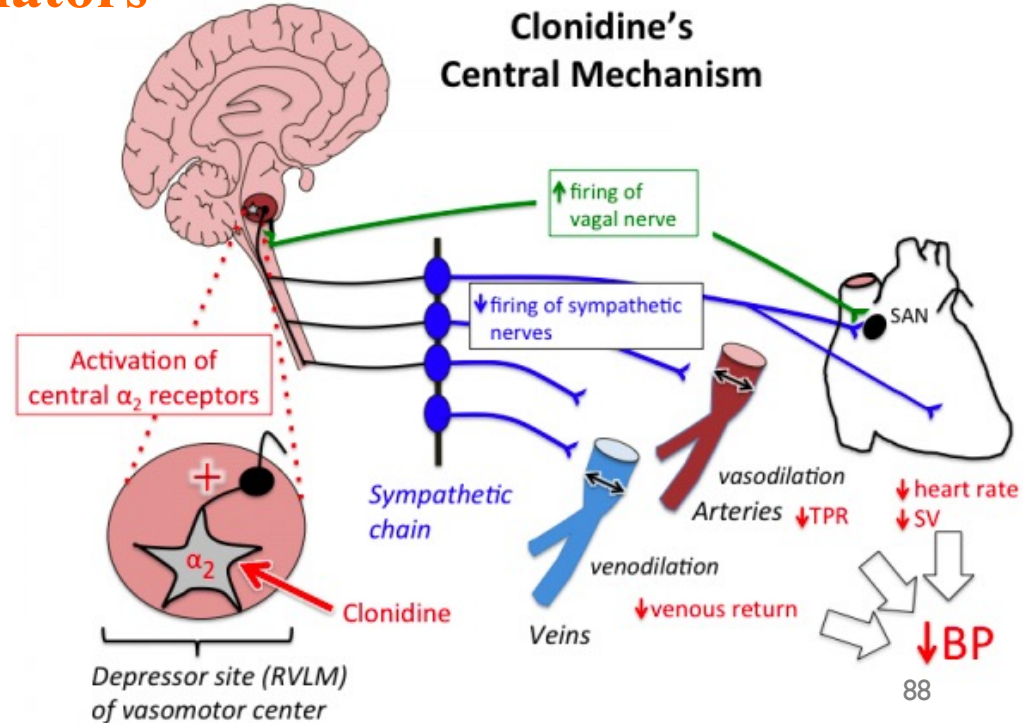
### Clonidine (Catapressan)

- Central  $\alpha_2$  agonists & ↓ NE release
- Has local anesthetic effects (prolong action of LA)
- Reduce sympathetic coronary artery tone
- Sedative effect

