Congestive Heart Failure (CHF)

Heart failure: cardiac output inadequate to provide body demand of oxygen (demand-supply)

Causes:
- myocardial ischemia
- coronary artery disease
- hypertension
- toxic injury by chemicals
- congenital or genetic abnormalities

Compensated heart failure:
- resting cardiac function, OK
- excessive stress or exercise, No

Congestive heart failure (CHF, uncompensated):
- resting cardiac function inadequate
- venous pooling → edema esp. lungs
- shortness of breath (dyspnea)

Blood pressure is well maintained in CHF:

i. ↑ sympathetic tone
   (tachycardia)
ii. ↓ parasympathetic tone
iii. activation of renin-angiotensin system
iv. ↑ blood volume
v. ↑ vasopressin release

Consequences:
- ↓ force of contraction
- ↓ CO, ↑ TPR, ↓ stroke volume
- ↑ venous pressure, ↓ tissue perfusion
- cardiac hypertrophy
- Na⁺ & water retention
- edema (especially lying down)
Heart Physiology

Electrical components:
- Action potential (AP) generation (spontaneous)
- AP conduction (via specialized conductive system)

Excitation - contraction coupling:
- Key role of IC Ca$^{++}$

Figure 16.3
Ion movements during the contraction of cardiac muscle.
**Therapy:**

Non-Drug
- rest
- salt restriction (2.5g/day $\rightarrow$ 1g/day)

Drug:
- Positive inotropic agents: - cardiac glycosides (digoxin, digitoxin)
  - catecholamines (dobutamine)
  - phosphodiesterase inhibitors (amrinone)
- Beta-blockers (caution, metoprolol)
- Diuretics (chlorothiazide)
- Angiotension converting enzyme (ACE) inhibitors (captopril)
- Vasodilators (noninotropic: hydralazine, beta natriuretic peptide)

**Frank-Starling curve:**

*Figure 16.8*

Ventricular function curves in the normal heart, in congestive heart failure (CHF), and in CHF treated with digitalis.
Digitalis Glycosides:

- use decreasing for acute and chronic treatment

**Digoxin, Digitoxin**

Source:  
- white and purple foxglove (Digitalis lanata and D. purpurea)  
- Mediterranean sea onion (Strophantus gratus) - ouabain  
- numerous other plants  
- certain toads

History:  
- ancient Egyptians (3000 years ago) - diuretic effect, tones the heart  
- 1785, clinical effect of the foxglove plant described (Digitalis purpurea)

Chemistry:

steroid nucleus:  
- lipophilic  
- essential for activity, OH is very reactive (synthesis)

unsaturated five-membered lactone ring:

- hydrophilic, essential for activity  
- opening the ring $\rightarrow$ loss of activity  
- saturation $\rightarrow$ loss of activity

series of sugars linked to C 3 of the steroid nucleus  
- non-essential, hydrophilic

*Figure 13–3. Structure of digoxin, a typical cardiac glycoside.*
**Pharmacokinetics:**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Bioavail.%</th>
<th>Bound%</th>
<th>Peak effect</th>
<th>T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>oral, iv</td>
<td>45-85</td>
<td>25</td>
<td>6 hr</td>
<td>35 hr (kidney)</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>oral, iv</td>
<td>&gt;90</td>
<td>90</td>
<td>12 hr</td>
<td>6-7 day (liver)</td>
</tr>
<tr>
<td>Amrinone</td>
<td>oral, iv</td>
<td>93</td>
<td>30</td>
<td>&lt;1 hr</td>
<td>4 hr (kidney, liver)</td>
</tr>
</tbody>
</table>

(Phosphodiesterase inhibitor)

Digoxin:
- absorption by gut bacteria (10% of population resistant, Eubact.lentum)
- unchanged excretion by the kidney BUT is not removed by dialysis
- skeletal muscle major organ reserve
- crosses the placenta

Digitoxin:
- good oral absorption (>90%)
- metabolized by the liver (cardioactive metabolites)
- large interpatient variations (bacterial flora)
- enterohepatic recycling (reabsorbed)

