HEART FAILURE PHARMACOLOGY

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
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LEARNING OBJECTIVES

- Understand the effects of heart failure in the body
- Understand how one gets heart failure
- Understand how each of the medications work to relieve the symptoms of heart failure
- Know which medications help prevent cardiac remodeling
- Know digoxin and nesiritide
WHAT IS HEART FAILURE - WHEN THE VENTRICLES CANNOT PUMP OUT ENOUGH BLOOD TO MEET THE DEMANDS OF THE BODY

**Diastolic**
Ventricular filling (enlargement/stiffness)

**Systolic**
Ventricular pumping (contractility)/ejection

**Right sided**
Back up of blood into the venous system

**Left sided**
Back up of blood into the pulmonary system
# RISK FACTORS FOR HEART FAILURE

## Table 1. Established and Hypothesized Risk Factors for HF

<table>
<thead>
<tr>
<th>Major Clinical Risk Factors</th>
<th>Toxic Risk Precipitants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, male sex</td>
<td>Chemotherapy (anthracyclines, cyclophosphamide, 5-FU, trastuzumab)</td>
</tr>
<tr>
<td>Hypertension, LVH</td>
<td>Cocaine, NSAIDs</td>
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<tr>
<td>Myocardial infarction</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Doxazosin</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Clinical Risk Factors</th>
<th>Genetic Risk Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>SNP (e.g., α2CDel322-325, β1Arg389)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Sleep-disordered breathing</td>
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<tr>
<td>Chronic kidney disease</td>
<td></td>
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<tr>
<td>Albuminuria</td>
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<tr>
<td>Homocysteine</td>
<td></td>
</tr>
<tr>
<td>Immune activation, IGF1, TNFα, IL-6, CRP</td>
<td></td>
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<tr>
<td>Natriuretic peptides</td>
<td></td>
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<tr>
<td>Anemia</td>
<td></td>
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<tr>
<td>Dietary risk factors</td>
<td></td>
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<tr>
<td>Increased HF</td>
<td></td>
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<tr>
<td>Sedentary lifestyle</td>
<td></td>
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<tr>
<td>Low socioeconomic status</td>
<td></td>
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<tr>
<td>Psychological stress</td>
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</tbody>
</table>

5-FU indicates 5-fluorouracil; SNP, single-nucleotide polymorphism; LVID, left ventricular internal dimension; LVH, left ventricular hypertrophy; NSAIDs, nonsteroidal antiinflammatory drugs; IGF, insulin-like growth factor; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; and HR, heart rate.
### WHAT CAUSES HEART FAILURE?

<table>
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<tr>
<th>Diastolic *PRESERVED EF</th>
<th>Systolic *DECREASED EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased ventricular stiffness</td>
<td>Damaged or reduced heart muscle (MI)</td>
</tr>
<tr>
<td>Mitral or tricuspid valve stenosis</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>Ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td>• Pressure overload</td>
</tr>
<tr>
<td></td>
<td>• Volume overload</td>
</tr>
</tbody>
</table>

- **Usually from prolonged uncontrolled hypertension**
- **Ischemic heart disease (MI)**
- **Uncontrolled risk factors**
WHAT HEART FAILURE CAUSES

Right heart failure
- Congestion of peripheral tissues
  - Dependent edema and ascites
  - GI tract congestion
  - Anorexia, GI distress, weight loss
- Liver congestion
  - Signs related to impaired liver function

Left heart failure
- Decreased cardiac output
- Pulmonary congestion
  - Activity intolerance and signs of decreased tissue perfusion
    - Impaired gas exchange
    - Cyanosis and signs of hypoxia
    - Cough with frothy sputum
    - Orthopnea
    - Paroxysmal nocturnal dyspnea

FIGURE 28-5 Manifestations of left- and right-sided heart failure.