# Cardiovascular Active Medications

## Vasodilators

### Clonidine (Catapressan)





# Cardiovascular Active Medications

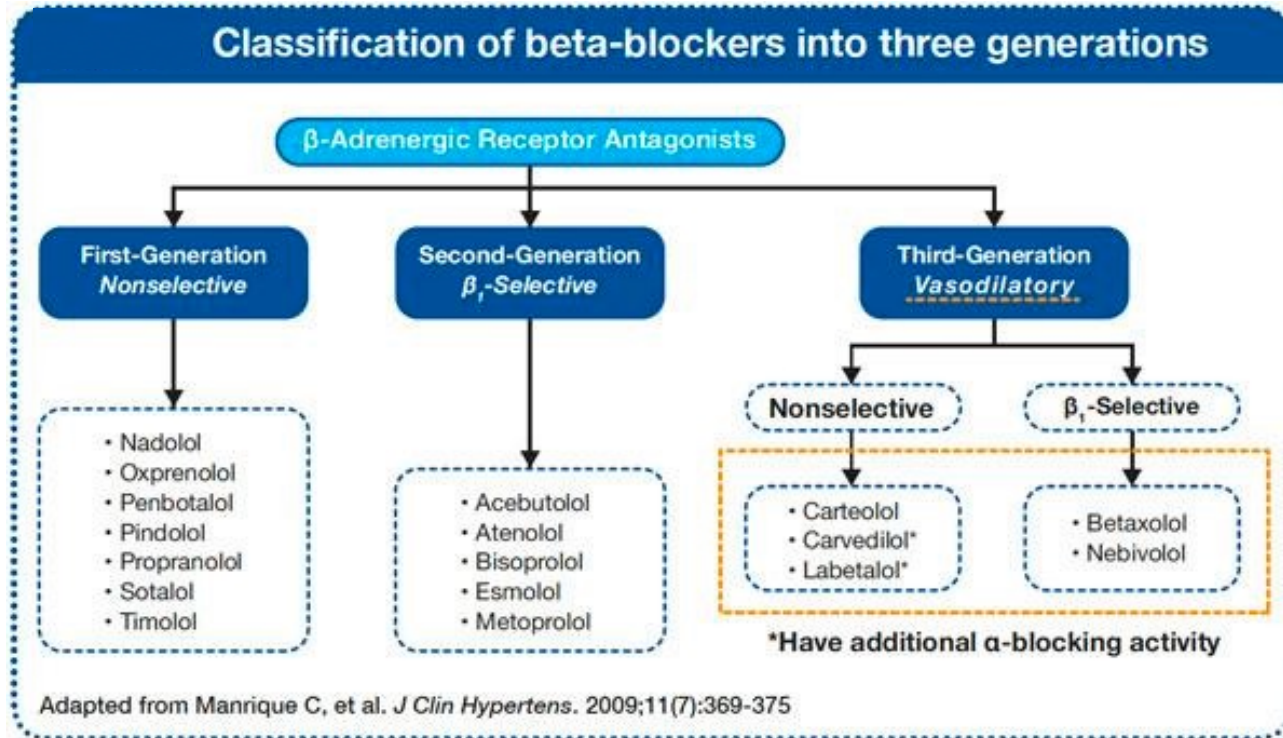
## Antihypertensive medications

### Beta blockers

- Also known as  $\beta$ -adrenergic blocking agents.
- They block norepinephrine and epinephrine from binding to beta receptors on nerves.
- They reduce heart rate, reduce Bp & may constrict the airways.

# Cardiovascular Active Medications

## Antihypertensive medications



# Cardiovascular Active Medications

## Antihypertensive medications

### Beta blockers

- Non-selective beta blockers: e.g. propranolol (Inderal), block  $\beta_1$  and  $\beta_2$  receptors  $\rightarrow$  heart, blood vessels, & airways.
- Selective beta blockers: e.g. metoprolol (seloken), block  $\beta_1$  receptors  $\rightarrow$  heart and do not affect air passages.
- Labetalol (Trandate) block  $\beta$  and  $\alpha$ -1 receptors.

# Cardiovascular Active Medications

## Antihypertensive medications

### Beta blockers

### BETA BLOCKER ACTIONS

$\beta_1$

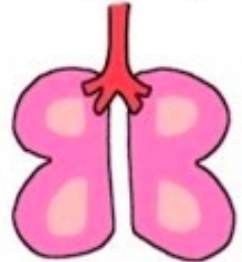
Blockers Affect  
(1 = Heart)



The Heart

$\beta_2$

Blockers Affect  
(2 = Lungs)



The Lungs

# Cardiovascular Active Medications

## Antihypertensive medications

### Metoprolol (Seloken)

- Selective  $\beta_1$  blockers
- Arterial hypertension & Angina pectoris
- Cardiac arrhythmias like SVT, AF& VES
- OPCAB surgery

# Cardiovascular Active Medications

## Antihypertensive medications

### Metoprolol (Seloken)

- Maintenance Rx after MI (when no ventricular failure)
- Symptomatic Rx of hyperthyroidism
- Prophylactic Rx of migraine
- 5 mg iv titration & can be repeated after 2 min
- Half doses in patient with liver failure.