**Mechanism of action:**

Cardiac glycosides (CG): potent, highly selective inhibitors of Na⁺/K⁺ ATPase (Na⁺ pump)

\[
\text{Na⁺/K⁺ ATPase: } \begin{align*}
\text{- membrane bound transporter (3 Na⁺ / 2 K⁺)} \\
\text{- found all over the body, } \alpha/\beta\text{-subunits} \\
\text{- 3 mammalian isoforms} \\
\text{- extracytoplasmic binding site for CG} \\
\text{- phosphorylation of cytoplasmic } \alpha\text{-subunit } \rightarrow \text{stabilize CG binding} \\
\text{- } [K^+]_{EC} \rightarrow \text{dephosphorylates } \alpha\text{-subunit } \rightarrow \text{CG binding (ie. ACEI)} \\
\text{- } [K^+]_{EC} \rightarrow \text{CG intoxication (ie. thiazide diuretics)}
\end{align*}
\]

Inhibition of (Na⁺, K⁺-ATPase)
- exchange Na⁺ - K⁺ (3:2)
- [Na⁺]IC (10 → 10.5 mM)
- Na⁺ - Ca⁺⁺ exchange (3:1)
- [Ca⁺⁺]IC
- SR uptake Ca⁺⁺ (stores)
- contractile force
Therapeutic consequence of CG:

- moderate but persistent positive ionotropic effect, ↑ sensitivity of the baroreceptor reflex

→ ↑ CO → ↓ sympathetic activity
→ ↓ HR and vascular tone
→ ↓ pre- and afterload to heart
→ ↓ heart size
→ ↓ oxygen demand

→ ↑ CO → ↑ renal blood flow
→ - improved GFR
→ ↓ renin-angiotensin activity level
→ ↑ Na⁺ excretion → ↓ body Na⁺
→ ↓ volume + vascular reactivity
→ ↓ pre- and afterload

Dosage & Toxicity:

<table>
<thead>
<tr>
<th></th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic [plasma]</td>
<td>0.5 – 2 ng/ml</td>
<td>10 – 25 ng/ml</td>
</tr>
<tr>
<td>Toxic [plasma]</td>
<td>&gt; 2 ng/ml</td>
<td>&gt; 35 ng/ml</td>
</tr>
</tbody>
</table>

Narrow therapeutic window (50%): → oscillatory afterdepolarization
→ ventricular tachycardia

Toxicity: ventricular tachycardia, delirium, fatigue, dizziness, nausea, vomiting

![Diagram](image1.png)

**FIGURE 16-5** Normal action potential, A, and changes in cardiac action potentials caused by subtoxic, B, and toxic, C, doses of the cardiac glycosides. A, Typical action potential recordings from the cardiac Purkinje fiber cells. Toxic doses produce oscillatory afterdepolarizations, B, and ventricular tachycardia, C.
Important interactions:

- Hypokalaemia → ↑ CG binding (esp. with diuretics)
- Quinidine → displaces CG from tissue binding
- Ca**-blockers → enhance effect, ie. increase toxicity (eg. verapamil)
- Catecholamines → enhance toxicity (synergist effect)

Treatment of Toxicity:

- a. discontinue agent
- b. K+ → ↓ arrhythmias (esp. with diuretics)
- c. use of antiarrhythmic agent eg. lidocaine, phenytoin
- d. use of antidigoxin antibodies eg. digoxin immune FAB (expensive)

Catecholamines:

Dobutamine  Dopamine

- ↑ cAMP → ↑ Ca** influx
- after CG, dobutamine most commonly used (iv) in acute emergency CHF not chronic

Phosphodiesterase Inhibitors:

Amrinone  Milrinone

- chronic CHF
- ↑ cAMP → ↑ Ca** influx (as per catecholamines)
- reported to have less inotropic effect
- long term exhibit higher mortality than CGs
- bronchodilation, benefit in asthma individual
Drugs without Positive Ionotropic Effects used in CHF

A. Angiotensin converting enzyme (ACE) inhibitors and receptor antagonists (ARBs)

- increasing use for CHF
- captopril, enalapril (ACEIs), Losartan, Saralazin (ARB’s, Ag receptor antagonists)
- increasing in use. maybe used in combination with CGs
- need to take before or after meals

