**POSITIVE INOTROPIC AGENTS**

Positively inotropic agents increase the strength of contraction of heart muscle (myocardial contractility). Drugs of this group include:

- **Cardioactive inotropes** (digoxin, digitoxin);
- **Phosphodiesterase inhibitors** (amrinone, milrinone);
- **Beta-adrenergic agonists** (dobutamine).

**BETA-ADRENERGIC AGONISTS**

**DIGOXIN**

**PHOSPHODIESTERASE III INHIBITORS**
• The Frank–Starling law of the heart states that the stroke volume of the heart increases in response to an increase in the volume of blood filling the heart (the end-diastolic volume) when all other factors remain constant.

• The Frank–Starling mechanism appears to make its greatest contribution to increasing stroke volume at lower work rates, and contractility has its greatest influence at higher work rates.
DIGITALIS (Foxglove)

This name indicates a group of pharmacologically active compounds (mainly *digitoxin* and *digoxin*) extracted mostly from the leaves of *Digitalis Lanata* or *Digitalis Purpurea*.

Both molecules include a lactone and a triple-repeating sugar called a glycoside. **Digitoxin** and **digoxin** differ in that digoxin has an additional hydroxyl group at the C-3 position on the B-ring (adjacent to the pentane).
NA$^+/K^+$ATPase Pump is the target of cardiac glycosides

- The Na$^+/K^+$-ATPase is composed of 2 subunits (α and β). The **α-subunit** binds ATP and both Na$^+$ and K$^+$ ions and contains the regulatory phosphorylation site. The smaller **β-subunit** is critical in facilitating the plasma membrane localization and activation of the α-subunit.

- Of the 4 α-subunit genes and 3 β-subunit genes, the **α$_1$ isoform** is the predominant and is ubiquitously expressed.

- The **α$_2$ isoform** is primarily expressed in muscle tissues (skeletal, smooth, and cardiac) as well as in adipose tissue, brain, and lung.

- The **α$_3$ isoform** is expressed primarily in the heart and neurons.

- The **α$_4$ isoform** is only expressed in the testes.

- The **β$_1$ isoform** is ubiquitously expressed and is associated with the α$_1$ subunit in the ubiquitously expressed α$_1$β$_1$ Na$^+,K^+$-ATPase complex.

- The **β$_2$ isoform** is predominantly expressed in neurons and heart cells.

- The **β$_3$ isoform** is expressed in testes but has also been detected in early developing neurons.
CARDIAC GLYCOSIDES – MECHANISM OF ACTION

CARDIAC GLYCOSIDES ACT BY BLOCKING THE NA⁺/K⁺ ATPase PUMP

1. Inhibiting Na/K-ATPase results in an *increased intracellular concentration of Na* ions and thus a decreased concentration gradient across the cell membrane.

2. This increased intracellular Na concentration *reverses potential of the Na/Ca exchanger*, that pumps Na out of the cell in exchange for pumping Ca in.

3. This leads to an *increase in cytoplasmic Ca concentration*, which improves cardiac contractility.
In addition to positive inotropic effects, cardiac glycosides display negative chronotropic and dromotropic effects.

Heart rate reduction by cardiac glycosides is due, in part, to vago-mimetic effects (early, low doses) and in part to extra-vagal effects (not influenced by atropine).
CARDIAC ACTION POTENTIAL (UPPER) AND EGC TRACE (LOWER) MODIFICATIONS UNDER DIGITALIS.

