Congestive Heart Failure (CHF)

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Leading Causes of Death in the U.S

Data NIH 2000
Congestive Heart Failure (CHF)

CO inadequate for body demand of oxygen (demand-supply)

4.7 million in USA

50% mortality @ 5 year

400,000 new cases each year

Blood flow at rest and exercise
**CHF - % Hospitalization**

Principal Ambulatory Care Sensitive Conditions Resulting in Hospitalization

- **Kidney Infection**: 9.20
- **Dehydration**: 16.40
- **Diabetes**: 11.10
- **Bacterial Pneumonia**: 13.90
- **Congest. Heart Failure**: 16.10

**Congestive Heart Failure (CHF) - Definition**

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

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

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

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 Physiology

<table>
<thead>
<tr>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca⁺⁺</th>
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<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
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<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
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Cardiac Glycosides inhibit Na⁺/K⁺-ATPase
**Cardiac Muscle Contraction**

![Diagram of cardiac muscle contraction](image)

Ion movements during the contraction of cardiac muscle.

**CHF Therapy Overview**

**Non-Drug:**
- rest (reduced activity)
- salt restriction (<1gm/day)

**Drug Therapy:**
A. Positive inotropic agents:
   - cardiac glycosides eg. digoxin, digitoxin
   - catecholamines eg. dobutamine
   - phosphodiesterase inhibitors eg. amrinone

B. Beta-blockers (caution) eg. metoprolol
C. Diuretics eg. thiazides, Loop
D. ACE inhibitors / ARB eg. captopril / losartan
E. Vasodilators (non-inotropic) eg. hydralazine, beta natriuretic peptide
Frank-Starling Curve

Need to bring curve to normal without an increase in HR

1. NORMAL HEART
   - Within limits, when cardiac muscle is stretched, its force of contraction increases, and hence, cardiac output increases.
   - However, if the ventricle is overly stretched, the effect of ventricular contraction is diminished.
   - A is the normal operating point in the healthy heart.

2. DECOMPENSATED HEART FAILURE
   - Initial reduction of contractility (B to C) due to CHF.
   - Symptoms of low cardiac output develop, for example, dyspnea and edema.

3. COMPENSATED HEART FAILURE
   - Ventricular end-diastolic pressure increases (B to C) in an effort to maintain an adequate cardiac output.
   - The increased ventricular end-diastolic pressure causes symptoms of congestion, for example, dyspnea.

4. DIGITALIS TREATMENT
   - Administration of digoxin shifts ventricular function curve toward normal.
   - Increased contractility (C to A) leads to increased cardiac output.
   - Decreased sympathetic reflexes and vascular tone cause decrease in ventricular end-diastolic pressure (A to B).

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)
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 C 3 of the steroid nucleus
- nonessential, hydrophilic

[Diagram of cardiac glycosides structure]

Figure 13-3. Structure of digoxin, a typical cardiac glycoside.

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:
- absorption by gut bacteria (10% Eubact. lentum)
- unchanged excretion by kidney, not removed by dialysis
- crosses the placenta

Digitoxin:
- good oral absorption
- metabolized by the liver (cardioactive metabolites)
- large interpatient variations (bacterial flora)
- enterohepatic recycling
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
- extracytoplasmic 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⁺ - Ca²⁺ exchange (3:1) (depolarized)
→ ↑ [Ca²⁺]IC
→ ↑ SR uptake Ca²⁺ (↑ stores)
→ ↑ contractile force

Cardiac Muscle Contraction

Figure 16.3
Ion movements during the contraction of cardiac muscle.
Therapeutic consequence of Cardiac Gycosides

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

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

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure</th>
<th>Digitalis</th>
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<tbody>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>End diastolic and venous pressure</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Blood volume</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart size</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
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%):
- → oscilatory afterdepolarization
- → ventricular tachycardia

Drug Interactions & Toxicity

Important interactions:
- Hypokalaemia → ↑ CG binding (esp. with diuretics)
- Quinidine → displaces CG from tissue binding
- Ca++-blockers → enhance effect (eg. verapamil)
- Catecholamines → enhance toxicity
- Cholestyramine → ↓ absorption of CG
- Thyroid state → Hyper ↓[CG], Hypo ↑[CG] via elimination

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

Dobutamine  Dopamine
- acute, emergency treatment
- ↑ cAMP → ↑ Ca++ influx
- after CG, dobutamine most commonly used (iv, acute)

Phosphodiesterase Inhibitors:
  Amrinone  Milrinone
- chronic and acute 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
Drugs without Positive Inotropic Effects used in CHF

A. Angiotensin converting enzyme (ACE) inhibitors / ARBs
   - Captopril
   - Lisinopril
   - Enalapril
   - Losartan (ARB)
   - side benefit → hypertension
   - decrease load
   - frontline, increasing in use
   - maybe used in combination with CG
   - hyperkalemia, dry cough (ACEI), loss of taste (Zn loss), angioedema, glossitis (<5%), tetrogenic
   - need to take before or after meals

ACEI – Angioedema; Glossitis

- Less than 5%
- Dry mouth
- Glossitis
- Oral ulceration (Stevens-Johnson Syndrome)
- Oral bleeding
B. Beta-Blockers

Metoprolol, Labetalol, Carvedilol

Main action to decrease HR and catecholamine action on the heart

Positive Actions
- ↓myocardial O₂ consumption (demand) by ↓HR and ↓force contraction
- ↓BP → ↓after load, ↓pre load (less)

Negative Actions
- remove positive sympathetic activity
- decrease cardiac contractility

β-Blockers: Heart Failure

• Old view (before 2002)
Contraindicated: β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart. Pindolol has less of this effect due to intrinsic activity.

