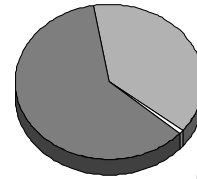


Treatment of Congestive Heart Failure

Michael A. Oszko, Pharm. D.

Hospitalization: The Predominant Contributor to Heart Failure Costs

60.6%
Hospitalization
\$23.1 billion



38.6%
Outpatient Care
\$14.7 billion
(3.4 visits/year /patient)

0.7%
Transplants
\$270 million

Total = \$38.1 billion
(5.4% of total healthcare costs)

O'Connell JB et al. *J Heart Lung Transplant.* 1994;13:S107-S112.

Heart Failure Definition

"The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return."

E. Braunwald

Epidemiology

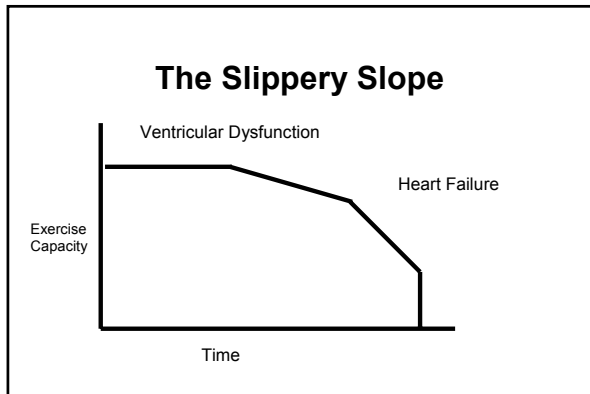
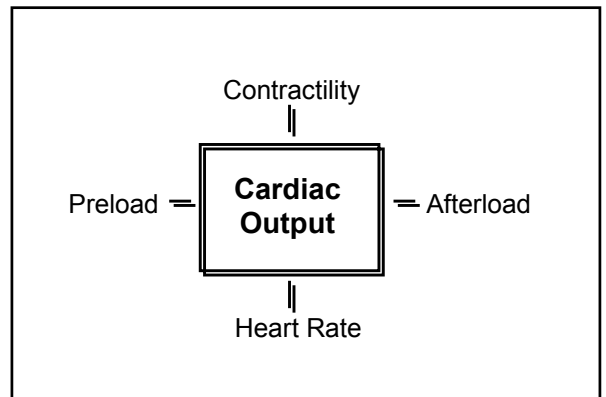
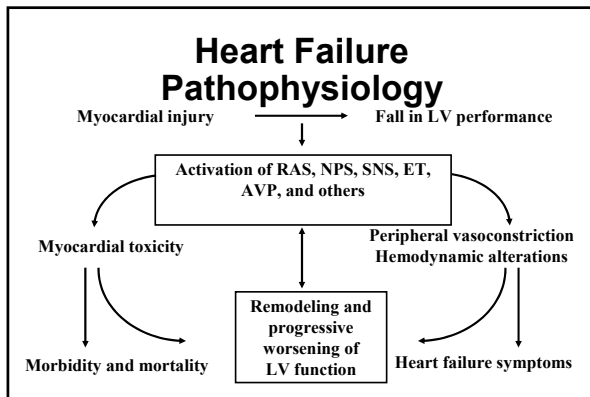
- ◆ Incidence - 400,000 new cases/yr
- ◆ Prevalence - 3-4 million
- ◆ 2 million hospitalizations
- ◆ Est. \$18-56 billion annually
- ◆ Survival
 - ❖ 1 year - 79-86% (50% w/ class IV)
 - ❖ 5 year - 38-57%

Hospitalization and Heart Failure

- ◆ Major public health problem
- ◆ Most frequent cause of hospitalization in patients older than 65 years
- ◆ Fourth leading cause of adult hospitalization in U.S.
- ◆ DRG 127 (heart failure):
 - ❖ Primary diagnosis ≈1,000,000 hosp/yr
 - ❖ Secondary diagnosis ≈2,000,000 hosp/yr
- ◆ Associated with high readmission rates

Terminology

- ◆ High vs. Low Output
- ◆ Acute vs. Chronic
- ◆ Left vs. Right-sided
- ◆ Systolic vs. Diastolic