INHIBITION OF NA/K ATPase RESULTS IN

- higher availability of intracellular calcium for actine/myosine linking (inotropic effect), WITH INCREASED MYOCARDIAL CONTRACTION

- perturbation of bioelectrical properties of the cell membrane potential. This latter effect facilitates basal depolarization, thus predisposing to:

- A MORE POSITIVE POTENTIAL (LESS RPID SLOPE IN THE RISING ACTION POTENTIAL)

- A HIGHER SPEED IN REPOLARIZING PROCESSES (INCREASED K⁺ CONDUCTANCE)
## PRINCIPAL PK FEATURES OF DIGOXIN VS DIGITOXIN

**DIGITOXIN has high lipophilicity;**
Well absorbed on OS administration; high PP binding; long half-life; significant liver re-entry. Inducer of liver enzymes

**DIGOXIN is more hydrophilic;**
Administered by OS or IV; medium PP binding; shorter half-life; kidney elimination

CAUTION: CONDITIONS IMPAIRING LIVER FUNCTION

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<table>
<thead>
<tr>
<th></th>
<th>DIGITOXIN</th>
<th>DIGOXIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABSORBANCE</strong></td>
<td>Intestinal 90-100%</td>
<td>Intestinal 70-80%</td>
</tr>
<tr>
<td><strong>PLASMA PROTEIN BINDING</strong></td>
<td>86-94%</td>
<td>25-30%</td>
</tr>
<tr>
<td><strong>METABOLISM</strong></td>
<td>HIGH HEPATIC</td>
<td>LOW HEPATIC</td>
</tr>
<tr>
<td><strong>ELIMINATION</strong></td>
<td>BILE DUCTS</td>
<td>RENAL</td>
</tr>
<tr>
<td><strong>HALF-LIFE ($t_{1/2}$)</strong></td>
<td>5-7 gg</td>
<td>33-36 h</td>
</tr>
<tr>
<td>Clearance (ml/min/Kg)</td>
<td>0.05</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>THERAPEUTIC RANGE</strong></td>
<td>14-16 ng/ml</td>
<td>1-2 ng/ml</td>
</tr>
</tbody>
</table>

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CAUTION: CONDITIONS REDUCING KIDNEY ELIMINATION

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DIGITOXIN has high lipophilicity; Well absorbed on OS administration; high PP binding; long half-life; significant liver re-entry. Inducer of liver enzymes

CAUTION: CONDITIONS IMPAIRING LIVER FUNCTION

DIGOXIN is more hydrophilic; Administered by OS or IV; medium PP binding; shorter half-life; kidney elimination

CAUTION: CONDITIONS REDUCING KIDNEY ELIMINATION
MEDICAL USE FOR CARDIAC GLYCOSIDES

• HEART FAILURE

Historically used to treat CHF, glycosides are still employed despite newer available treatments. When used in conjunction with diuretics and vasodilators, digoxin improves CO and ejection fraction, and reduces filling pressures and pulmonary capillary wedge pressure (this reduces pulmonary congestion and edema); heart rate changes very little.

Although the direct effect of digoxin is vasoconstriction, when given to patients in HF, the systemic vascular resistance falls. This most likely results from the improvement in CO, which leads to withdrawal of compensatory vasoconstrictor mechanisms.

Digitalis compounds have a small direct diuretic effect on the kidneys.
ATRIAL FIBRILLATION and FLUTTER

The mechanism of this beneficial effect of digoxin is its ability to activate vagal efferent nerves to the heart (parasympathomimetic effect). Vagal activation can reduce the conduction of electrical impulses within the atrioventricular node to the point where some of the impulses will be blocked. When this occurs, fewer impulses reach the ventricles and ventricular rate falls.

Digoxin also increases the effective refractory period within the atrioventricular node.
Therapeutic and toxic potentials of cardiac glycosides

When initiating treatment, a special dosing regimen involving "loading doses" is used to rapidly increase digoxin plasma levels. This process is termed "digitalization."

For digoxin, the therapeutic plasma concentration range is 0.5 - 1.5 ng/ml. Plasma concentrations above 2.0 ng/ml can lead to digitalis toxicity, manifested as arrhythmias, some of which may be life-threatening.

If toxicity occurs with digoxin, it may take several days for the plasma concentrations to fall to safe levels because of the long half-life. In case of digoxin toxicity an immune Fab (Digibind) is used to rapidly reduce plasma digoxin levels.