Adverse effects:
- severe hypotension in hypovolemic patients, bilateral renal a. stenosis
- hyperkalemia
- dry cough, skin rushes, glossitis
- altered sense of taste (loss of zinc)
- contraindicated 2nd and 3rd trimester of pregnancy (tetrogenic)
- drug interactions with potassium-sparing diuretics, NSAIDs

B. Beta-blockers (caution)

eg. Metoprolol, Labatalol, Carvedilol

- decrease O₂ demand more than supply, ↓ preload
- decrease BP, ↓ afterload
- decrease cardiac contractivity, decrease sympathetic activity
- metoprolol (beta1-selective)
- labatalol, carvedilol (block alpha- and beta-receptors)

Features of beta-adrenoceptor antagonists (end in –olol, if –alol have unique feature

- Selective vs non-selective (A to M, beta1-selective)
- Partial agonist activity (ISA)
- Membrane stabilizing action (LA-action)
- Lipid solubility (least important feature)
Dr. Ishac

Heart Failure

Adverse effects:
- ↓ myocardial reserve (blockade of cardiac β₁-ARs)
- asthma (blockade of bronchial beta₂-ARs)
- peripheral vascular insufficiency
- diabetes (blockade of hepatic beta₂-ARs)
- ↑ plasma TG and ↓ HDL
- CNS: nightmares, mental depression, insomnia
- withdrawal syndrome (supersensitivity of beta-receptors)

Labetalol, Carvedilol
- alpha and beta-receptor blocker
- beta/alpha = 3:1

![Diagram of beta-adrenoceptor blockers]

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β₁</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3–4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6–9 hours</td>
<td>40</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β₁</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14–22 hours</td>
<td>90</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9–12 hours</td>
<td>80</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes²</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85</td>
</tr>
<tr>
<td>Cefiprolol</td>
<td>β₁</td>
<td>Yes¹</td>
<td>No</td>
<td>Low</td>
<td>4–5 hours</td>
<td>70</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td></td>
</tr>
<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
<td>30</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14–24 hours</td>
<td>33</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
<td>90</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>3½–6 hours</td>
<td>30²</td>
</tr>
<tr>
<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>90</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4–5 hours</td>
<td>50</td>
</tr>
</tbody>
</table>

¹Partial agonist effects at β₂ receptors. ²Labetalol also causes α₁-selective blockade. ³Bioavailability is dose-dependent.
C. **Diuretics (important class)**
   eg. Loop diuretics (acute, chronic), thiazide diuretics (chronic)

   - ↓ plasma volume → ↓ venous return (preload)
   - relieve pulmonary congestion & peripheral edema
   - K⁺ loss (loop & thiazide), interaction with CG (increase toxicity)
   - glucose intolerance, photosensitivity

**Thiazides:**
(eg. chlorothiazide)
- act on early distal tubule
- inhibit Na⁺ reabsorption

**Loop Diuretics:**
(eg. furosemide)
- act on loop of Henle
- most potent

**Adverse effects**

- potassium depletion (hypokalemia): hazardous in persons taking digitalis
- magnesium depletion
- impair glucose tolerance (diabetes)
- increase serum lipids
- increase serum uric acid concentration (gout)
- photosensitivity

**Potassium Sparing Agents:**
(eg. spironolactone)
- act on late distal tubule, weak action
- hyperkalemia
- used in combination therapy
- spironolactone (blocks action of aldosterone)

D. **Direct Vasodilators** (not calcium antagonists)
   - useful in combination therapy
   - dilation of venous vessels → ↓ preload
   - hydralazine → ↑ cGMP → relaxation
   - isosorbide dinitrate (arterial and venous relaxation)

   - hydralazine and isosorbide dinitrate (Afro-Americans)

   a. - Beta natriuretic peptide [Nesiritide (Natrecor)]
      Increasing use for severe CHF (Class IV), iv. administration
      Binds to a receptor on the surface of the vascular smooth muscle cell and activates cGMP, leading to smooth muscle relaxation and vasodilation. Arterial and venous dilation decrease preload and afterload.
      Main adverse effect - hypotension

**Recommended References:**

Kelly, R.A. and Smith, T.W.: Pharmacological Treatment of Heart Failure