Heart Failure
“A patho-physiological state in which abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the metabolic requirements or to do so only with elevated filling pressures”

“CHF is a clinical syndrome in which heart failure is accompanied by symptoms and signs of pulmonary and/or peripheral congestion”

Should objective evidence of LV dysfunction be required for diagnosis of CHF?
Clinical features: congestive heart failure in USA
Normal contraction: systolic and diastolic dysfunction
Pathology of Heart Failure

**Systolic Dysfunction**

<table>
<thead>
<tr>
<th>Causative Factor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of muscle</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Pressure overload</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Volume overload</td>
<td>Valvular regurgitation</td>
</tr>
<tr>
<td>Decreased contractility</td>
<td>Dilated cardiomyopathy</td>
</tr>
</tbody>
</table>

Peripheral changes in Heart Failure

- Increased systemic vascular resistance
- Venoconstriction
- Decreased baroreceptor responsiveness
- Decreased glomerular filtration rate
- Increased arterial venous O$_2$ difference
- Peripheral edema
Compensatory Mechanisms that can overshoot

- Increased systemic vascular resistance
- Excess tachycardia
- Excess fluid retention
- Excess catecholamine secretion
- Excess rennin-angiotensin

Prognosis in Heart Failure

- In people diagnosed with heart failure, sudden death occurs at 6 to 9 times the rate of the general population

- 5-year mortality rate is 50%

- Median survival following onset is 1.7 years for men and 3.2 years for women

Natural History of CHF

100%

Progression

Further damage
Excessive wall stress
Neurohormonal activation
Myocardial ischemia

Mechanism of Death

Percent Surviving

Sudden death 40%
Worsening CHF 40%
Other 20%

Annual Mortality

<5% 10% 20-30% 30-80%

Asymptomatic Mild Moderate Severe

Left Ventricular Dysfunction and Symptoms

PROGNOSTIC FACTORS IN HEART FAILURE

LV dysfunction
Coronary artery disease
Arrhythmias

Exercise tolerance
Plasma norepinephrine
Serum sodium

Na+
New York Heart Association Functional Classification

I. No limitations of physical activity, no symptoms with ordinary activities
II. Mild/slight limitation, symptoms with ordinary activities
III. Moderate/marked limitation, symptoms with less than ordinary activities
IV. Severe limitation, symptoms of heart failure at rest

Symptoms: Dyspnea or fatigue

Adapted from Criteria Committee of the New York Heart Association, 1994.
Diagnosis of Heart Failure

Signs of Physical Exam – General
- Decrease in blood pressure
- Tachycardia
- Cardiomegaly
- Cool extremities

Signs of Physical Exam – Left Heart Failure
- Rales
- Pleural effusion
- Decreased pulse pressure
- Pulsus alternans
- Abnormal apical impulse
- Decreased heart sounds
- Apical S3
- Mitral regurgitation

Signs of Physical Exam – Right Heart Failure
- Elevated jugular venous pressure
- Hepatojugular reflux
- Hepatomegaly
- Peripheral edema
- Pleural effusion
- Ascites
- Right-sided S3
- Tricuspid regurgitation

Initial Testing: Rule Out Alternative Diagnoses
- CBC (anemia, systemic illness)
- Chemistries (renal or hepatic dysfunction, diabetes)
- Urinalysis (renal disease, nephritic syndrome)
- Thyroid function tests (especially in AF, elderly)
- Arterial O₂ saturation
- ECG
- Chest X ray
- Measurement of LV function (usually echocardiogram)
BNP

- BNP is a 32 amino acid peptide.
- It is released in response to stretch and increased volume in the ventricles.
- Rapid, point of care assay for BNP now available.
- It is helpful in Diagnosis, assessment of severity and prediction of prognosis of CHF patients.

