Advances in Heart Failure

22 June 2009
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Chronic left heart failure

Definition:
- Chronic heart failure is a syndrome with following features:
  - Symptoms of heart failure at rest or during exercise
  - Clinical signs of heart failure
  - Objective evidence of structural or functional abnormality of the heart

Heart Failure: Epidemiology

- Estimated 550,000 new cases occur/yr
- Estimated to rise to 772,000/year by yr 2040
- More than 5 million Americans have HF (300K to 800K with advanced—NYHA Class IV—Heart Failure)
- Estimated to increase to 10 million by yr 2040
- Among Medicare beneficiaries, HF is the leading cause of hospitalization
- Cost of HF treatment—>35 billion $ in 2007

Heart Disease and stroke statistics: 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee
Circulation; 2007; 115: e69-e17

Heart Failure: Epidemiology

- Heart failure is the 3rd most prevalent CVD
- Prevalence and age:
  - 20-39—less than 1%
  - 80 or older—about 20%
- Life time risk of developing heart failure:
  - 20 % for both women and men
- Life time risk of developing heart failure without CAD:
  - Age 40—men-11.4 %, women -15.4 %
Heart Failure: Epidemiology

• Mortality: nearly 50,000 annually
• Morbidity:
  • 6.5 million days of hospital stay/yr
  • 12-15 million office visits/yr


Heart Failure: Epidemiology

Increasing rate of hospitalizations:
1979—1,274,000
2004—3,860,000
More than 80% were among patients 65 yrs or older.


Heart Failure: Epidemiology

Racial differences in the incidence of CHF
Overall incidence / 1000 person-years
African American—4.6
Hispanic ——3.5
White ——2.4
Chinese AM ——1.0


Heart Failure: Epidemiology

Is there gender and race differences?
• Age—adjusted incidence rate /1000 person-years:
  • Caucasian men: 6.0
  • African—American men: 9.1
  • Caucasian women: 3.4
  • African-American women: 8.1

( Loehr LR et al : Heart failure Incidence and Survival (from the Atherosclerosis Risk in Communication Study).
• AM H J Cardiol, 2008,101, 1016)
Advances in heart failure

Most common clinical subsets of chronic heart failure:
- Systolic heart failure (SHF) also termed Heart failure with reduced ejection fraction (HFREF)
- Diastolic heart failure (DHF) also termed Heart failure with preserved ejection fraction (HFPEF)

Systolic Heart Failure
Clinical Definition
- A clinical syndrome of heart failure
- resulting from reduced left ventricular ejection fraction
- “Heart failure with reduced ejection fraction”

Diastolic Heart Failure
- Diastolic Heart Failure - contemporary clinical definitions:
  - “A clinical syndrome characterized by the symptoms and signs of heart failure
  - a preserved ejection fraction, and abnormal diastolic function”
- Other clinical definitions:
  - “Heart failure with preserved systolic function”
  - “Heart failure with normal or near normal ejection fraction”
Heart Failure: Epidemiology

- Risk factors
  - increasing age
  - hypertension
  - CAD
  - diabetes
  - obesity
  - insulin resistance
  - genetic factors
  - use of cardiotoxins

Heart Failure: Epidemiology

- Insulin resistance cardiomyopathy
- (ICRM)
- Heart failure in absence of frank diabetes
- Insulin resistance is a risk factor for both systolic and diastolic heart failure

Insulin Resistance in IDCAM

- 43 of 240 patients from HF clinic with IDCAM, no DM, and no renal/hepatic/pituitary or adrenal disease
- 40 age matched and BMI matched controls
- Oral glucose tolerance testing on all 83 sub.

R. Witteles et al, JACC 2004
**Insulin Sensitivity and Prognosis in Systolic Heart Failure**

- 105 male pts from Brompton HF clinic with chronic HF
- Insulin sensitivity ($S_I$) with IV Gluc Tol. Test
- 44 month followup for survival comparing pts below versus above median $S_I$ (1.82)
- Pts above median had a higher peak VO$_2$ and higher LVEF

W. Doehner et al, JACC 2005

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**Systolic Vs Diastolic Heart Failure**

