Cardiovascular System & Its Diseases

Lecture #4
Heart Failure & Cardiac Arrhythmias

Dr. Derek Bowie,
Department of Pharmacology & Therapeutics,
Room 1317, McIntyre Bldg, McGill University
derek.bowie@mcgill.ca
Cardiovascular System & Its Diseases:

Congestive Heart Failure

Pathophysiology: What Is It?

“Chronic or acute state resulting from failure of the heart to meet oxygen demands of the body”

Underlying Problems:

Left Ventricular Dysfunction (original explanation)
(i.e. failure to pump / hemodynamic model, treat with positive inotropic agents)

Neuroendocrine Activation (now included)
(prevent or delay re-modeling)
Pathophysiology: What Is It?

Progressive and highly lethal disease state that may follow:

- Uncontrolled Hypertension
- Diabetes
- Myocardial Infarction
- Valve Dysfunction
- Viral Myocarditis
- Other Conditions
Congestive Heart Failure

Pathophysiology: Classification

Clinical Congestive Heart Failure
(New York Heart Association)

Class I: Failure is associated with no limitations on ordinary activities and symptoms but are revealed during exercise.

Class II: Characterized by slight limitation on ordinary activity resulting in fatigue and palpitations

Class III: No symptoms at rest but fatigue etc with less than ordinary physical activity

Class IV: Associated with symptoms even at rest
Cardiovascular System & Its Diseases:

Congestive Heart Failure

Pathophysiology: Disease Progression

**Primary Effects** (Hemodynamic Model):
- Reduced Cardiac Output
- Excessive Sympathetic Discharge
- Salt & Water Retention

Pharmacological Intervention Useful

**Long-term Effects** (Neuroendocrine Activation):
- Remodeling
- Cardiac Hypertrophy
- Cardiac Apoptosis

Reaching An Endpoint Stage
Cardiovascular System & Its Diseases:

**Congestive Heart Failure**

**Pathophysiology:** Cardiac Output

**Determined By Several Factors**

**Preload:** *(Atrial Pressure)* Increased in heart failure due to increased blood volume and venous tone **Treated with salt restriction and diuretics**

**Afterload:** *(Vascular Resistance)* Increased due to reflex sympathetic outflow and renin-angiotensin system though elevated **afterload** may further reduce cardiac output **Reduction of arterial tone**

**Contractility:** Reduction in intrinsic contractility and therefore reduction in pump performance **Inotropic drugs to increase contractility**

**Heart Rate:** Increases through sympathetic NS compensation
Pathophysiology: Depression of Ventricular Performance

*Increase in atrial pressure during HF leads to reduced pump function*

Ventricular Performance

Preload
Cardiovascular System & Its Diseases:

Congestive Heart Failure

Pathophysiology: Compensatory Responses

Figure 13-2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.
# Cardiovascular System & Its Diseases:

## Congestive Heart Failure

### THERAPEUTIC OVERVIEW

| PROBLEM | Force of contraction ↓  
|         | Ventricular dilatation  
|         | Cardiac output ↓  
|         | Total peripheral resistance ↑  
|         | Venous pressure ↑  
|         | Development of edema  
|         | Tissue perfusion ↓  
|         | Exercise tolerance ↓  
| GOAL    | Reverse signs and symptoms of heart failure, improve quality of life  
|         | Arrest ventricular remodeling  
|         | Increase survival  
| NONDRUG THERAPY | Cardiac work reduction through rest and salt restriction  
| DRUG THERAPY | Diuretics  
|             | Vasodilators  
|             | ACE inhibitors  
|             | Positive inotropic drugs:  
|             | Cardiac glycosides  
|             | Sympathomimetics  
|             | Phosphodiesterase inhibitors  
|             | β-Blockers |
Congestive Heart Failure

Pharmacological Intervention: Overview of Drug Strategy

Figure 3-4. Pathophysiologic processes and drug targets in heart failure. Activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system initially compensates for diminished cardiac performance but thereafter accelerates the process of cardiac failure. Drugs that interfere with these compensatory responses are useful in therapy. β-blockers probably have several additional sites of action.
Pharmacological Intervention: **Positive Inotropic Drugs**

**Drugs:** Cardiac Glycosides (e.g. Digoxin*) steroidal molecules from digitalis and other plants

**Mechanism:** Block Na⁺ / K⁺-ATPase positive inotropic effect

  Cardiac parasympathetic effect slow AV conduction, useful in atrial fibrillation

**Indications:** Primarily for Heart Failure

  Atrial Fibrillation

**Side-effects:** Very Toxic

  Cause Cardiac Arrhythmias

  GI upset

  Neuroendocrine effects rare
Pharmacological Intervention: Positive Inotropic Drugs