Physiologic Effects of the RAAS and NPS

**RAAS (Renin-Angiotensin Aldosterone System)**

- Activation of AT1 receptors by angiotensin II: Vasoconstriction, Sodium retention, Increased aldosterone release, Increased cellular growth, Increased sympathetic nervous activity

**NPS (Natriuretic Peptide System)**

- ANP, BNP: Sodium excretion, Vasodilation, Decreased aldosterone levels, Inhibition of RAAS, Inhibition of sympathetic nervous activity
The Natriuretic Peptide System is Overwhelmed in Acute Decompensated Heart Failure

Endothelin
Aldosterone
Angiotensin II
Epinephrine

ANP  BNP

BNP Concentration for the Degree of CHF Severity

**BNP Concentration for the Prediction of Clinical Events**

Death or Heart Failure Hospitalization

![Graph showing BNP levels over time for different categories of patients](image)


---

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

![Bar graph showing mean BNP concentrations](image)

General Measures for the Management of Heart Failure

- **Decrease risk of new cardiac injury**
  - Smoking cessation; weight reduction in obese patients; control of BP, lipids, diabetes; Discontinue alcohol use

- **Maintain fluid balance**
  - Moderate salt restriction (≤ 3 grams daily); Daily weight measurement

- **Improve physical conditioning**
  - Moderate exercise to prevent physical deconditioning

- **Avoid**
  - Antiarrhythmic agents to suppress asymptomatic ventricular arrhythmias,
  - Most calcium antagonists, NSAIDs

Approach to the Patient with Heart Failure

Assessment of LV function (echocardiogram, radionuclide ventriculogram)

- EF ≤40%

Assessment of fluid volume status

- Signs and symptoms of fluid retention
  - Diuretic (titrate to euolemic state)
- No signs and symptoms of fluid retention
  - ACE inhibitor
  - β-blocker
  - Digoxin

Steering Committee and Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. Am J Cardiol. 1999;83 9 suppl 2A:IA-7A.
<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Compensated (early) heart failure</th>
<th>Decompensated (late) heart failure</th>
<th>Late heart failure + loop diuretic</th>
<th>Late heart failure + ACE inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF (mL/min/1.73 m²)</td>
<td>750-1200</td>
<td>600-1000</td>
<td>375-600</td>
<td>400-700</td>
<td>500-750</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>90-140</td>
<td>90-140</td>
<td>70-110</td>
<td>75-115</td>
<td>80-120</td>
</tr>
<tr>
<td>FF (%)</td>
<td>17-21</td>
<td>23-27</td>
<td>29-33</td>
<td>27-31</td>
<td>25-29</td>
</tr>
<tr>
<td>U_Na,V (µmol/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U_K,V (µmol/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td>U_Na/V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD0 (ng %)</td>
<td>8-12</td>
<td>8-12</td>
<td>20-40</td>
<td>20-30</td>
<td>10-15</td>
</tr>
<tr>
<td>ANP (pmol/L)</td>
<td>5-10</td>
<td>15-30</td>
<td>25-50</td>
<td>20-40</td>
<td>20-40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Refractory heart failure</th>
<th>Refractory failure + diuretic, ACEI, and spironolactones</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF (mL/min/1.73 m²)</td>
<td>375-600</td>
<td>500-750</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>70-110</td>
<td>80-120</td>
</tr>
<tr>
<td>FF (%)</td>
<td>28-33</td>
<td>25-29</td>
</tr>
<tr>
<td>U_Na,V (µmol/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U_K,V (µmol/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td>U_Na/V</td>
<td></td>
</tr>
<tr>
<td>ALD0 (ng %)</td>
<td>20-40</td>
<td>18-15</td>
</tr>
<tr>
<td>ANP (pmol/L)</td>
<td>25-50</td>
<td>21-40</td>
</tr>
</tbody>
</table>
RALES: Aldosterone receptor blockade improves outcomes in severe heart failure