# Cardiovascular Active Medications

## Antihypertensive medications

### Labetalol (Trandate)

- Selective  $\alpha_1$  and nonselective  $\beta$ -adrenergic blocker
- Mild, moderate or severe arterial hypertension
- Pregnancy hypertension
- Angina pectoris with hypertension

# Cardiovascular Active Medications

## Antihypertensive medications

### Labetalol (Trandate)

- Pheochromocytoma
- Not recommended in children
- Bolus IV 20-50 mg , can be repeated after 5 min
- Infusion 2 mg/min
- Effect may stay for 6 -18 hour



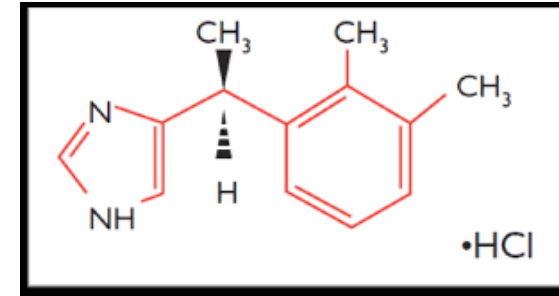
<b><u>Drug name</u></b>	<b><u>Heart rate</u></b>	<b><u>Contractility</u></b>	<b><u>CO</u></b>	<b><u>BP</u></b>	<b><u>SVR</u></b>
<b><u>Phenylephrine</u></b>	↓	No effect	No change or ↓	↑	↑
<b><u>Ephedrine</u></b>	Slightly ↑	↑	↑	↑	Slightly ↑
<b><u>Norepinephrine</u></b>	Variable	↑	↑ or ↓	↑	markedly ↑
<b><u>Epinephrine</u></b>	↑	↑	↑ may ↓ in high doses	↑	↑ may ↓ in very low doses
<b><u>vasopressin</u></b>	No change or slightly ↓	No effect	No change or ↓	↑	↑
<b><u>dobutamine</u></b>	↑ or no change	↑	↑	Usually ↑ or unchanged	Usually ↓, slightly ↑ in B blocker patient
<b><u>dopamine</u></b>	↑	↑	↑ may ↓ in high doses	↑	↓, ↑ in high doses
<b><u>isoproterenol</u></b>	↑	↑	↑	variable	↓
<b><u>Milrinone</u></b>	Usually no change	↑	↑	variable	↓

# Cardiovascular Active Medications

Sympathomimetic agents

## Dexmedetomidine

- Received FDA approval for sedation in 1999.
- Selective  $\alpha_2$ -adrenergic agonist.
- Resembles clonidine.
- Has sedative and analgesic properties



