

Treatment of Congestive Heart Failure

Michael A. Oszko, Pharm. D.

Heart Failure Definition

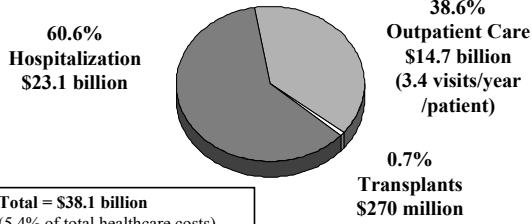
“The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return.”

E. Braunwald

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

Hospitalization: The Predominant Contributor to Heart Failure Costs



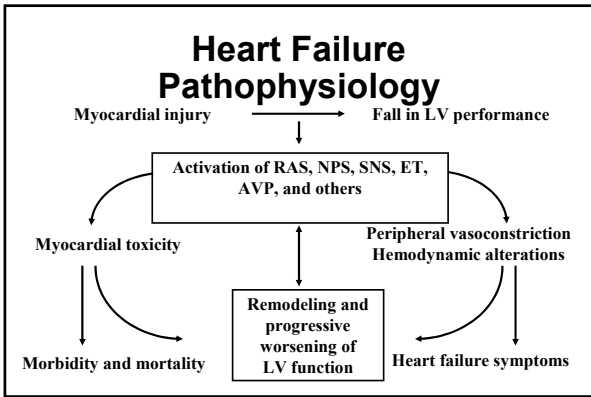
O'Connell JB et al. *J Heart Lung Transplant*. 1994;13:S107-S112.

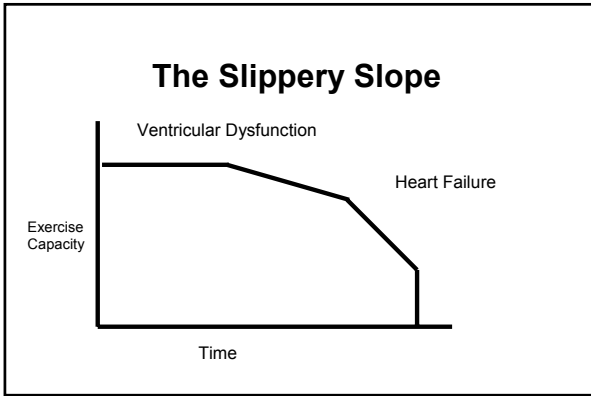
Epidemiology

- ◆ 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%

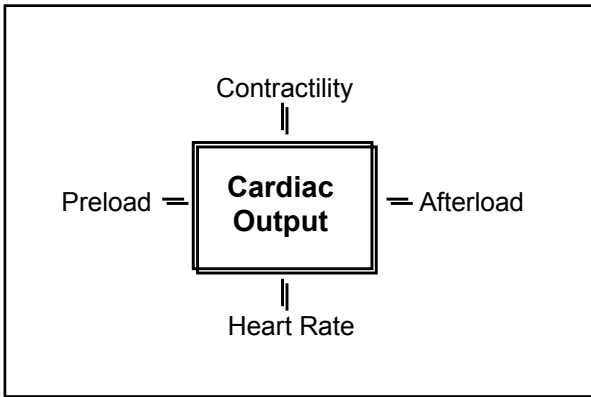
Terminology

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





- ### 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



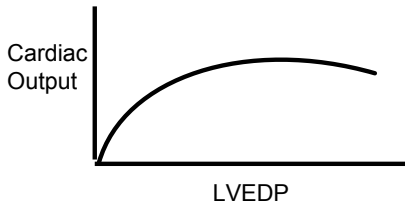
**Congestive Heart Failure
Compensatory Mechanisms**

- Frank-Starling Phenomenon
- Increased Sympathetic Tone
- Activation of RAS
- Myocardial Hypertrophy

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



Compensation Mechanisms

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

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

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.