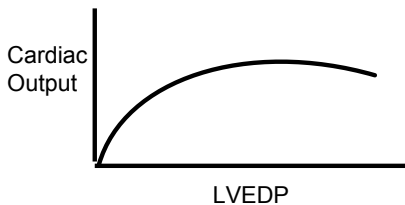
- ### Congestive Heart Failure Compensatory Mechanisms
- Frank-Starling Phenomenon
 - Increased Sympathetic Tone
 - Activation of RAS
 - Myocardial Hypertrophy

- ### NYHA Functional Classes
- ◆ I - No sx w/ physical activity
 - ◆ II - Slight limitation with ordinary activity
 - ◆ III - Marked limitation with less than ordinary activity
 - ◆ IV - Sx at rest

Frank-Starling Phenomenon

For any given ventricular state, the force of contraction is increased (up to a limit) when ventricular end-diastolic fiber length is stretched by increasing filling pressure.

Frank - Starling Curve



Diagnosis of CHF— Still Very Difficult (cont'd)

- ◆ Tests such as echocardiograms are expensive (>\$500.00)

Until now there has been no single blood test that differentiates a patient with heart failure from a patient without heart failure.

Compensation Mechanisms

- ◆ Sympathetic NS activation
- ◆ Ventricular dilation
- ◆ Ventricular hypertrophy
- ◆ RAAS activation

Assessment of Severity and Progression of CHF

- ◆ Symptoms do not correlate well with left ventricular dysfunction or with prognosis
- ◆ Many “markers” are elevated in CHF (cytokines, catecholamines, etc.) but are not useful in assessing severity or following progression:
 - ❖Wide variability in values
 - ❖Difficult to measure
 - ❖Not often elevated until CHF is severe

Diagnosis of CHF— Still Very Difficult

- ◆ Symptoms and signs like shortness of breath and edema have a broad differential diagnosis
- ◆ Physical exam is neither sensitive nor specific for CHF and, even in good hands, there are often errors
- ◆ One third of patients with CHF have normal pumping function of the heart

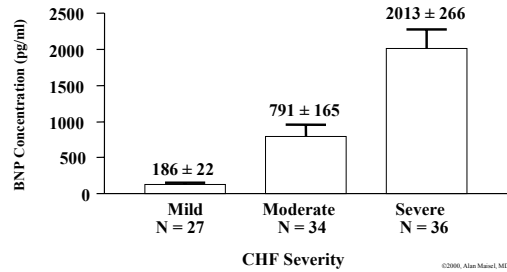
B-Type Natriuretic Peptide (BNP)

- ◆ Found only in the cardiac ventricles
- ◆ Released in response to stretch and increased volume in the ventricle
- ◆ BNP levels correlate with:
 - ❖Left ventricular end-diastolic pressure
 - ❖NYHA classification
 - ❖Objective CHF diagnosis in patients 55 or older

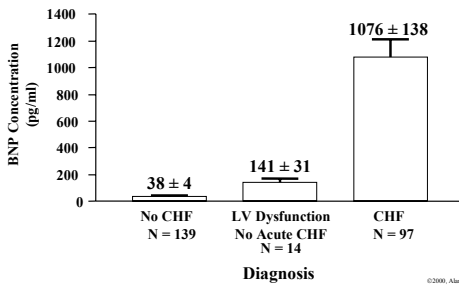
B-Type Natriuretic Peptide (BNP) Assay

- ◆ Completely automatic
- ◆ Uses 2 cc's of whole blood
- ◆ Gives reproducible results within 15 minutes
- ◆ Small enough to use at the bedside, in the emergency room, or in any point-of-care laboratory

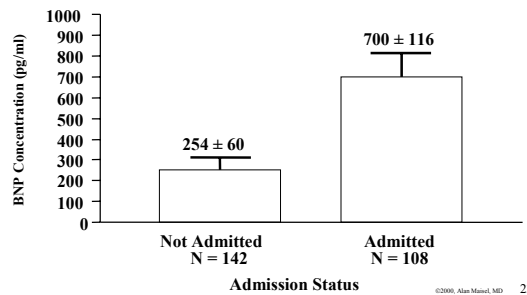
BNP Concentration for the Degree of CHF Severity