• New view
May be used for CHF with caution. Not suitable in unstable heart failure, or evidence of bronchospasm, fluid overload, significant bradycardia (decreased cardiac reserve) or depression.
MERIT-HF: Use of Metoprolol in CHF

- Metoprolol (n=1990) vs Placebo (n=2001)
- β₁-selective, no ISA, LA-action
- USA & 13 European countries
- All received conventional medication
- Monitored 1 – 1.5 years

- Mortality ↓34%
- Hospitalization ↓29%
- Felt better ↑25%

Mechanism of Action

- β-Adrenoceptor blockers
  - ↓ cns sympathetic outflow
  - ↓ BP
  - ↓ cardiac output
  - ↓ peripheral resistance
  - ↓ angiotensin II
  - ↓ aldosterone
  - ↓ sodium, water retention
  - ↓ blood volume
  - ↓ decrease in blood pressure
**Beta-Blockers in CHF: 2002 Guideline**

**C. 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

**D. Direct Vasodilators**
- not Ca⁺⁺ antagonists
- dilation of venous vessels → ↓ preload
- dilation of arterioles → ↓ afterload
- hydralazine → ↑ cGMP → relaxation
- hydralazine+isosorbide dinitrate (BiDil)
- beta natriuretic peptide short T₁/₂ 20 sec; (iv., severe CHF) → ↑ cGMP
**Vasodilators**

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

**Hydralazine**
- EDRF / Nitric oxide (NO) / cGMP involvement
- dilate arterioles but not veins
- ↓ TPR → ↓ BP → reflex tachycardia

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

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**Actions of Vasodilators**

<table>
<thead>
<tr>
<th>Ca** Antagonists</th>
<th>Open K* Channels</th>
<th>Nitric Oxide (NO)</th>
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<tbody>
<tr>
<td>Verapamil</td>
<td>Minoxidil</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Diazoxide</td>
<td>β-natriuretic peptide</td>
</tr>
</tbody>
</table>

**Ca** channel blockers

- ATP → cAMP
- MLCK→ MLCK-P~O~2~
- Myosin-LC kinase
- Myosin-LC

**Open K* Channels**

- cAMP
- MLC
- Myosin-LC

**Nitric Oxide (NO)**

- NO
- GMP
- Guanylyl cyclase

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**Diagram:**

- Ca** channel blockers
- ATP
- cAMP
- Myosin-LC kinase
- Myosin-LC
- MLCK
- MLCK-P~O~2~
- Contraction
- Relaxation

- GTP
- MLCK
- Myosin-LC
- Myosin-LC-P~O~4~
- Contraction
- Relaxation
Table 2. Drugs Commonly Used for Treatment of Chronic Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Loop diuretics*</td>
<td></td>
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<tr>
<td>Bumetanide</td>
<td>0.5 to 1.0 mg once or twice daily</td>
<td>Titrated to achieve dry weight</td>
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<td>(up to 10 mg daily)</td>
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<tr>
<td>Furosemide</td>
<td>20 to 40 mg once or twice daily</td>
<td>Titrated to achieve dry weight</td>
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<td>(up to 400 mg daily)</td>
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<tr>
<td>Torsemide</td>
<td>10 to 20 mg once or twice daily</td>
<td>Titrated to achieve dry weight</td>
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<td></td>
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<td>(up to 200 mg daily)</td>
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<td>ACE Inhibitors</td>
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<tr>
<td>Captopril</td>
<td>6.25 mg 3 times daily</td>
<td>50 mg 3 times daily</td>
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<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10 to 20 mg twice daily</td>
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<tr>
<td>Lisinopril</td>
<td>5 to 10 mg once daily</td>
<td>40 mg once daily</td>
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<tr>
<td>Ramipril</td>
<td>2.5 to 5.0 mg once daily</td>
<td>20 to 40 mg once daily</td>
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<tr>
<td>Betaxazole</td>
<td>1.25 to 2.5 mg once daily</td>
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Pharmacotherapy of Congestive Heart Failure: 2004

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
</table>
| Class I (no limitations on activity) | ACE Inhibitor/AT 
, - RB |
| Class II (slight, mild limitation of activity) | Digoxin*, Furosemide, ACE Inhibitor/AT 
, - RB, Beta blocker |
| Class III (marked limitation of activity) | Bi-Ventricle pacing Bidil Digoxin*, Furosemide, Thiazide, ACE Inhibitor/AT 
, - RB, Beta blocker/ K+-sparing |
| Class IV (complete rest, confined to bed or chair) | Bi-Ventricle pacing Bidil Digoxin*, Furosemide (IV), Thiazide, ACE Inhibitor/AT 
, - Receptor blocker, K+-sparing/Inotropic Therapy/ Beta-Natriuretic Peptide |

Recommended Digoxin not be used in the female for routine CHF. 8/10/04
Recommended Pharmacotherapy of CHF requires 4 or more agents