# Cardiovascular Active Medications

## Sympathomimetic agents

### Dexmedetomidine

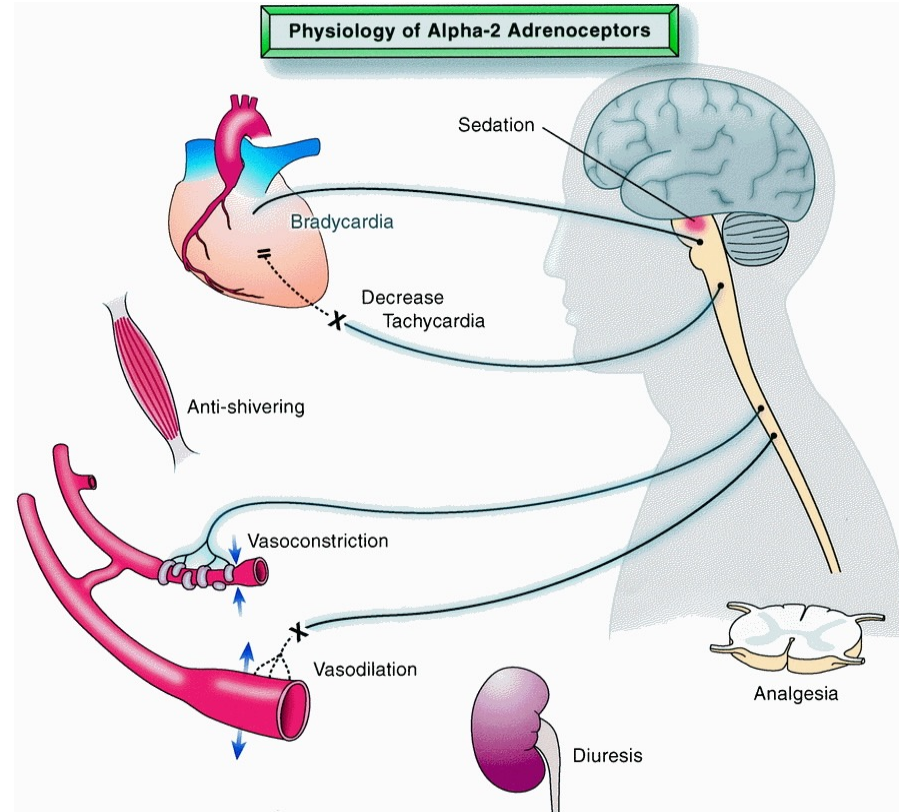
- Selectivity:  $\alpha_2:\alpha_1$  1620:1.
- $t_{1/2}$  elimination = 2 hours.
- 94% protein bound.
- Distribution  $t_{1/2}$  = 6 minutes.
- Context-sensitive  $t_{1/2}$  : 4 minutes for 10-minute infusion,
- Context-sensitive  $t_{1/2}$  : 250 minutes for > 8-hour infusion



# Cardiovascular Active Medications

Sympathomimetic agents

Dexmedetomidine

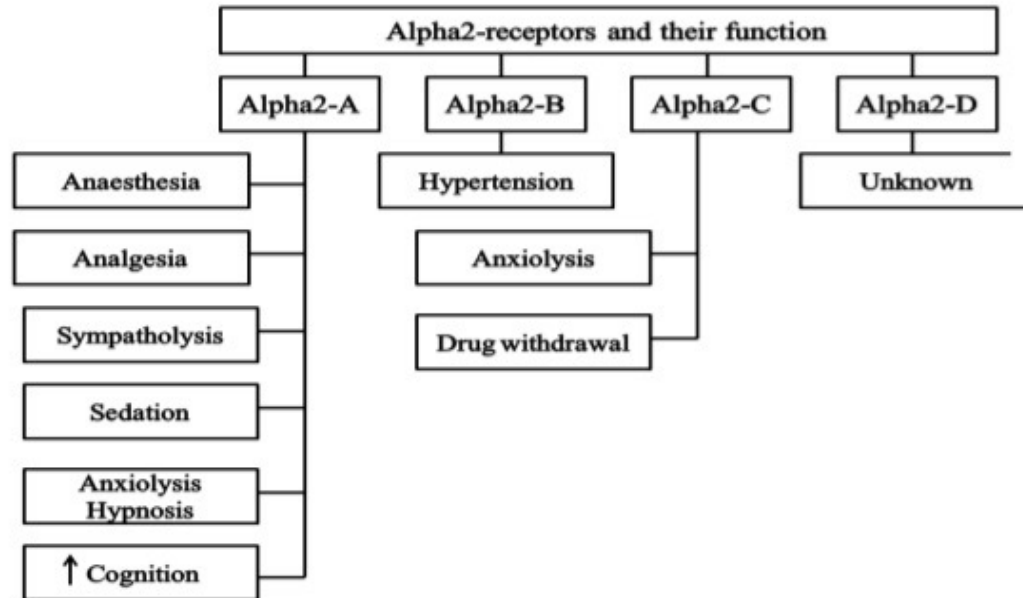
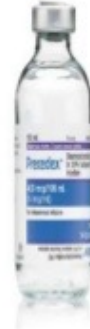