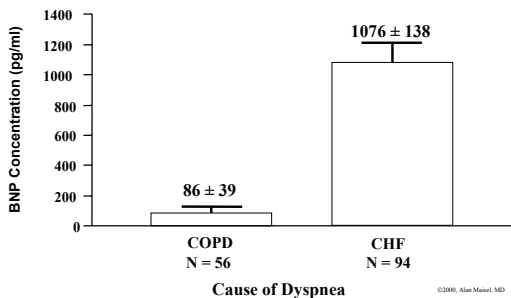
BNP Levels of Patients Diagnosed Without CHF, With Baseline Left Ventricular Dysfunction, and With CHF



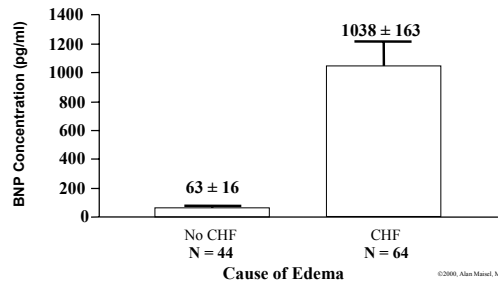
Hospital Admission vs BNP



BNP Levels in Patients With Dyspnea Secondary to CHF or COPD



BNP Levels in Patients With Edema Diagnosed With or Without CHF



Treatment Goals

- ◆ Reduce or eliminate symptoms
- ◆ Improve quality of life
- ◆ Prolong survival

Congestive Heart Failure Diuretics

- “First-line” agents
- Symptomatic relief
- Unproven benefit
- Agent selection?

Treatment Objectives

- Reduce Cardiac Workload
- Enhance Myocardial Contractility
- Control Excessive Na/H₂O Intake
- Interrupt compensatory mechanisms

Diuretics

- ◆ Thiazides - not useful in CHF
- ◆ Loop diuretics
 - ❖ Bumetanide
 - ❖ Furosemide
 - ❖ Torsemide
- ◆ Metolazone
- ◆ Potassium sparing
 - ❖ Spironolactone

Congestive Heart Failure Nonpharmacological Treatment

- Sodium Restriction
- Restricted Activity
- Cardiac Rehabilitation

Diuretics Clinical Pearls

- ◆ Dose = “whatever it takes” to produce a diuresis
- ◆ Metolazone prior to loop
- ◆ BID dosing: what does “BID” mean?

Diuretics

Resistance

- Reduced Renal Function
- Hypochloremia
- NSAID's
- Gut Edema

Digoxin

- ◆ Positive chronotropic and inotropic agent
- ◆ Efficacy
 - ❖ No effect on mortality
 - ❖ Decreases hospitalizations

Diuretics

Monitoring

- Patient's Observation
- Potassium, Magnesium
- Glucose

Digoxin

Key Points

- Do not "Overdo" It
- Renally Eliminated
- Dependent on LBW
- Do not Depend on Serum Levels
- Remember Drug Interactions
- Watch electrolytes carefully

Aldosterone Antagonists

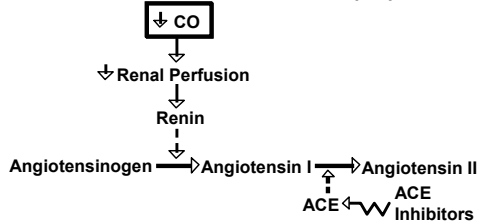
- ◆ Spironolactone (Aldactone)
- ◆ Eplerenone (Inspra)
 - ❖ Brand-new!
- ◆ Both are 25-50 mg qd
- ◆ Indications are different

ACE Inhibitors

Results of MOA

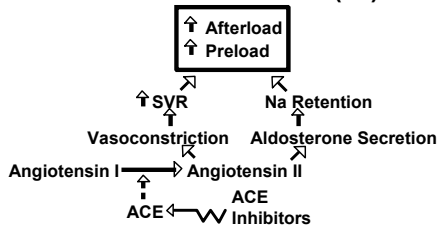
- Less Sodium/Water Retention
- Less Arterial Vasoconstriction
- Potassium Retention
- Lower Renal Perfusion Pressure

