Congestive Heart Failure (CHF)

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CO inadequate for body demand of oxygen (demand-supply)
2.5 million in USA
50% mortality @ 5 year
350,000 new cases each year

CHF - % Hospitalization
Principal Ambulatory Care Sensitive Conditions Resulting in Hospitalization

Heart Physiology
Cardiac Glycosides inhibit Na⁺/K⁺-ATPase
**Cardiac Muscle Contraction**

Polarized

**CHF Therapy Overview**

Non-Drug:
- rest
- 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

D. ACE inhibitors eg. captopril

E. Vasodilators (noninotropic) eg. hydralazine

**Frank-Starling Curve**

Need to bring curve to normal without an increase in HR

**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

**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)

**Digitalis Glycosides**

| Agent     | Route | Bioavail. % | Bounded% | Peak effect | T1/2
|------------|-------|-------------|----------|-------------|-----|
| Digoxin    | oral, iv | 45-65 | 25 | 6 hr | 35 hr (kidney)
| Digitoxin  | oral, iv | >80 | 90 | 12 hr | 6-7 day (liver)

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

**Figure 19.8**

[Diagram illustrating the Frank-Starling curve and cardiac muscle contraction]

[Diagram showing the chemical structure of cardiac glycosides and digitalis glycosides]
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+ - Ca++ exchange (3:1) (depolarized)
  - ↑ [Ca++]
- ↑ SR uptake Ca++ (↑ stores)
- ↑ contractile force

Cardiac Muscle Contraction

Therapeutic consequence of Cardiac Gycosides

Moderate but persistent positive inotropic 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
- ↑ renin angiotensin activity level
- ↑ Na+ excretion → ↓ body Na+
- ↑ volume + vascular reactivity
- ↓ pre- and afterload

Doseage & Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxic (plasma)</th>
<th>Therapeutic (plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>&gt; 2 ng/ml</td>
<td>0.5 – 2 ng/ml</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>&gt; 20 ng/ml</td>
<td>10 – 25 ng/ml</td>
</tr>
</tbody>
</table>

Narrow therapeutic window: → oscilatory afterdepolarization → ventricular tachycardia

Toxic effects
- delirium
- fatigue
- dizziness
- nausea
- vomiting

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

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

Catecholamines

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

- Dopamine
  - chronic treatment
  - additional benefit → asthma
  - ↑ cAMP → ↑ Ca++ influx (as per catecholamines)
  - reported to have less inotropic effect
  - long-term higher mortality than cardiac glycosides

Phosphodiesterase Inhibitors:
  - Amrinone
  - Milrinone
    - chronic treatment
    - additional benefit → asthma
    - ↑ cAMP → ↑ Ca++ influx (as per catecholamines)
    - reported to have less inotropic effect
    - long-term higher mortality than cardiac glycosides
Catecholamines – Mechanism of Action in CHF

Drugs without Positive Inotropic Effects used in CHF
A. Angiotensin converting enzyme (ACE) inhibitors
  - Captopril
  - Enalapril
    - side benefit → hypertension
    - decrease load
    - increasing in use
    - maybe used in combination with CG
    - loss of taste (Zn loss), glossitis (<5%)
    - need to take before or after meals

Use of Beta-blockers in CHF

MERIT-HF : Use of Metoprolol in CHF

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.

β-Blockers

Metoprolol, Labetalol, Carvedilol

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

Negative Actions
- remove positive sympathetic activity
- decrease cardiac contractility
Mechanism of Action

Drugs without Positive Ionotropic Effects used in CHF

C. Diuretics
- ↓ plasma volume → ↓ venous return (preload)
- relieve pulmonary congestion & peripheral edema
- K⁺ loss, interaction with CG

D. Direct Vasodilators
- not Ca⁺⁺ antagonists
- dilation of venous vessels → ↓ preload
- hydralazine → ↑ cGMP → relaxation

Agents used in the treatment of HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hyperten- sion</th>
<th>CHF</th>
<th>Arrhyth- mia</th>
<th>Angina</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>⬤ ⬤ ⬤</td>
<td>⬤</td>
<td>⬤ ⬤ ⬤ ⬤ ⬤</td>
<td>⬤ ⬤ ⬤ ⬤ ⬤</td>
<td>Caution: CHF (unstable CHF, bronchospasm, significant bradycardia); or in diabetes, asthma (use β₁-selective)</td>
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<tr>
<td>ACEI</td>
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<td>⬤</td>
<td>⬤ ⬤ ⬤</td>
<td>⬤ ⬤ ⬤</td>
<td>Low GFR, renal failure</td>
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<tr>
<td>Vasodilators</td>
<td>⬤ ⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>Low GFR, CG; Caution in diabetes</td>
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<tr>
<td>Antiarrhythmics</td>
<td>⬤ ⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>Many Rx interactions, low K⁺ importance, low K⁺ toxicity</td>
</tr>
<tr>
<td>Nitrates</td>
<td>⬤ ⬤</td>
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Beta-Blockers in CHF: 2002 Guideline

Persistent diastolic symptoms, headache, dizziness

Unstable heart failure

Any of

Excessive use of diuretics including diuretics and diuretics

Decompensated heart failure

Adequate heart failure not selected

Unstable heart failure

Cardiac glycosides

Caution when using diuretics including diuretics and diuretics

Low GFR, renal failure

Many Rx interactions, low K⁺ importance, low K⁺ toxicity

Nitrates

Unstable heart failure