Potassium supplementation can also reverse the toxic effects of digoxin if the toxicity is related to hypokalemia.
**DIGITALIS TOXICITY AND PLASMA POTASSIUM LEVELS**

Both HIGH and LOW potassium levels are involved in toxic effects of cardiac glycosides.

Digoxin causes hyperkalemia (high potassium). The Na/K ATPase pump normally causes sodium to leave cells and potassium to enter cells. Blocking this mechanism results in higher serum potassium levels.

Digoxin toxicity is worsened in states of hypokalemia (low potassium) since digoxin normally binds to the ATPase pump on the same site as potassium. When potassium levels are low, digoxin can more easily bind to the ATPase pump exerting the inhibitory effects.
Digoxin toxicity is a life-threatening condition. The most common symptoms are gastrointestinal and include nausea, vomiting, abdominal pain and diarrhea. The cardiac manifestations are the most concerning and can be fatal. Digoxin toxicity can induce literally every arrhythmia except for rapidly conducted atrial arrhythmias.
• An often described, but rarely seen, visual adverse effect of digoxin is a disturbance of color vision (mostly yellow and green) called xanthopsia. Vincent van Gogh's "Yellow Period" may have somehow been influenced by concurrent digitalis therapy.

• Other oculotoxic effects of digoxin include generalized blurry vision, as well as seeing a "halo" around each point of light. The latter effect can also be seen in van Gogh's Starry Night.

• Evidence of van Gogh's digoxin use is supported by multiple self portraits that include the foxglove plant, from which digoxin is obtained. (e.g. Portrait of Dr. Gachet)
Many commonly used drugs interact with digitalis compounds.

- The Class IA antiarrhythmic, quinidine, competes with digoxin for binding sites and depresses renal clearance of digoxin. These effects increase digoxin levels and can produce toxicity.
- Similar interactions occur with calcium-channel blockers and nonsteroidal anti-inflammatory drugs.
- Other drugs that interact with digitalis compounds are amiodarone (Class III antiarrhythmic) and beta-blockers.
- Diuretics can indirectly interact with digoxin because of their potential for decreasing plasma potassium levels (i.e., producing hypokalemia).

**Hypokalemia** results in increased digoxin binding to the Na⁺/K⁺-ATPase (possibly through increased phosphorylation of the enzyme) and thereby enhances digoxin's therapeutic and toxic effects.

**Hypercalcemia** enhances digitalis-induced increases in intracellular calcium, which can lead to calcium overload and increased susceptibility to digitalis-induced arrhythmias.

**Hypomagnesemia** also sensitizes the heart to digitalis-induced arrhythmias.
Figure 2. Effects of inotropic therapy on intracellular calcium handling in cardiac myocytes.

## CATECHOLAMINES

**Adrenergic activity of some sympathomimetic amines**

<table>
<thead>
<tr>
<th></th>
<th>Alpha Peripheral</th>
<th>Beta&lt;sub&gt;1&lt;/sub&gt; Cardiac</th>
<th>Beta&lt;sub&gt;2&lt;/sub&gt; Peripheral</th>
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<tbody>
<tr>
<td>Norepinephrine</td>
<td>++++</td>
<td>++++</td>
<td>0</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Dopamine*</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>DOBUTAMINE</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Metoxamine</td>
<td>++++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CATECHOLAMINES IN ACUTE HEART FAILURE

Acts on $D_1$, $\beta_1$ and $\alpha_1$. with a progressive dose-dependent engagement. Initial increase in kidney perfusion, then inotropic activity, then increased peripheral resistance. Only IV infusion

DOPAMINE

β₁, β₂ receptor agonist. Inotropic and chronotropic positive effect; increases oxygen demand and cardiac work. General vasodilation, with subsequent compensatory tachycardia. Used in acute HF with high peripheral resistances

ISOPROTERENOL

ADRENALINE

Activates all β₁, β₂ and α₁ receptors, with positive inotropic and chronotropic effects. May induce arrhythmias, increases oxygen demand and cardiac work. May induce anxiety, tremors. Used for cardiac arrest (IV or intracardiac administration). Used for anaphylactic shock due to bronchodilator activity