ACE Inhibitors Mechanism of Action (1a)

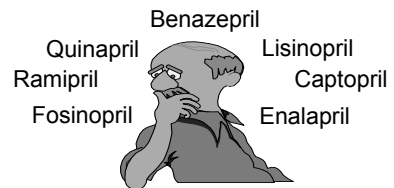


ACE Inhibitors Have Revolutionized the Treatment of CHF

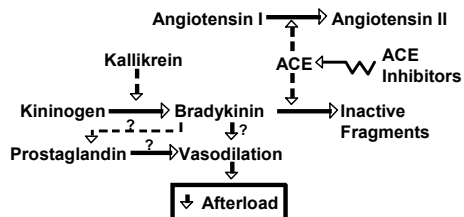
ACE Inhibitors Mechanism of Action (2a)



ACE Inhibitors Agent Selection



ACE Inhibitors Mechanism of Action (3a)



ACE Inhibitors Adverse Effects

- ◆ Renal Insufficiency
- ◆ Hyperkalemia
- ◆ Hypotension
- ◆ Cough
- ◆ Rash

Angiotensin II Antagonists

- ◆ Like ACE-I, affects the RAAS
- ◆ Efficacy in CHF? Too early to tell
 - ❖ ELITE: Losartan decreased mortality more than captopril
 - ❖ ELITE II - No significant differences, but fewer ADRs with losartan

Beta Blockers Differences

- ◆ β_1 Selectivity
- ◆ ISA
- ◆ α_1 Blocking Activity
- ◆ Carvedilol (Coreg)

Congestive Heart Failure Vasodilators

- Hydralazine + ISDN Reduces Mortality
- Second-line Agents After ACE Inhibitors
- Alpha-1 antagonists have no value

Aldosterone Antagonists

- ◆ Spironolactone (Aldactone)
- ◆ Eplerenone (Inspra)



Congestive Heart Failure Calcium Channel Blockers

- For the Most Part, AVOID
- Amlodipine demonstrates some promise
 - No indication for CHF
 - May be used if another indication for a CCB exists (e.g. HTN, CAD)

Spironolactone

- ◆ NEJM 9/2/99
- ◆ Aldosterone antagonist
- ◆ 30% reduction in total & cardiac mortality, and hospitalizations
- ◆ Dose 25-50 mg qd
- ◆ Many indications
- ◆ Cautions: hyperkalemia
- ◆ ADR: gynecomastia

Eplerenone

- ◆ www.inspra.com
- ◆ Aldosterone antagonist
- ◆ Different indications
 - ❖ CHF post MI
 - ❖ Hypertension
- ◆ Cautions: hyperkalemia
- ◆ ADR: gynecomastia
- ◆ Dose: 25-50 mg qd

Adjunctive Therapy

- ◆ CAD
 - ❖ Nitrates (+/- Hydralazine)
 - ❖ Amlodipine
- ◆ Hyperlipidemia
 - ❖ HMG Co-A reductase inhibitor ("statins")
- ◆ A-fib
 - ❖ Amiodarone

Drug Selection

	NYHA Functional Class			
	I	II	III	IV
ACE-I				
A-II Blocker				
Beta Blocker				
Digoxin				
Diuretic				
Spirolactone				

Drugs to Avoid

- ◆ Calcium-channel blockers
- ◆ Alpha-blockers (doxazosin, terazosin)
- ◆ NSAIDS
- ◆ Type I antiarrhythmics
- ◆ Sympathomimetic agents
- ◆ TCADs

Drug Selection

	NYHA Functional Class			
	I	II	III	IV
ACE-I				
A-II Blocker	+	+	+	+
Beta Blocker	+	+	+	
Digoxin		+/-	+	+
Diuretic		+	+	+
Spirolactone			+	+

Treatment of Atrial Fibrillation

Michael A. Oszko, Pharm.D.

