Pharmacotherapy of Heart Failure (CHF) 
Inotropics and Other Agents

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Congestive Heart Failure (CHF) - Definition
Compensated heart failure:
- resting cardiac function, OK
  - excessive stress or exercise, No

Congestive heart failure: (CHF, Decompensated):
- resting cardiac function inadequate
- venous pooling → edema, esp. lungs
- shortness of breath, fatigue
- ejection fraction of less than 40%

Causes
- coronary artery disease (70%)
- hypertension
- primary cardiomyopathy
- toxic injury by chemicals
- congenital or genetic abnormalities
- drug: adriamycin (doxorubicin)

CHF Therapy Overview
Non-Drug:
- exercise as tolerated
- salt restriction

Drug Therapy:
A. Positive inotropic agents:
  - cardiac glycosides eg. digoxin
  - catecholamines eg. dobutamine
  - phosphodiesterase III inhibitors eg. inamrinone
B. Beta-blockers (caution) eg. metoprolol
C. Diuretics eg. thiazides, loop, K-sparing
D. ACE inhibitors / ARB eg. lisinopril / losartan
E. Vasodilators (non-inotropic) eg. hydralazine, beta-type natriuretic peptide (nesiritide)

Hemodynamic Changes “Hormonal Storm”
BP is well maintained in CHF:
- ↑ sympathetic tone (tachycardia)
- ↓ parasympathetic tone
- activation of renin-angiotensin system
- ↑ blood volume
- ↑ vasopressin release

Consequences:
- ↓ force of contraction
  - ↓ CO, ↑ TPR, ↓ stroke volume
- ↑ venous pressure, ↓ tissue perfusion
  - cardiac hypertrophy
  - Na⁺ & water retention
  - edema

Heart failure: “Hormonal Storm”
Need to break the cycle
activation of sympathetic nerve system and of renin-angiotensin-aldosterone axis
additional neuro-humoral activation promoted
vicious cycle
heart tissue remodeling (hypertrophy)
pumping function disrupted

Adapted from The Heart, 3rd Ed. Page 163
Heart Physiology

Cardiac Glycosides Chemistry

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

Unsaturated five-membered lactone ring:
- hydrophilic, essential for activity
- opening the ring → loss of activity
- saturation → loss of activity

Series of sugars linked to C3 of the steroid nucleus
- nonessential, hydrophilic

Cardiac Muscle Contraction

Cardiac Glycosides

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

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

Mechanism of Action

Cardiac glycosides (CG)
- Inhibition of Na+/K+ ATPase (Na+ pump)
- membrane bound transporter (3 Na+ / 2 K+)
- found all over the body, α/β-subunits
- 3 mammalian isoforms
- extracellular binding site for CG
- phosphorylation of cytosol α-subunit → stabilize CG binding
- ↓ [K+]EC → dephosphorylates α-subunit → CG binding
- ↓ [K+]EC → phosphorylates α-subunit → ↑ CG intoxication

Inhibition of (Na+, K+)-ATPase
- ↓ exchange Na+ - K+ (3:2)
- ↑ [Na+]IC (8 → 9 - 9.5 mM)
- ↑ Na+ - Ca++ exchange (3:1) (depolarized)
- ↑ [Ca+]IC
- ↑ SR uptake Ca++ (↑ stores)
- ↑ contractile force

Cardiac Muscle Contraction

Page 2
Therapeutic consequence of Cardiac Glycosides

Moderate but persistent positive inotropic effect, \( \uparrow \) sensitivity of the baroreceptor reflex

\[ \rightarrow \uparrow \text{CO} \rightarrow \downarrow \text{sympathetic activity} \]
\[ \rightarrow \downarrow \text{HR and vascular tone} \]
\[ \rightarrow \downarrow \text{pre- and afterload to the heart} \]
\[ \rightarrow \downarrow \text{heart size} \]
\[ \rightarrow \downarrow \text{oxygen demand} \]
\[ \rightarrow \uparrow \text{renal blood flow} \]
\[ \rightarrow \text{improved GFR} \]
\[ \rightarrow \downarrow \text{renin-angiotensin activity level} \]
\[ \rightarrow \uparrow \text{Na}^+ \text{excretion} \rightarrow \downarrow \text{body Na}^+ \]
\[ \rightarrow \uparrow \text{CO} \rightarrow \downarrow \text{renal blood flow} \]
\[ \rightarrow \text{improved GFR} \]
\[ \rightarrow \downarrow \text{pre- and afterload} \]