RALES = Randomized Aldactone Evaluation Study
Diuretic therapy in CHF

• First line therapy in symptomatic CHF
• Produce most rapid symptomatic benefit
• Need not be limited to loop diuretics
• Activate neurohormonal responses
• Induce potassium and magnesium loss

Diuretics: Recommendations

Generally prescribed for all patients with heart failure and past or present history of fluid retention

Should not be used as monotherapy even if symptoms of heart failure are controlled and if patient’s clinical status is stabilized

Should generally be combined with ACE inhibitor and β-blocker

Ultimate goal is to reduce symptoms and eliminate signs of fluid retention through continued treatment

Daily measurement of patient’s weight provides guide to drug dosage and Efficacy

ACE Inhibition: Effect on Renal Function

ACE inhibition reduces angiotension II

Efferent arterial vasoconstriction reversed

GFR reduced

Filtration of BUN and serum creatinine reduced

BUN and serum creatinine levels increase
Effect of ACE inhibition on morbidity and mortality in heart failure patients – an analysis of 32 trials


HOPE: Risk reduction with ACE inhibition

ACE Inhibitors: Recommendations

Use for all patients with heart failure caused by LV systolic dysfunction (with/without HF symptoms) unless contraindicated

Use with diuretics inpatients with present or past history of fluid retention

Use for long-term management, not for stabilizing acutely-ill patients

Initiate at very low doses, followed by gradual dose increments as tolerated

Assess renal function and serum potassium periodically


---

**Some contrasts between angiotensin receptor blockade and ACE inhibition**

<table>
<thead>
<tr>
<th>Principal mechanism of action</th>
<th>ARBs</th>
<th>ACE-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-II vasoconstriction</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma A-II</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Prostaglandin E₂ and prostacyclin</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Nitric oxide release</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Uric acid levels</td>
<td>↓↑</td>
<td>–</td>
</tr>
<tr>
<td>Cough</td>
<td>Not observed</td>
<td>Class specific</td>
</tr>
</tbody>
</table>

---


— = no effect
ELITE II: ARB vs ACEI in heart failure

Val-HeFT: ARB vs usual therapy in heart failure – study overview

ELITE II = Evaluation of Losartan in the Elderly


Val-HeFT = Valsartan in Heart Failure Trial

ACE inhibitors vs ARBs in heart failure: Clinical summary

- Ace inhibitors: Remain the first choice for treatment of patients with heart failure
- Angiotensin receptor blockers: Consider as an alternative for patients who cannot tolerate ACE inhibitors, or as adjunctive therapy with ACE inhibitors
- For patients taking both ACE inhibitors and β-blockers the addition of an ARB has no benefit and may be contraindicated


Digitalis: Use in Clinical Practice and Recommendations

Digoxin alleviates symptoms and improves clinical status, thus decreasing risk of hospitalization, but has little or no effect on survival.

Recommendations: Use to improve clinical status of patients with heart failure due to LV systolic dysfunction.

Use with diuretic, ACE inhibitor, and β-blockers.

Direct Vasodilator Therapy in CHF

- Improve LV performance by reducing afterload and preload
- Increase cardiac output and reduce LVFP
- Hydralazine + isosorbide dinitrate prolongs survival
- Produce only limited symptomatic improvement
- Activate neurohormonal response
- Frequently associated with tolerance and side effects
ß-Adrenergic Receptor Blockers

ß-Blockers primarily inhibit effects of sympathetic nervous system

Deleterious effects of sympathetic nervous system are mediated through actions on ß₁-, ß₂-, and a₁-adrenergic receptors

Three types of ß-Blockers; those that:

- Selectively inhibit ß-adrenergic receptors (eg, metoprolol and bisoprolol)
- Inhibits both ß₁- and ß₂-adrenergic receptors (eg, propranolol and bucindolol)
- Inhibit ß₁- and ß₂- and a₁-adrenergic receptors (eg, carvedilol)

Carvedilol is the only ß-blocker approved by the FDA for management of chronic heart failure.

