Congestive Heart Failure (CHF)

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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

- Congestive Heart Failure: 16.19
- Diabetes: 11.53
- Bacterial Pneumonia: 11.99

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>In</th>
<th>Out</th>
<th>A</th>
<th>Ca^++</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>150</td>
<td>A</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Cardiac Glycosides inhibit Na/K-ATPase

Cardiac Muscle Contraction

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 / ARB eg. captopril
E. Vasodilators (non-inotropic) eg. hydralazine

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 C3 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 → phosphorolylates 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

Figure 16.3
for movements during the contraction of cardiac muscle.

Therapeutic consequence of Cardiac Gycosides

Moderate but persistent positive inotropic effect,
↑ sensitivity of the baroreceptor reflex

- → ↑ CO → ↓ sympathetic activity
- → ↓ 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

Tissue 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

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

- Acute, emergency treatment
- \( \uparrow \) cAMP \( \rightarrow \uparrow \) Ca\(^{++}\) influx
- After CG, dobutamine most commonly used (iv, acute)

Phosphodiesterase Inhibitors:
- Amrinone
- Milrinone
- Chronic treatment
- Additional benefit \( \rightarrow \) asthma
- \( \uparrow \) cAMP \( \rightarrow \uparrow \) Ca\(^{++}\) influx (as per catecholamines)
- Reported to have less inotropic effect
- Long-term higher mortality than cardiac glycosides or other treatments

Phosphodiesterase Inhibitors - Mechanism of Action in CHF

Drugs without Positive Inotrope Effects used in CHF

A. Angiotensin converting enzyme (ACE) inhibitors / ARBs
- Captopril
- Enalapril
- Losartan (ARB)
- Side benefit \( \rightarrow \) hypertension
- Decrease load
- Increasing in use
- Maybe used in combination with CG
- Dry cough (ACEI), loss of taste (Zn loss), glossitis (<5%), tetrogenic
- Need to take before or after meals

Use of Beta-blockers in CHF

- Old view (before 2002)
  - Contraindicated: \( \beta \)-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)
- \( \beta \)-selective, no ISA, LA-action
- USA & 13 European countries
- All received conventional medication
- Monitored 1 – 1.5 years
- Mortality \( \downarrow 34\% \)
- Hospitalization \( \downarrow 29\% \)
- Felt better \( \uparrow 25\% \)
Beta-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 Inotropic Effects used in CHF

C. Diuretics
- loop (acute & chronic), thiazide diuretics (chronic)
- ↓ 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
- dilation of arterioles → ↓ afterload
- hydralazine → ↑ cGMP → relaxation

Classification of Hypertension – JNC VI

<table>
<thead>
<tr>
<th>Diastolic (mmHg)</th>
<th>Systolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;130 &lt; 85</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139 85-89</td>
</tr>
<tr>
<td>Stage 1 (mild)</td>
<td>140-159 90-99</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160-179 100-109</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>180-209 110-119</td>
</tr>
<tr>
<td>Stage 4 (very severe)</td>
<td>&gt;209 &gt;119</td>
</tr>
</tbody>
</table>

*Require three measurements (repeat visits)
BP lowest in the morning → ↑ during the day

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></td>
<td></td>
</tr>
<tr>
<td>Bumetamide</td>
<td>0.5 to 1.0 mg once or twice daily</td>
<td>10 to 20 mg once or twice daily</td>
</tr>
<tr>
<td>Torasemide</td>
<td>20 to 40 mg once or twice daily</td>
<td>40 to 80 mg once or twice daily</td>
</tr>
<tr>
<td>Furosemide</td>
<td>10 to 60 mg once or twice daily</td>
<td>60 to 120 mg once or twice daily</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>25 mg twice daily</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5 to 10 mg once daily</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 to 20 mg once daily</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>Captopril</td>
<td>25 mg twice daily</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>0.5 mg once daily</td>
<td>1 mg once daily</td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>0.3 or 0.6 mg sublingual</td>
<td>1 mg sublingual</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10 mg once daily</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>Nitroglycerine sustained release</td>
<td>10 to 30 mg every 5-10 min</td>
<td>100 mg every 5-10 min</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>0.1 to 0.3 mg once daily</td>
<td>0.3 to 0.6 mg once daily</td>
</tr>
</tbody>
</table>

*ACE indicates angiotensin converting enzyme
†Relative dosages are used liberally to tailor therapy for individual patient needs in chronic heart failure
‡No significant difference between initial and sustained-release formulations
§Hydralazine is available as isosorbide dinitrate and triaminodinitrate by mouth
Blood Pressure Classification – JNC VII

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>CHF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</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 (not β1-selective)</td>
</tr>
<tr>
<td>Ca++-Blockers</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>CHF, Gingival hyperplasia</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Low GFR, renal insufficiency, glucose intolerance, isotropic</td>
</tr>
<tr>
<td>Diuretics</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Low GFR, hypokalemia → CG; glucose intolerance → diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Many Rx interactions, (K+) important, low K+→ toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Flushing, dizzienss, headache, reflex tachycardia</td>
</tr>
<tr>
<td>Na+-Channel blockers</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Effects enhanced in depolarized tissue</td>
</tr>
<tr>
<td>Nitrates</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Tolerance, flushing, dizziness, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>