- **Digoxin block of Na⁺/K⁺ ATPase**
  - Less expulsion of cytosolic Ca²⁺ by Na⁺/Ca²⁺ exchanger
  - Increased elevation cytosolic Ca²⁺ from sarcoplasmic reticulum
  - Increased Contractility
Figure 13-5. Effects of a cardiac glycoside, ouabain, on isolated cardiac tissue. The top tracing shows action potentials evoked during the control period, early in the "therapeutic" phase, and later, when toxicity is present. The middle tracing shows the light (L) emitted by the calcium-detecting protein aequorin (relative to the maximum possible, $L_{max}$) and is roughly proportionate to the free intracellular calcium concentration. The bottom tracing records the tension elicited by the action potentials. The early phase of ouabain action (A) shows a slight shortening of action potential and a marked increase in free intracellular calcium concentration and contractile tension. The toxic phase (B) is associated with depolarization of the resting potential, a marked shortening of the action potential, and the appearance of an oscillatory depolarization, calcium increment, and contraction (arrows). (Unpublished data kindly provided by P Hess and H Gil Wier.)
Pharmacological Intervention: Diuretics

**Drugs:** Diuretics (e.g. Furosemide)

**Mechanism:** Lower blood volume

**Indications:** Useful in almost all Heart Failure patients

- Loop diuretics: Furosemide, acute pulmonary edema & severe, chronic heart failure
- Thiazides: Hydrochlorothiazide, Mild chronic failure
- Spironolactone: Aldosterone antagonist

**Side-effects:** Hypokalemia
Pharmacological Intervention: Angiotensin Antagonists

- **Drugs:** ACE inhibitors (e.g. Captopril) & Receptor Antagonists (e.g. Losartan)

- **Mechanism:** Reduce Angiotensin II synthesis
  - ACE inhibitors
  - Block AT1-type receptors
  - Angiotensin receptor inhibitors

- **Indications:** First line agents (with diuretics) in Heart Failure
  - AT1-type antagonists used if ACE inhibitors are not tolerated

- **Side-effects:** Renal Damage
  - ACE inhibitors
  - Contraindicated in Pregnancy
  - AT1 antagonists
Pharmacological Intervention: Other Drugs

**Congestive Heart Failure**

- **β-Blockers**: Metoprolol, prolong life in chronic heart failure
  - Mechanism unknown may involve reduced renin secretion

- **β-Agonists**: Dobutamine, β1 selective for severe heart failure
  - Increases cardiac force, reduces afterload result of increasing cardiac output

- **Phosphodiesterase Inhibitors**: Theophylline, acute decompensation in HF
  - Increases cAMP levels in cardiac and vascular tissue

- **Vasodilators**: Nitroglycerin, acute decompensation in Heart Failure
  - Reduce afterload (increasing ejection fraction) and preload (reduce myocardial $O_2$ requirement)
Cardiovascular System & Its Diseases:

**Congestive Heart Failure**

**Pharmacological Intervention:** Summary of Drug Strategy

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Drugs</th>
<th>Beneficial Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic failure (oral)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Thiazides, furosemide,</td>
<td>Reduced preload, afterload; spironolactone, reduced aldosterone effects</td>
</tr>
<tr>
<td></td>
<td>spironolactone</td>
<td></td>
</tr>
<tr>
<td>Cardiac glycoside</td>
<td>Digoxin</td>
<td>Positive inotropic effect</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Hydralazine, isosorbide</td>
<td>Reduced preload, afterload</td>
</tr>
<tr>
<td></td>
<td>dinitrate</td>
<td></td>
</tr>
<tr>
<td>Angiotensin antagonists</td>
<td>Captopril, losartan</td>
<td>Reduced remodeling, preload, afterload, apoptosis</td>
</tr>
<tr>
<td>β blockers</td>
<td>Carvedilol, metoprolol</td>
<td>Reduced afterload, reduced remodeling, apoptosis</td>
</tr>
<tr>
<td><strong>Acute failure (parenteral)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide</td>
<td>Reduced pulmonary vascular pressures, preload</td>
</tr>
<tr>
<td>β₁ Agonists</td>
<td>Dobutamine</td>
<td>Increased cardiac force, output</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Nitroprusside, nitroglycerin</td>
<td>Reduced preload, afterload</td>
</tr>
</tbody>
</table>
Back To Basics: Cardiac Electrophysiology