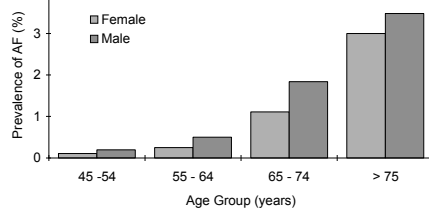
Atrial Fibrillation Background

- ◆ Relatively Common Arrhythmia
- ◆ May be Sustained or Paroxysmal
- ◆ Usually Associated with Another Disorder

Atrial Fibrillation If Not Treated

- Thromboembolic Events
- Worsened CHF
- Reduced Exercise Tolerance
- Angina Pectoris

Atrial Fibrillation Prevalence



Atrial Fibrillation Therapeutic Goals

- Restore NSR/Control VHR
- Avoid Thromboembolism
- Improve Exercise Capacity
- Avoid Medication AE

Atrial Fibrillation Associated Disorders

- ◆ Hypertension
- ◆ Coronary Artery Disease
- ◆ Valvular Heart Disease
- ◆ Congenital Heart Disease
- ◆ Thyrotoxicosis
- ◆ Electrolyte Abnormalities

Atrial Fibrillation Conversion to NSR

- DCC
- Pharmacologic therapy

Atrial Fibrillation Agent Selection

- Digoxin
- Verapamil/Diltiazem
- Beta Blockers
- “Traditional” Antiarrhythmics
- Amiodarone

Atrial Fibrillation Beta Blockers

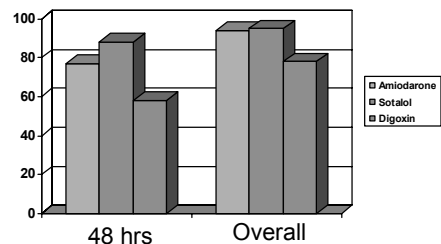
- More Rapid Onset
- Controls Exercise-Induced Increases in HR
- Use Cautiously in CHF
- Many AE’s

Atrial Fibrillation Digoxin

- Slow Onset
- Does Not Control Exercise- Induced Increases in HR
- Safe to Use in CHF
- Low Therapeutic Index

Efficacy

Ann Emerg Med 2000; 36:1-9



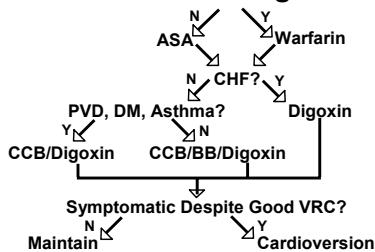
Atrial Fibrillation Calcium Channel Blockers

- More Rapid Onset
- Controls Exercise-Induced Increases in HR
- Use Cautiously in CHF
- Good AE Profile

Atrial Fibrillation Poor Prognosis for NSR

- Recurrent Arrhythmia
- Enlarged Left Atrium
- Arrhythmia Duration > 1 year
- CHF

Candidate for Anticoagulation?



Warfarin

Length of Treatment

- If Remain in AF, then Lifetime
- Cardioversion: 3 Weeks Prior
4 Weeks Post

Warfarin

- ◆ Anticoagulant
- ◆ Vitamin K antagonist
- ◆ Many drug interactions
 - ❖ Protein binding
 - ❖ CYP450 metabolism

Warfarin

Dosage/Monitoring

- Usually Start with 5-10 mg qd x 2-3 d
- Thereafter, Individualize!
- Frequent PT's
- Target INR = 2.0-3.0
- AE : Bleeding

Atrial Fibrillation

Warfarin – Contraindications

- Patient – Poor Compliance
- Patient – Adverse Effect Risk
- Lone AF and < 60 yo

Warfarin

“INR”

- International Normalized Ratio
- Standardizes PT Results Between Institutions (reagents)

$$\text{INR} = \left(\frac{\text{PT}_p}{\text{PT}_c} \right)^{\text{ISI}}$$



Warfarin

Selected Drug Interactions

- **Trimethoprim/Sulfa**
- **Cimetidine**
- **ASA/NSAID's**
- **Antibiotics**
- **Amiodarone**



Warfarin

Patient Education

- **Compliance**
- **Side Effects**
- **Dietary Instructions**
- **Frequent PT's**
- **Drug Interaction**