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

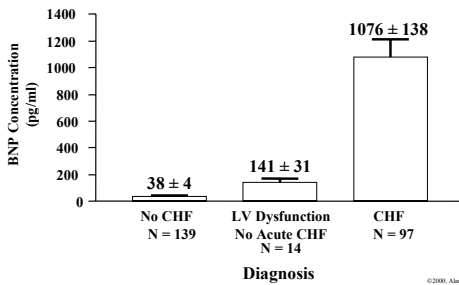
B-Type Natriuretic Peptide (BNP)

- ◆ 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

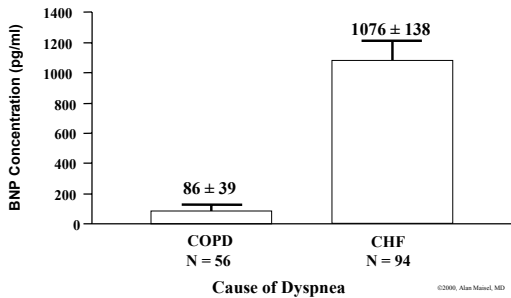
- ◆ Completely automatic
- ◆ Uses 2 cc's of whole blood
- ◆ Gives reproducible results within 15 minutes
- ◆ Small enough to use at the bedside, in the emergency room, or in any point-of-care laboratory

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



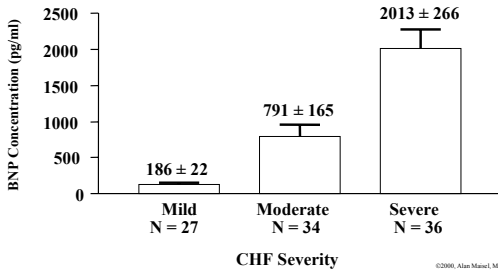
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BNP Levels in Patients With Dyspnea Secondary to CHF or COPD



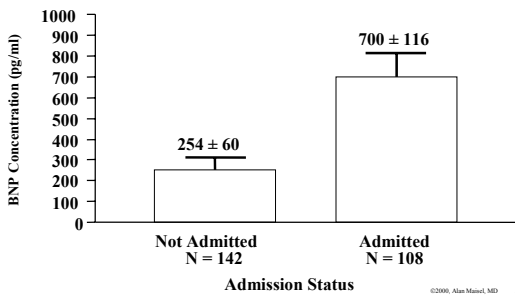
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BNP Concentration for the Degree of CHF Severity



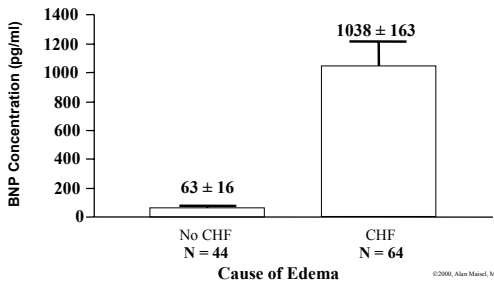
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Hospital Admission vs BNP



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BNP Levels in Patients With Edema Diagnosed With or Without CHF



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Treatment Goals

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

Treatment Objectives

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

Congestive Heart Failure Nonpharmacological Treatment

- Sodium Restriction
- Restricted Activity
- Cardiac Rehabilitation

Congestive Heart Failure

Diuretics

- "First-line" agents
- Symptomatic relief
- Unproven benefit
- Agent selection?