Cardiac effects of Cardiac Glycosides

1. Increase in contractile force (inotropic effect)
2. Increase in vagal activity - cardiac slowing (chronotropic effect)
3. Major effects on electrophysiologic parameters
   a. decreased A-V conductivity due to decreased CV and an increase in the refractory period
   b. EKG changes
      1. T wave becomes inverted
      2. ST segment becomes depressed
      3. PR interval becomes prolonged
4. Heart size is decreased due to more complete ventricular emptying

Summary of the Effects of CHF and the Results of Digitalis Administration

<table>
<thead>
<tr>
<th>Heart Failure</th>
<th>Digitalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial contractility</td>
<td>( \downarrow )</td>
</tr>
<tr>
<td>End diastolic and venous pressure</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>( \downarrow )</td>
</tr>
<tr>
<td>Blood volume</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Heart rate</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Heart size</td>
<td>( \uparrow )</td>
</tr>
</tbody>
</table>

Digitalis Glycosides

<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>
</tbody>
</table>

Digoxin:
- Water insoluble
- Absorption by gut bacteria (10% resistant Eubact. lentum)
- Unchanged excretion by kidney (85%), not removed by dialysis
- 15% liver metabolism, can cross the placenta

Digitoxin:
- Good oral absorption
- Mainly metabolized by the liver (cardioactive metabolites)
- Large interpatient variations (intestinal flora)
- Enterohepatic recycling

Dosage & Toxicity

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

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

Toxic effects:
- Tachycardia
- Delirium
- Fatigue
- Nausea
- Vomiting
- Vision disturbances (halo effect, mostly yellow and green)
Therapeutic Index

Digoxin Drug Interactions
Many potential interactions:
- **Hypokalemia** → ↑ CG binding (esp. with diuretics)
- **Hyperkalemia** → ↓ CG binding (ACEI/ARB, K-sparing)
- **Quinidine** → displaces CG from plasma binding
- **Ca++-blockers** → enhance effect (eg. verapamil)
- **Amiodarone** → ↑ serum [CG] (↓ clearance)
- **Cholestyramine** → decrease CG absorption
- **Hyperthyroidism** - decreases digoxin levels
- **Hypothyroidism** - increases digoxin levels
- **Antibiotics** → ↑ bioavailability (eg. erythromycin)
- **Altered renal function** and many other drugs

Digoxin Treatment of Toxicity
Digoxin increases quality of life but not survival. Patients must be closely monitored for signs of toxicity OR therapeutic failure (loss of effect).

- a. discontinue agent (GC), lower dose
- b. discontinue K+ depleting diuretics
- c. K+ replacement → ↓ arrhythmias (esp. with diuretics)
- d. use of antiarrhythmic agent eg. lidocaine, phenytoin
- e. antidigoxin antibodies eg. digoxin immune FAB (used for high toxicities ie. suicide)

Catecholamines
- **Dobutamine (Dopamine)**
  - short-acting, metabolism by COMT, MAO
  - acute, emergency treatment iv
  - ↑ cAMP → ↑ Ca++ influx
  - can induce angina, arrhythmias (discontinue)
  - dopamine can activate renal D-receptors

Phosphodiesterase III Inhibitors:
- **Inamrinone (was Amrinone)**, Milrinone
  - acute and chronic treatment
  - additional benefit → asthma
  - ↑ cAMP → ↑ Ca++ influx (as per catecholamines)
  - reported to have less inotropic effect
  - long-term higher mortality than cardiac glycosides or other treatments

Catecholamines – Mechanism of Action in CHF

Angiotensin converting enzyme (ACE) inhibitors / ARBs
- **Captopril**, **Lisinopril**, **Enalapril**, **Losartan (ARB)**
  - side benefit antihypertensive, decrease load
  - frontline, cornerstone therapy, increasing in use, ↑ survival
  - used in combination with CG, tissue remodeling
  - hyperkalemia, dry cough (ACEI only), loss of taste (Zn loss), angioedema (<1%, less with ARBs), glossitis (<5%), tetrogenic
**Renin-Angiotensin System**

- **Renin** → **Angiotensin I**
- **ACE inhibitors** (Lisinopril)
- **Angiotensin II** → **AT II**
- **BK-R** → **Angiotensinogen**
- **Bradykinin** → **NO**
- **Inactive Peptides**
- **Vasodilation**
- **Anti proliferation**
- **↑ Kinins**
- **↑ NONO**
- **↑ Vasoconstriction**
- **Cell growth**
- **↑ Aldosterone**
- **↑ Antidiuretic hormone**
- **Enzymatic activity**
- **Blockade**

**Actions of Angiotensin-Converting Enzyme (ACE) Inhibitors/ARBs**
- Decrease activity of sympathetic NS
- ↓ TPR, CO unchanged, HR unchanged
- No reflex ↑ HR, probably due to resetting of baroreceptor reflex sensitivity
- ↓ aldosterone production → ↓ Na/Water retention
- ↑ bradykinin level (inhibit metabolism, only ACEIs)
- Improves intrarenal hemodynamics
- Less effective in elderly and Afro-Americans