# Cardiovascular Active Medications

Sympathomimetic agents

Dexmedetomidine

## Dexmedetomidine

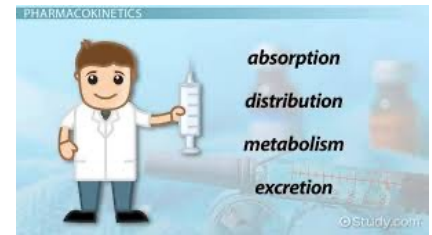


# Cardiovascular Active Medication

Sympathomimetic agents

**Dexmedetomidine**

- Metabolism & elimination → liver and kidney.
- Nearly 100% biotransformation.
- Metabolites all inactive → elimination via urine (95%).
- Significant increase in half-life with **liver failure**.
- No significant effect of renal insufficiency.



# Cardiovascular Active Medication

Sympathomimetic agents

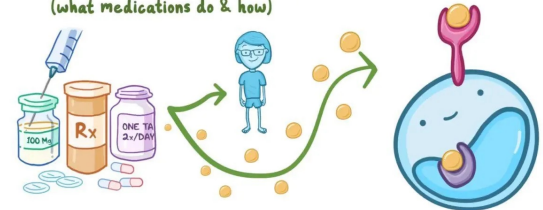
Dexmedetomidine

- Induces dose-dependent effects.
- No adverse influence on blood pressure and rarely causes apnea.
- Disrupts respiratory responses to hypoxia and hypercapnia



## PHARMACODYNAMICS

MECHANISMS & EFFECTS of MEDICATIONS  
(what medications do & how)



# Cardiovascular Active Medication

Sympathomimetic agents

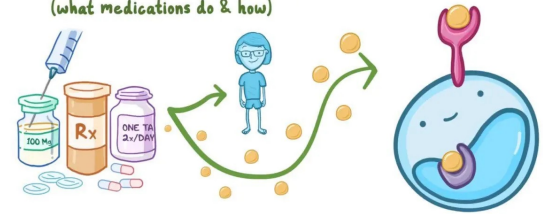
## Dexmedetomidine

- ↓ Cerebral Blood Flow (CBF).
- ↓ Brain metabolism and oxygen consumption.
- Improved cognitive performance.
- Can reduce postoperative shivering

**Neuroprotective**



### PHARMACODYNAMICS MECHANISMS & EFFECTS of MEDICATIONS (what medications do & how)



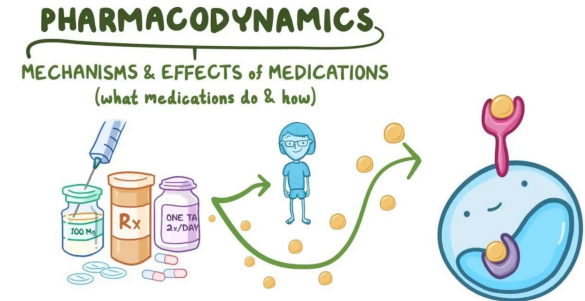


# Cardiovascular Active Medication

Sympathomimetic agents

## Dexmedetomidine

- Bifasic effect on Cardiovascular System (CVS).
  - Hypertension.
  - Hypotension.
  
- Bradycardia

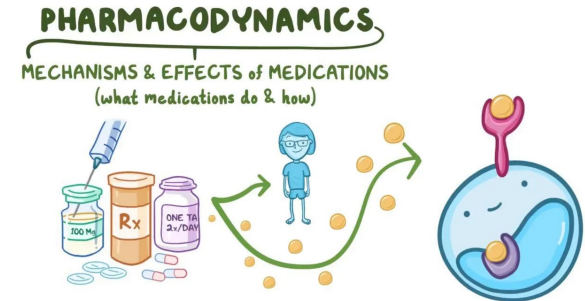


# Cardiovascular Active Medication

Sympathomimetic agents

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# Cardiovascular Active Medication

Sympathomimetic agents

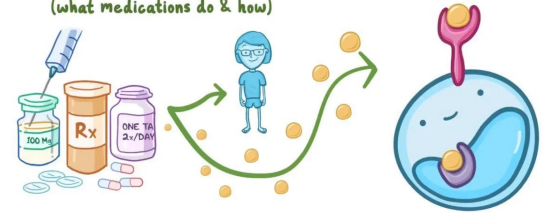
Dexmedetomidine

## Endocrinologie

- Reduced release of catecholamines.
- Reduced release of insulin.
- No inhibition of steroidogenesis.



