Congestive Heart Failure (CHF)

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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

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**

Cardiac Glycosides inhibit Na⁺/K⁺-ATPase

**Cardiac Muscle Contraction**

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

**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

Digoxin
Kidney
Digitoxin
Liver
(-OH, C12)

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 - 9.5 mM)
- ↑ Na⁺ - Ca⁺⁺ exchange (3:1) (depolarized)
- ↓ [Ca⁺⁺]ᵢc
- ↑ SR uptake Ca⁺⁺ (↑ stores)
- ↑ contractile force

Therapeutic consequence of Cardiac Glycosides

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

Cardiac Muscle Contraction

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

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure</th>
<th>Digitalis</th>
</tr>
</thead>
<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%):
→ oscillatory afterdepolarization
→ ventricular tachycardia

Toxic effects:
tachycardia
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
- 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

ACEI – Angioedema; Glossitis

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

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
  - front line, 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
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

Drugs without Positive Ionotropic Effects used in CHF

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

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>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>0.5 to 1.0 mg once or twice daily</td>
<td>Strive to achieve dry weight (up to 10 mg daily)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>30 to 60 mg once or twice daily</td>
<td>Strive to achieve dry weight (up to 400 mg daily)</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>1.0 to 2.0 mg once or twice daily</td>
<td>Strive to achieve dry weight (up to 200 mg daily)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times daily</td>
<td>60 mg 3 times daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg once daily</td>
<td>15 mg once daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5 mg once daily</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>10 mg twice daily</td>
<td>40 mg twice daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Beta-receptor blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>9.125 mg twice daily</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol succinate extended release</td>
<td>12.5 to 25 mg daily</td>
<td>250 mg once daily</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>12.5 to 25 mg once daily</td>
<td>12.5 to 25 mg once daily</td>
</tr>
</tbody>
</table>

Pharmacotherapy of Congestive Heart Failure: 2004

NYHA | Pharmacotherapy
Class I (no limitations on activity) | ACE Inhibitor/AT\(_1\) - RB
Class II (slight, mild limitation of activity) | Digoxin*, Furosemide, ACE Inhibitor/AT\(_1\) - RB, Beta blocker
Class III (marked limitation of activity) | Bi-Ventricle pacing, Digoxin*, Furosemide, Thiazide, ACE Inhibitor/AT\(_1\) - RB, Beta blocker, K+-spiring
Class IV (complete rest, confined to bed or chair) | Bi-Ventricle pacing, Digoxin*, Furosemide (IV), Thiazide, ACE Inhibitor/AT\(_1\) - RB, Beta blocker, K+-spiring/Inotropic Therapy/ Beta-Natruretic Peptide

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