**Guidelines to ACE Inhibitor Therapy**

- **Contraindications**
  - Pregnancy (C & D)
  - Renal artery stenosis
  - Renal insufficiency (relative)
  - Hyperkalemia
  - Arterial hypotension
  - Dry cough
  - Angioedema
- **Alternatives**
  - Hydralazine + ISDN in Afro-Americans

**ACEI – Angioedema; Glossitis**
- Angioedema (<1%)
- Dry mouth
- Glossitis (<5%)
- Oral ulceration
- Oral bleeding

**Drugs without Positive Inotropic Effects**

**Diuretics (frontline)**
- Loop (acute & chronic), thiazide diuretics (chronic)
- Potassium-sparing used in combo Rx
- ↓ plasma volume → ↓ venous return (preload)
- Relieve pulmonary congestion & peripheral edema
- K+ loss (loop, thiazides): interaction with CG

**Direct Vasodilators**
- Not Ca++ antagonists
- Dilation of venous vessels → ↓ preload
- Dilation of arterioles → ↓ afterload
- Hydralazine → direct vasodilation → relaxation
- Nitrates (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- Beta-type natriuretic peptide (iv., severe CHF) → ↑ cGMP

**Diuretics: Overview**

- **Loop diuretics** (Furosemide)
  - Inhibit Na-K-2Cl ion cotransporter, ↑Na+, H2O reabsorption: ascending loop of Henle
  - Hypokalemia, hypomagnesemia, hypercalcaemia ototoxicity, most potent
- **Thiazides** (Hydrochlorothiazide)
  - Inhibit Na-Cl symporter, ↑Na+, H2O reabsorption in distal convoluted tube
  - Hypokalemia, hypercalcaemia, ↑uric acid → gout, DM-2
- **K+-sparing** (Spironolactone)
  - Aldosterone antagonism at collecting tube
  - Hyperkalemia, least potent, adjunct
  - Decreases mortality
Diuretics: Reduction of volume overload

↓ plasma volume
↓ afterload
↓ preload
↓ peripheral edema
↓ pulmonary congestion
↓ HF symptoms

Drugs without Positive Inotropic Effects

Diuretics (frontline)
- loop (acute & chronic), thiazide diuretics (chronic)
- potassium-sparing used in combo Rx
- ↓ plasma volume → ↓ venous return (preload)
- relieve pulmonary congestion & peripheral edema
- K⁺ loss (loop, thiazides): interaction with CG

Direct Vasodilators
- not Ca** antagonists
- dilation of venous vessels → ↓ preload
- dilation of arterioles → ↓ afterload
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- nitrates (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- beta-type natriuretic peptide (iv., severe CHF) → ↑ cGMP

Vasodilators

- relax smooth muscle of arterioles → ↓ TPR
- high clinical value (in combinations and hypertensive emergencies)

Hydralazine
- direct vasodilation
- dilate arterioles but not veins
- ↓ TPR → ↓ BP → reflex ↑ HR
- Lupus syndrome

Adverse effects:
- reflexory sympathetic activation
- headache, nausea, sweating, flushing
- palpitations, ↑ HR → angina
- lupus reaction (mainly in slow acetylators)

Bidil: Isosorbide-dinitrate (ISDN) & Hydralazine

• Approved 2005 for HF in Afro-Americans
• 1st race-based drug
• Blacks do not respond well to ACEIs/ARBs and beta-blockers
• Bidil was found to reduce mortality among blacks by 43%

Actions of Vasodilators

Ca⁺⁺ Antagonists
Verapamil
Diltiazem
Nifedipine

Open K⁺ Channels
Minoxidil
Diazoxide

Direct Vasodilation
Hydralazine

Nitric oxide (NO)
β-natriuretic peptide
Nitroprusside
Nitrates

Bidil: Isosorbide-dinitrate & Hydralazine

Isosorbide-dinitrate

Hydralazine

conversion to NO

↓ vascular tone

↑ venous filling ↓ arterial resistance

↓ arterial resistance

↓ cardiac load
Lupus erythematosus

- Chronic inflammatory disease
- Autoimmune disease

Drug induced: Procainamide, Hydralazine, Isoniazid

Beta-Blockers

**Metoprolol, Carvedilol, Bisoprolol (EBM)**

**Positive Actions**
- ↓ myocardial O₂ consumption (demand) by ↓ HR and ↓ force contraction
- ↓ BP → ↓ afterload, ↓ preload (less)