**β-blockers in heart failure: Key clinical trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Target daily dose</th>
<th>Risk reduction/total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol (n = 1094)</td>
<td>Carvedilol</td>
<td>50-100 mg</td>
<td>65% (P &lt; 0.001)</td>
</tr>
<tr>
<td>MERIT-HF (n = 3718)</td>
<td>Metoprolol</td>
<td>200 mg</td>
<td>34% (P = 0.0062)</td>
</tr>
<tr>
<td>CIBIS II (n = 2647)</td>
<td>Bisoprolol</td>
<td>10 mg</td>
<td>33% (P &lt; 0.0001)</td>
</tr>
</tbody>
</table>


---

**Mortality in US Carvedilol Heart Failure Program**

![Graph showing survival and cause of death](image-url)

Patients receiving diuretics, ACE inhibitors, ± digoxin; mean follow-up 6.5 months.

Adapted from Packer et al., 1996.
**Time Course of Response to Carvedilol in Heart Failure**

Clinical benefits

Clinical deterioration

Months

---

**Effect of Carvedilol on Progression in Mild or Moderate Heart Failure**

MILD

- Carvedilol (n=232)
- Placebo (n=134)

<table>
<thead>
<tr>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Risk reduction</td>
</tr>
<tr>
<td>Event-free survival</td>
</tr>
</tbody>
</table>

Moderate

- Carvedilol (n=133)
- Placebo (n=145)

<table>
<thead>
<tr>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Risk reduction</td>
</tr>
<tr>
<td>Event-free survival</td>
</tr>
</tbody>
</table>

*All-cause mortality or cardiovascular hospitalization.

Patients receiving diuretics, ACE inhibitors, + digoxin.
Colucci et al, 1996

Packer et al, 1996.
Effect of Carvedilol on Left Ventricular Ejection Fraction

Data from 4 US double-blind placebo-controlled trials: mean follow-up 6.5 months.
Patients receiving diuretics, ACE inhibitors, ± digoxin.

Effect of Carvedilol on Hospitalizations in Heart Failure

Patients receiving diuretics, ACE inhibitors, ± digoxin; mean follow-up 6.5 months.
Adapted from Fowler et al, JPP.
β-Blockade: Recommendations

Use for all patients with stable NYHA Class II or III heart failure due to LV systolic dysfunction unless contraindicated

Use with diuretic and ACE inhibitors; ensure that patients are not fluid-overloaded

Use for long-term management, not for stabilizing acutely-ill patients

Initiate at very low doses, followed by gradual dose increments as tolerated

Monitor patients for hypotension, bradycardia, and fluid retention during uptitration period (85-90% of patients in clinical trials were maintained on long-term therapy)

Aims of heart failure management and therapeutic approaches

To achieve improvement in symptoms

- Diuretics
- Digoxin
- ACE inhibitors
To achieve improvement in survival
- ACE inhibitors
- β-blockers
- Oral nitrates pous hydralazine
- Spironolactone


**Common Errors in the Management of Heart Failure**
- Other conditions and reversible causes not identified or treated
- Heart failure not considered (COPD misdiagnosed)
- LV function not assessed
- Inadequate pharmacologic treatment
- Noncompliance not addressed
- Revascularization not considered
- Inadequate patient education
- Inappropriate monitoring of progress
  - Testing overutilized
  - Activity- and symptom-based measures underutilized

**Indications for Hospital Management**
- Clinical or ECG evidence of acute myocardial ischemia
- Pulmonary edema or severe respiratory distress (O₂ sat <90%)
- Severe complicating medical illness
- Anasarca
- Symptomatic hypotension or syncope
- Failure of outpatient management
- Inadequate home support

**Diastolic Heart Failure**

**Symptoms and signs of CHF** Normal LV function Diastolic dysfunction
- Syndrome of dyspnea, fatigue and fluid retention in presence of normal LV function (in absence of heart valve disease)
- Diastolic dysfunction; abnormal ventricular distensibility, relaxation or filling regardless of presence or absence of symptoms and normal or abnormal LV function
- Prevalence: 15% of CHF patients <65 yrs.
  50% of patients with CHF >80 yrs.