**PHARMACODYNAMICS**  
MECHANISMS & EFFECTS OF MEDICATIONS  
(what medications do & how)



# Cardiovascular Active Medication

Sympathomimetic agents

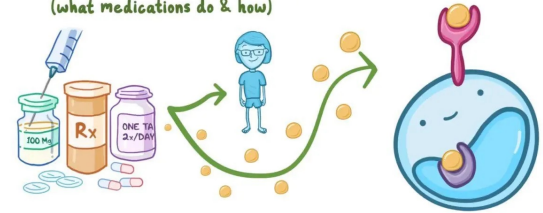
Dexmedetomidine

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**PHARMACODYNAMICS**  
MECHANISMS & EFFECTS OF MEDICATIONS  
(what medications do & how)



# Cardiovascular Active Medication

Sympathomimetic agents

Dexmedetomidine

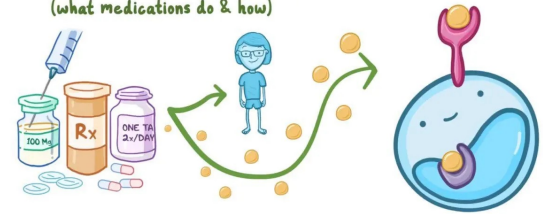
Endocrinologie

Renal

- Diuresis.
- ↑ Glomerular Filtration Rate (GFR).
- Inhibition of renin release.



**PHARMACODYNAMICS**  
MECHANISMS & EFFECTS OF MEDICATIONS  
(what medications do & how)



# Cardiovascular Active Medication

Sympathomimetic agents

Dexmedetomidine

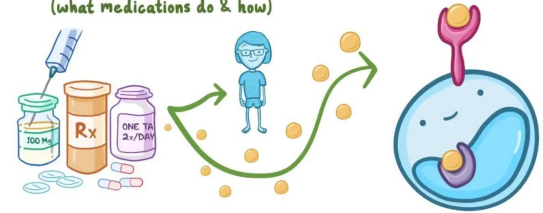
Gastrointestinal

- ↓ Salivary flow.

- ↓ Gastrointestinal (GI) motility



**PHARMACODYNAMICS**  
MECHANISMS & EFFECTS of MEDICATIONS  
(what medications do & how)



## Cardiovascular Active Medications

Sympathomimetic agents

**Dexmedetomidine**

**Gastrointestinal**

- ↓ **Salivary flow.**
- ↓ **Gastrointestinal (GI) motility**



## Cardiovascular Active Medications

Sympathomimetic agents

Dexmedetomidine

Avoid

- Low blood pressure.
- Hypovolemic shock.
- Conduction disorders.





## Cardiovascular Active Medications

Sympathomimetic agents

Dexmedetomidine

**DOSIS.**

- Bolus of 0.5-1.0  $\mu\text{g}/\text{kg}$ , slowly over several minutes.
- Effect seen in 5-10 minutes, diminished within 30-60 minutes
- 0.2-0.7  $\mu\text{g}/\text{kg}/\text{hour}$  infusion.
- Dose adjustment in the elderly, liver failure, or in combination with other sedatives

# Cardiovascular Active Medications

## References

- Hensley F, Martin D. A practical approach to cardiac anesthesia. 2008.
- Paul G. Barash. Clinical Anesthesia, 6th edition.
- G Edward Morgan. Clinical Anesthesiology 2nd edition.