THE HEART TRIES TO COMPENSATE
PROBLEMS ASSOCIATED WITH HEART FAILURE

Remodeling
- Refers to the structural damage that can take place in the heart after prolonged stress
  - Chamber dilation, fibrosis, abnormal cells, reduction in cardiac muscle cells

Compensation
- Your body’s attempt to make up for the lack of oxygen and nutrients to the tissues

Decompensation
- When your body cannot fill the void any longer
STRATEGIES FOR TREATING HEART FAILURE

**Reduce Heart Rate**
- Regulate SNS

**Reduce Preload**
- Venous return of blood to the heart
- Blood volume
- RAAS

**Reduce Afterload**
- Arteries
- Regulate SNS
- RAAS
At Risk for Heart Failure

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF.
- Hypertension
- Atherosclerotic disease
- Diabetes
- Obesity
- Metabolic syndrome
- Patients with cardiovascular risk factors or family history of HF

**STAGE B**
Structural heart disease but without signs or symptoms of HF.
- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic valvular disease

**THERAPY**
- **GOALS**
  - Treat hypertension
  - Encourage smoking cessation
  - Treat lipid disorders
  - Encourage regular exercise
  - Discourage alcohol intake, illicit drug use
  - Control metabolic syndrome
- **DRUGS**
  - ACEI or ARB in appropriate patients (see text)

**STAGE C**
Structural heart disease with prior or current symptoms of HF.
- Known structural heart disease
- Shortness of breath and fatigue, reduced exercise tolerance

**THERAPY**
- **GOALS**
  - All measures under Stage A and B
  - Dietary salt restriction
- **DRUGS FOR ROUTINE USE**
  - Diuretics for fluid retention
  - ACEI
  - Beta-blockers
- **DRUGS IN SELECTED PATIENTS**
  - Aldosterone antagonist
  - ARBs
  - Digitalis
  - Hydralazine/nitrates
- **DEVICES IN SELECTED PATIENTS**
  - Biventricular pacing
  - Implantable defibrillators

**STAGE D**
Refractory HF requiring specialized interventions.
- Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

**THERAPY**
- **GOALS**
  - Appropriate measures under Stages A, B, C
  - Decision re: appropriate level of care
- **OPTIONS**
  - Compassionate care, end-of-life care/hospice
  - Extraordinary measures
    - Heart transplant
    - Chronic inotropes
    - Permanent mechanical support
    - Experimental surgery or drugs
ACEI & ARBS

**REDUCE PRELOAD**
- Reduced aldosterone release
- Dilate veins (long-term use effect)

**REDUCE AFTERLOAD**
- Relaxation of arterial smooth muscle

**PREVENT/REVERSE REMODELING**
- Decrease in SNS tone
  - EPI causes fibrotic processes in the heart
- Angiotensin II receptors in the heart cause hypertrophy
- Angiotensin I receptors in the heart
Three beta blockers have been studied to show decrease in morbidity and mortality with their use in heart failure

- Metoprolol succinate
- Cavedilol
- Bisoprolol

**How BB work in HF**

- Caution – may reduce cardiac output
- Decreased concentrations of catecholamines
  - Upregulation of beta receptors
  - Decrease heart rate
  - Decreased hypertrophy & remodeling

**ADRs**

- Bronchial constriction
- Reduced cardiac output
  - Ventricular failure
- Fatigue
- Reduced exercise tolerance
- Unpleasant dreams, insomnia, depression
- Deleterious effect on lipid panel
- Withdrawal - taper
DIURETICS

Thiazide
- Mild HF

Loop
- Marked fluid retention
  - Edema of lungs & limbs

PS
- Adjunct
  - Increase diuresis
  - Correct electrolyte imbalance

Therapeutic effects in HF treatment (thiazide & loops)
- Reduce preload
- Reduced blood volume
- Reduce cardiac size

Potassium Sparing
- Reduce morbidity & mortality
- Reduction in aldosterone action
- All with mod/severe HF
DIGOXIN

Increase the refractory period – negative chronotropic
Decrease conduction velocity – negative dromotropic
Increase contractility of the heart – positive inotropic