Cardiac Arrhythmias

SA Node:
Small collection of cells that initiate atrial systole

AV Node:
1. Provides delay in impulse transmission
2. Protects ventricles from atrial fibrillation

Bundle of His:
1. Divides R and L bundles
2. Provides orderly depolarization of ventricles

P wave:
atrial Systole

PR interval:
delay at AV node

QRS complex:
Ventricular systole

T wave:
ventricular repolarization
Figure 14–3. Schematic diagram of the ion permeability changes and transport processes that occur during an action potential and the diastolic period following it. The size and weight of the arrows indicate approximate magnitudes of the ion channel currents. Multiple subtypes of potassium and calcium currents, with different sensitivities to blocking drugs, have been identified.
Cardiovascular System & Its Diseases:

Cardiac Arrhythmias

Back To Basics: Ion Channels Adopt Different Conformational States

Similar functional behavior is also found with $K^+$ and $Ca^{2+}$ channels
Cardiovascular System & Its Diseases:

Cardiac Arrhythmias

Pathophysiology: Aetiology

Two main causes:
(i) Abnormal Pacemaker Activity
(ii) Cardiac Conduction
(iii) Or Both

Risk Factors:
Ischemia, Hypoxia, Acidosis/Alkalosis, Electrolyte Abnormalities
Excessive Catecholamine Exposure, Autonomic Influences,
Drug Toxicity (e.g. antiarrhythmic drugs), Scarred/Diseased Tissue

Treatment:
(i) Electrical Devices pacemakers, defibrillators
(ii) Electrical ablation of abnormal pathways
(iii) Drug Treatment
Cardiovascular System & Its Diseases:

Cardiac Arrhythmias

Pathophysiology: Impulse Formation

3 Ways Of Slowing Normal Pacemaker Activity

1. More Negative Diastolic Potential (e.g. open K+ channels)
2. Reduction Of Diastolic Depolarization (e.g. block Na+ or Ca2+ channels)
3. More Positive Threshold Potential (e.g. shift voltage sensitivity)
Cardiovascular System & Its Diseases:

Cardiac Arrhythmias

**Pathophysiology:** Abnormal Pacemaker Activity

**Early Afterdepolarization**
(Often occur at slow heart rate)

**Delayed Afterdepolarization**
(occur at fast heart rates)
Cardiovascular System & Its Diseases:

Cardiac Arrhythmias

Pathophysiology: Disturbance Of Cardiac Conduction

Re-entry is a common disturbance of conduction
Pharmacological Intervention: Summary Of Drug Types

Cardiac Arrhythmias

Antiarrhythmic Drugs are divided into five groups:

**Class I:** Na\(^+\) channel blockers (e.g. Quinidine)

**Class II:** β-Blockers (e.g. Propanolol)

**Class III:** I\(_{Kr}\) channel blockers (e.g. Sotalol)

**Class IV:** L-type Ca\(^{2+}\) channel blockers (e.g. Verapamil)

**Class V:** Miscellaneous including adenosine, K\(^+\) and Mg\(^{2+}\) ions

*** Anti-arrhythmic drugs have a very low therapeutic index and can provoke arrhythmias and heart failure. Recent trial showed that prophylactically treated patients had 2.5 fold increase in mortality than placebo patients ***
Cardiovascular System & Its Diseases:

**Cardiac Arrhythmias**

**Pharmacological Intervention: Mechanism of Action**

**Class I: Na\(^+\) channel blockers**

IA: slow intraventricular conduction (increase QRS) & increase ventricular AP (increase QT)

IB: selective for abnormal tissue

IC: slow intraventricular conduction only

**Class II: \(\beta\)-Blockers** (e.g. Propanolol)

Slow AV conduction and prolong PR interval

**Class III: \(I_{Kr}\) channel blockers** (e.g. Sotalol)

Prolong ventricular AP therefore prolong PR interval

**Class IV: L-type Ca\(^{2+}\) channel blockers** (e.g. Verapamil)

Slow AV conduction & prolongs PR interval

**Class V: Miscellaneous** including adenosine, K\(^+\) and Mg\(^{2+}\) ions
Francoise Laplante is a 63 year old bank executive who complains of difficulty sleeping and difficulty climbing stairs because of easy fatigue and shortness of breath.

She is not sleeping well. Her personal history reveals that she has smoked 15 cigarettes per day since she was a teenager and she has one or 2 glasses of wine per day. Her family history is unremarkable save for type II diabetes and obesity in her mother and one sister. Her past history includes essential hypertension and an anterior wall myocardial infarction at age 59.

Identify the Risk Factors of Cardiovascular Disease?
Francoise Laplante is a 63 year old bank executive who complains of difficulty sleeping and difficulty climbing stairs because of easy fatigue and shortness of breath.