**Causes of Left Ventricular Diastolic Dysfunction**
- Left ventricular hypertension:
  - Hypertensive heart disease
  - Aortic stenosis
- Ischemic heart disease
- Cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Infiltrative cardiomyopathy – amyloidosis, sarcoidosis, hemochromatosis
- Pericardial disease: constrictive pericarditis effusion with tamponade
- Diabetes mellitus

**Diastolic Dysfunction**

**Diastolic Heart Failure: Treatment Goals and Methods**

<table>
<thead>
<tr>
<th>Treatment Goals</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce the congestive state</td>
<td>Salt restriction and diuretics, ACE inhibitors or angiotensin receptor blockers, Dialysis or plasmaphoresis</td>
</tr>
<tr>
<td>Control hypertension and promote regression of LVH</td>
<td>Antihypertensive agents</td>
</tr>
<tr>
<td>Prevent and treat myocardial ischemia</td>
<td>Nitrates, beta blockers, calcium blockers, Bypass surgery, angioplasty</td>
</tr>
<tr>
<td>Prevent tachycardia</td>
<td>Beta-blockers, calcium blockers, Ablation of AV node and pacing</td>
</tr>
<tr>
<td>Maintain atrial contraction (Sinus rhythm)</td>
<td>Antiarrhythmic agents</td>
</tr>
<tr>
<td>Improve LV relaxation</td>
<td>Beta adrenergic stimulation, Systolic unloading, Treat ischemia, Calcium-blockers (in hypertrophic cardiomyopathy)</td>
</tr>
</tbody>
</table>
• Prevent fibrosis and promote regression of fibrosis
  ACE inhibitors or angiotensin receptor blockers
  Spironolactone
  Anti-ischemic agents

• Attenuate neurohormonal activation
  Beta-blockers, ACE inhibitors

Interventricular asynchrony in advanced CHF with LBBB pattern

Consequences of LBBB

Mechanical:

- Interventricular dyssynchrony
- Prolonged delay between onset of LV and RV contraction
- Relative decrease in the duration of LV diastole
- Prolonged IVRT, Shortened LV filling period
- Intraventricular dyssynchrony
- Paradoxical septal motion with decreased regional ejection fraction
- Inhomogenous, discoordinate LV contraction.

Hemodynamic:

- Reduced LVEF / CO / MAP / dP/dt
Surgical treatment for heart failure
- Heart transplant (including xenotransplantation)
- Coronary artery bypass surgery
- Left ventricular restoration
- Mitral valve repair / replacement
- Left ventricular assist devices
- Abiocor artificial hearts

Other non-surgical measures:
- Biventricular pacing
- Intermittent inotropic infusions

Stage A
At high risk for HF but without structural heart disease or symptoms of HF
eg: patients with CAD, HTN, DM, Fhx CM

Treat HTN, lipid disorders
Encourage smoking cessation, regular exercise
Discourage ETOH intake and illicit drug use.
ACE-I in selected patients.

Stage B
Structural heart disease but without symptoms of heart failure
eg: patients with Previous MI
LV systolic dysfunction
Asymptomatic valve disease.

Stage A measures
ACE-I
Beta-blockers

Stage C
Structural heart disease with prior or current symptoms of CHF

Stage D
Refractory heart failure
Requiring specialized interventions
Marked symptoms at rest
Despite maximal medical therapy

Therapy
Stage A measures
Diuretics
ACE-I
Beta-blockers
Digitalis
Dietary salt restriction

Therapy
Stage A, B, C measures
Mechanical assist devices
Heart transplantation
Inotropic infusion for palliation
Hospice care.