Are from PSN effects

Next slide
DIGOXIN

Increase contractility of the heart – positive inotropic

1. The Na/K ATPase pump moves Na against its concentration gradient outside the cell
2. A Ca/Na exchanger allows Na to flow into the cell, in exchange for a calcium (driven by concentration gradient)
3. This creates a charge gradient and maintains a concentration gradient for Ca to follow

UNDER NORMAL CIRCUMSTANCES

- Sodium
- Potassium
- Calcium
DIGOXIN

Increase contractility of the heart – positive inotropic

UNDER NORMAL CIRCUMSTANCES

1. The Na/K ATPase pump is inhibited
2. Less Ca is lost in the Ca/Na exchanger
3. Ca still moves in the cell – higher Ca levels are maintained

WITH DIGOXIN
DIGOXIN — NARROW THERAPEUTIC WINDOW

**Kinetics**
- 65-80% bioavailability
- Distributes well, CNS
- Excreted unchanged by kidneys
  - Dose adjust

**ADRs**
- At high/toxic doses, SNS outflow
- Arrhythmia — too much calcium in heart
- Bigeminy
- AV block
- Ventricular tachycardia
- Ventricular fibrillation
- Diarrhea & vomiting
- CNS — Halos, disorientation & hallucinations
DIGOXIN — EXTRA BEATS

Too much calcium
- Delayed after depolarization
- Potassium increase = more positive resting membrane potential

Normal sinus rhythm
Premature Ventricular Beats (PVB) - bigeminy
Digoxin interacts with the following substances:

- Potassium
  - Hyperkalemia – decreases the effects of digoxin
  - Hypokalemia – Increases the effects of digoxin
- Thiazide and loop diuretics
  - Cause hypokalemia
- Potassium sparing diuretics
  - Cause hyperkalemia
- Calcium supplementation
- Magnesium supplementation

**Antidote = Potassium or anti-digoxin antibody**
DIGOXIN – DIGIFAB CALCULATIONS

Page 514 in your book

For digoxin tablets, oral solution, or intramuscular injection:

\[
\text{Dose (mg)} = \frac{\text{Dose ingested (mg)} \times 0.8}{0.5} \times 38
\]

For digoxin capsules, or IV digoxin:

\[
\text{Dose (mg)} = \frac{\text{Dose ingested (mg)}}{0.5} \times 38
\]

When the amount of digoxin ingestion is unknown and the steady-state serum level is unavailable, 760 mg of digoxin immune Fab (ovine) is usually administered because it is reportedly sufficient to treat most life-threatening ingestions. A common strategy is to administer 380 mg and observe for client response, with an additional 380 mg administered if needed.
HYDRALAZINE - VASODILATOR

Therapeutic effects

Dilated arteries (reduce afterload)
Reduce remodeling – long-term effect
Increase cardiac output

Used in patients with
- High peripheral vascular resistance
- Low ventricular output

ADRs

Headache
Nausea
Palpitations
Lupus like symptoms
- Arthralgia, myalgia, skin rash
Fever
Peripheral neuropathy
NITRATES - ISOSORBIDE DINITRATE

**Therapeutic effects**

- Dilated veins (reduce preload)
- Reduce remodeling – long-term effect

**Used in patients with:**
- High ventricular filling pressure
- Pulmonary congestion & SOB

**ADRs**

- Headache
- Orthostatic hypotension
- Tachycardia
NESIRITIDE

Non-selective dilation of vessels

Brain Natriuretic Peptide (BNP)

What is BNP
- Substances released in HF patients to attempt to balance the activation of the RAAS system

What does BNP (with ANP in the body) do?
- Natriuresis
- Diuresis
- Vasodilation
- Decreased aldosterone
- Decreased hypertrophy
- Inhibition of SNS and RAAS
NISIRITIDE

Uses/ADRs

Uses:
- Reduce preload and afterload
- Acute decompensated heart failure

ADRs:
- Severe hypotension
- Ventricular arrhythmias
- Renal damage

Kinetics

Used as continuous IV infusion – very short half life

Metabolized by vascular enzymes and excreted in the urine
QUESTIONS