DOBUTAMINE

Preferential activation of $\beta_1$ receptors. This may translate in efficacious positive inotropism with no renal effects. IV infusion with short half-life (2-3 min)
A phosphodiesterase inhibitor blocks one or more of the subtypes of the enzyme phosphodiesterase (PDE), thereby preventing the inactivation of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by the respective PDE subtype(s).
According to the cell type and function, the PDE isoenzymes may mediate very different biological effects. Of the 11 subtypes of PDE, the PDE III and the PDE V isoforms are among the most important target for drug inhibitors.
PDE V INHIBITORS

Sexual stimulation causes the release of NO from nerves and endothelial cells in the penis. NO activates guanylyl cyclase, which converts GTP into cyclic GMP. In turn, cGMP mediates smooth-muscle relaxation in the penis, resulting in increased blood flow and penis erection. PDE5, which is the major PDE subtype in penile tissue, degrades cGMP. Therefore inhibiting PDE5 allows cGMP to remain active thereby promoting erection.

**SILDENAFIL**

**VARDENAFIL**

**TADALAFIL**
PDE V INHIBITORS

Adverse effects

Retinal PDE6
Color-tinged vision
Blurred vision

Small-vessel PDE5
Flushing
Headache
Epistaxis
Mild decrease in blood pressure

Gastrointestinal tract PDE5
Heartburn

Penile PDE5
Erections and priapism

Muscle PDE5
Muscle aches and backaches

Therapeutic effects

Coronary PDE5
Mild vasodilatation

Induced right ventricular myocardial PDE5
Right ventricular PDE3
↑ Inotropy
Regression of hypertrophy

Induced pulmonary-artery smooth-muscle cell PDE5 (PDE1?)
Vasorelaxation
↓ Proliferation
↑ Apoptosis
PDE III INHIBITORS

Both PDE3A and PDE3B are expressed in vascular smooth muscle cells and are involved in regulation of cardiac and vascular smooth muscle contractility. PDE3 inhibitors have been used for the treatment of heart failure, but present several unwanted arrhythmic side-effects.

In general, PDE3 inhibitors
- antagonize platelet aggregation
- block oocyte maturation
- increase contractility of the heart
- enhance vascular smooth muscle relaxation and airway smooth muscle relaxation
### MAIN PK FEATURES OF PDE III INHIBITORS

<table>
<thead>
<tr>
<th>Feature</th>
<th>AMRINONE</th>
<th>MILRINONE</th>
<th>ENOXIMONE</th>
</tr>
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<tbody>
<tr>
<td>Bioavailability</td>
<td>93% (per OS)</td>
<td>80%</td>
<td>55%</td>
</tr>
<tr>
<td>Plasmatic peak</td>
<td>45 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life ($t_{1/2}$)</td>
<td>2.4-4 hours</td>
<td>0.8 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td>PP binding</td>
<td>35-49%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver (low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney elim</td>
<td>25%</td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td>Vol Distr (l/Kg)</td>
<td>1.3</td>
<td>0.32</td>
<td>1.8</td>
</tr>
<tr>
<td>Conc Plasm</td>
<td>3.7 microg/ml</td>
<td>150-250 ng/ml</td>
<td>18 microg/ml</td>
</tr>
</tbody>
</table>

**SIDE EFFECTS**
- Angina, vomiting.
- Severe thrombocytopenia dose- and time-dependent.

**NOTE**
- Administration **ONLY IV** for short time
- Administration **per OS** on repeated cycles
- Slightly better tolerated
Levosimendan exerts its positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner.

It also has a vasodilatory effect, by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle to cause smooth muscle relaxation.

The combined inotropic and vasodilatory actions result in an increased force of contraction, decreased preload and decreased afterload. Moreover, by opening also the mitochondrial (ATP)-sensitive potassium channels in cardiomyocytes, the drug exerts a cardioprotective effect.