She is not sleeping well. Her personal history reveals that she has smoked 15 cigarettes per day since she was a teenager and she has one or 2 glasses of wine per day. Her family history is unremarkable save for type II diabetes and obesity in her mother and one sister. Her past history includes essential hypertension and an anterior wall myocardial infarction at age 59.

Risk Factors:
Smoking, Older Age, Diabetes, Family History, Hypertension & Myocardial infarction
Congestive Heart Failure

Case Study

Current medication includes metoprolol 50 mg twice daily and hydrochlorothiazide 25 mg daily, metformin 1000 mg twice daily and insulin 20 units at bed time.

Physical exam reveals a tired looking woman with BP 140/80 mm Hg, P 60 beats/min and regular and respiratory rate 22/minute. Jugular venous pressure is elevated and there are crackles heard at both lung bases plus ankle edema. Echocardiography shows no valve disease, enlarged dilated left ventricle and a decreased ejection fraction.

Identify the drugs being used?

What do the symptoms indicate?
Cardiovascular System & Its Diseases:

Congestive Heart Failure

Case Study

Current medication includes metoprolol 50 mg twice daily and hydrochlorothiazide 25 mg daily, metformin 1000 mg twice daily and insulin 20 units at bed time.

Physical exam reveals a tired looking woman with BP 140/80 mm Hg, P 60 beats/min and regular and respiratory rate 22/minute. Jugular venous pressure is elevated and there are crackles heard at both lung bases plus ankle edema. Echocardiography shows no valve disease, enlarged dilated left ventricle and a decreased ejection fraction.

Drugs being used:
Metoprolol (β-blocker); Hydrochlorothiazide (diuretic)
Metformin (oral hypoglycemic); Insulin

What do the symptoms indicate:
Venous distension, edema of lungs & ankles indicate volume overload Heart Failure Patient!
The patient is started on captopril 5 mg twice daily and furosemide 40 mg daily and the hydrochlorothiazide is discontinued. One week later she reports that she is moderately improved and able to sleep at night. Her ankle swelling is improved.

Identify the drugs being used?

Why was hydrochlorothiazide stopped?
The patient is started on captopril 5 mg twice daily and furosemide 40 mg daily and the hydrochlorothiazide is discontinued. One week later she reports that she is moderately improved and able to sleep at night. Her ankle swelling is improved.

Identify the drugs being used:
- Captopril (ACE inhibitor), furosemide (loop diuretic)

Cessation of hydrochlorothiazide: Ineffective
Identify the drugs being used?

What do the symptoms indicate?

She does very well for the next 18 months but once again develops shortness of breath with minimal exertion and is found to have developed atrial fibrillation, basilar lung crackles and ankle edema.

Her treatment is altered to include digoxin and larger doses of furosemide. Small doses of diltiazem are later added to improve heart rate control and improved blood pressure control.
Congestive Heart Failure

Case Study

She does very well for the next 18 months but once again develops shortness of breath with minimal exertion and is found to have developed atrial fibrillation, basilar lung crackles and ankle edema.

Her treatment is altered to include digoxin and larger doses of furosemide. Small doses of diltiazem are later added to improve heart rate control and improved blood pressure control.

Identify the Drugs:
- Digoxin (improves contractility) & Diltiazem (Ca channel blocker)

What do the symptoms indicate:
- Further deterioration of Heart Failure
## Overview of Lecture Series

<table>
<thead>
<tr>
<th>1. Cardiovascular System</th>
<th>Bits ‘N’ Pieces</th>
<th>Blood, Heart, Blood-Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Keeping It Under Control</td>
<td>Heart Rate, Blood Pressure</td>
</tr>
<tr>
<td></td>
<td>When Things Go Wrong</td>
<td>Hypertension, Heart Failure, Arrhythmias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Hypertension</th>
<th>Aetiology</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Sympatheplegic Drugs, Diuretics, Vasodilators, Angiotensin Antagonists</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Myocardial Ischemia</th>
<th>Aetiology</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Symptomatic: Nitrites, Calcium Channel Blockers, β-Blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic: Lipid lowering, Anti-coagulant, Anti-platelet drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Heart Failure &amp; Cardiac Arrhythmias</th>
<th>Aetiology</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Heart Failure: Nitrites, Calcium Channel Blockers, Diuretics, Angiotensin Antagonists, β-Blockers, b-Receptor Agonist, Cardiac Glycosides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmias: Channel Blockers (Groups I – IV), Miscellaneous</td>
</tr>
</tbody>
</table>