**Negative Actions**
- remove positive sympathetic activity
- decrease cardiac contractility

**MERIT-HF : Use of Metoprolol in CHF**

- Metoprolol vs Placebo, USA & 13 other countries
- β₁-selective, no ISA, LA-action
- LVEF <0.40 and NYHA class II-IV heart failure
- Stabilized by optimum standard therapy (diuretics/ACEI)
- 2.4 years, terminated early after 1 year

- Mortality ↓ 34%
- Risk ↓ 39%
- Hospitalization ↓ 29%
- Felt better ↑ 25%
- Prevent 1 death per 27 patients treated per year

**Beta-blockers on survival in chronic heart failure**

**Beta-Adrenoceptor Antagonists**

Multiple possible mechanisms of action:

i. CNS effect to decrease sympathetic NS tone
ii. ↓ renin secretion: beta1-receptors mediate renin release
iii. block cardiac beta1-receptors: ↓ HR → ↓ CO → ↓ BP

↓ cns sympathetic outflow
↓ BP

Decrease in blood pressure
**Beta-type Natriuretic peptide - Nesiritide (Natrecor)**

- binds to A-type receptor on vascular smooth muscle cell
- activates cGMP → muscle relaxation and vasodilation
- arterial & venous dilation → ↓ preload & afterload
- dilation of afferent renal arterioles leads to increased GFR and decreased sodium reabsorption, causing a diuresis
- SNS and RAA systems are also suppressed
  - acute decompensated heart failure
  - use - severe (Class IV) CHF
  - iv administration (T1/2: 20 mins, duration: 2 hrs))
- Main adverse effect - hypotension

**Natriuretic peptides: ANP, BNP, CNP**

- atrial natriuretic peptide (ANP, 28 aa), brain natriuretic peptide (BNP, 32 aa) and C-type natriuretic peptide (CNP, 22 aa) are peptides released in response to atrial and ventricular volume/pressure expansion.
- ANP and BNP are released from the atria and ventricles, respectively, and both promote vasodilatation and natriuresis.
- BNP, in particular, produces selective afferent arteriolar vasodilation and inhibits sodium reabsorption in the proximal convoluted tubule.
- BNP inhibits renin and aldosterone release and, possibly, adrenergic activation as well.
- ANP and BNP are elevated in chronic heart failure.
- BNP, in particular, has potentially important diagnostic, therapeutic, and prognostic implications - Nesiritide, a recombinant BNP

**Pharmacotherapy of Congestive Heart Failure: 2004**

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (no limitations on activity)</td>
<td>ACE Inhibitor/AT1 - RB</td>
</tr>
<tr>
<td>Class II (slight, mild limitation of activity, comfortable at rest)</td>
<td>Digoxin*, Furosemide, ACE Inhibitor/AT1 - RB, Beta-blocker</td>
</tr>
<tr>
<td>Class III (marked limitation of activity, only comfortable at rest)</td>
<td>Bi-Ventricle pacing, Bidil</td>
</tr>
<tr>
<td>Class IV (complete rest, confined to bed or chair)</td>
<td>Digoxin*, Furosemide (IV), Thiaizide, ACE Inhibitor/AT1 - RB, Receptor blocker, K+-sparing</td>
</tr>
</tbody>
</table>

Recommended Digoxin* not be used in females for routine CHF. 8/10/04
Recommended Pharmacotherapy of CHF requires 4 or more agents
Bidil: (isosorbide dinitrate (ISDN) and hydralazine) African Americans very effective

**Summary: Pharmacotherapy of Heart Failure**

- Improved survival
  - ACE inhibitors/ARBs, β-blockers, K-sparing
- Increased mortality
  - Phosphodiesterase III inhibitors (chronic)
- Neutral on survival
  - Digoxin, Loop diuretics, Thiazides
- Quality of life
  - Digoxin, Loop diuretics, Thiazides, β-blockers
- Reduction of edema
  - Loop diuretics, Thiazides
- Tissue Remodeling
  - ACE inhibitors/ARBs, K-sparing
- Prevention of ischemia
  - β-blockers, Anticoagulant therapy
- Hemodynamic improvement: All agents
  - ACEI, ARBs, Diuretics, β-blockers, K-sparing

**Type-A natriuretic peptide receptor**

<table>
<thead>
<tr>
<th>Biologic Effect</th>
<th>BNP</th>
<th>ATII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasconstriction</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Diuresis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Natriuresis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Parasympathetic activity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Renin secretion</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Aldosterone secretion</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Myocyte hypertrophy</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Binding of atrial natriuretic peptide, brain natriuretic peptide, or Nesiritide to ligand binding domain results in ATP binding, and conformational change in the hinge region allows for activation of the guanylyl cyclase domain and biologic effects.