Diuretics

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

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

**Diuretics
Monitoring**

- Patient's Observation
- Potassium, Magnesium
- Glucose

Aldosterone Antagonists

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

Digoxin

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

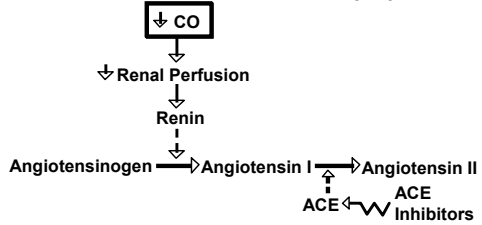
Digoxin Key Points

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

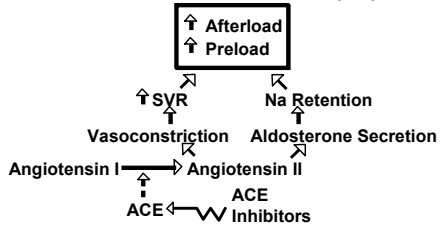
ACE Inhibitors Results of MOA

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

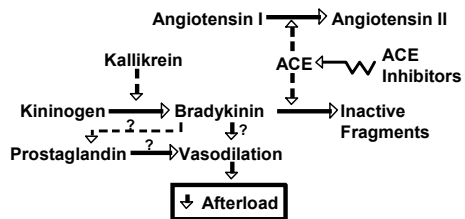
ACE Inhibitors Mechanism of Action (1a)



ACE Inhibitors Mechanism of Action (2a)



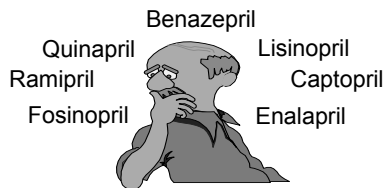
ACE Inhibitors Mechanism of Action (3a)



**ACE Inhibitors
Have Revolutionized
the Treatment
of CHF**



**ACE Inhibitors
Agent Selection**



**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

Congestive Heart Failure Vasodilators

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

Congestive Heart Failure Calcium Channel Blockers

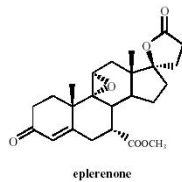
- For the Most Part, AVOID
- Amlodipine demonstrates some promise
 - No indication for CHF
 - May be used if another indication for a CCB exists (e.g. HTN, CAD)

Beta Blockers Differences

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

Aldosterone Antagonists

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



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

Drug Selection

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

Drug Selection

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

Adjunctive Therapy

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

Drugs to Avoid

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

Treatment of Atrial Fibrillation

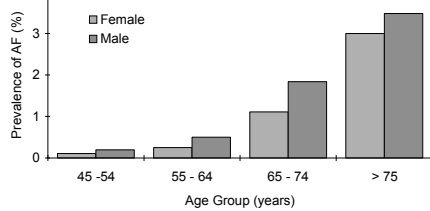


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Atrial Fibrillation Background

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

Atrial Fibrillation Prevalence



Atrial Fibrillation Associated Disorders

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

**Atrial Fibrillation
If Not Treated**

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

**Atrial Fibrillation
Therapeutic Goals**

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

**Atrial Fibrillation
Conversion to NSR**

- DCC
- Pharmacologic therapy

**Atrial Fibrillation
Agent Selection**

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

**Atrial Fibrillation
Digoxin**

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

**Atrial Fibrillation
Calcium Channel Blockers**

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

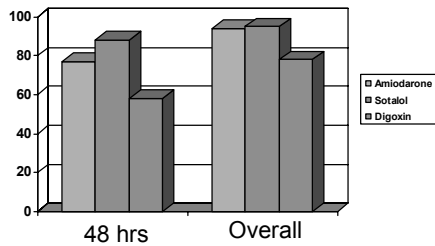
Atrial Fibrillation

Beta Blockers

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

Efficacy

Ann Emerg Med 2000; 36:1-9

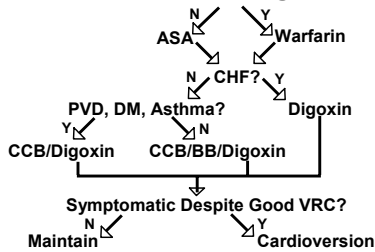


Atrial Fibrillation

Poor Prognosis for NSR

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

Candidate for Anticoagulation?



Warfarin

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



Atrial Fibrillation Warfarin – Contraindications

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



Warfarin

Length of Treatment

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



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

Warfarin

"INR"

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

$$INR = \left(\frac{PT_p}{PT_c} \right)^{ISI}$$



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