- ADHERE – All enrolled discharges

<table>
<thead>
<tr>
<th>Profile</th>
<th>SHF</th>
<th>DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>&lt;40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Age</td>
<td>69.9</td>
<td>74.2*</td>
</tr>
<tr>
<td>Female</td>
<td>39%</td>
<td>62.2%*</td>
</tr>
<tr>
<td>CAD</td>
<td>63%</td>
<td>54%*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42%</td>
<td>46%*</td>
</tr>
<tr>
<td>AF</td>
<td>29%</td>
<td>33%*</td>
</tr>
</tbody>
</table>

* < 0.0001

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**Heart Failure : Framingham Criteria for Diagnosis**

- Major Criteria :
  - PND or Orthopnea
  - Neck vein distention
  - Rales
  - Cardiomegaly
  - Acute pulmonary edema
  - S3 gallop
  - Increased venous pressure > 6 Cm
  - Hepatojugular reflux

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**Heart Failure : Framingham Criteria for Diagnosis**

- Minor Criteria :
  - Ankle edema
  - Night Cough
  - Dyspnea on exertion
  - Pleural effusion
  - Decreased maximal vital capacity
  - Tachycardia (rate > 120 bpm)
- Major or minor criteria :
  - weight loss > 4.5 KG in five days in response
  - treatment
  - TWO MAJOR or ONE MAJOR and TWO MINOR
Question 1

In diastolic heart failure, the cardiac output is uniformly normal since the contractile properties of the myocardium are preserved?

- True
- False
- Of course, why would you even ask such a basic question?
Myofiber disarray / severe interstitial fibrosis

Heart Failure: Diagnosis

- Physical examination:
  - Signs of heart failure-diagnostic of cardiac cause
  - e.g., S3, elevated JVP, positive HJR,
  - Presence of cardiac patholohy-very suggestive of cardiac cause
  - Chest X-ray: very helpful when findings of pulmonary venous congestion or pulmonary hypertension are present
  - ECG- normal electrocardiogram – a negative predictive value over 90%
  - BNP-elevated in heart failure normal in patients with non cardiac dyspnea

ACC/AHA and HFSA Guidelines on the Use of BNP Measurement in Patients with Heart Failure

<table>
<thead>
<tr>
<th>ACC/AHA 2005 Heart Failure Guideline Update</th>
<th>HFSA 2006 Practice Guideline: Acute HF Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement of B-type natriuretic peptide (BNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of heart failure is uncertain. (Level of evidence: A)</td>
<td>The diagnosis of decompensated heart failure should be based primarily on signs and symptoms. (Level of evidence: C)</td>
</tr>
<tr>
<td>The value of serial measurements of BNP to guide therapy for patients with heart failure is not well established. (Level of Evidence: C)</td>
<td>When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with heart failure. (Level of evidence: A)</td>
</tr>
</tbody>
</table>

Systolic Vs Diastolic Heart Failure Neurohormonal dysfunction

<table>
<thead>
<tr>
<th>Control</th>
<th>SHF</th>
<th>DHF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>54%</td>
<td>31%</td>
<td>60%</td>
</tr>
<tr>
<td>NE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pg/ml</td>
<td>169</td>
<td>287</td>
<td>306</td>
</tr>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pg/ml</td>
<td>3</td>
<td>28</td>
<td>56</td>
</tr>
</tbody>
</table>

(Kitzman D.W et al JAMA,2002)
Table 2. Adverse effects of neurohormones

Myocyte hypertrophy
Vascular smooth muscle cell hypertrophy
Fibroblast growth
Promotion of programmed cell death
(apoptosis)
Promotion of atherothrombosis
Stimulation of proinflammatory modulators
Ventricular and vascular remodeling
Abnormal central and peripheral hemodynamics

Diastolic Heart Failure: Remodeling

- Concentric LVH
- LV cavity size small (decreased LV volume / LV mass ratio)
- Decreased LV end-diastolic volume
- Increased left atrial or biatrial enlargement

Table 1. Systolic heart failure—remodeling

- Usually eccentric hypertrophy
- Disproportionate increase in ventricular cavity size
- Increased ventricular mass
- Cavity mass ratio increased
- Wall thickness—decreased or unchanged
- Increased wall stress
- Reduced ejection fraction
- Altered ventricular shape and geometry
- Frequent mechanical dyssynchrony with or without electrical dyssynchrony

Heart Failure

- Classification based on the severity of symptoms:
  - NYHA class I - asymptomatic
  - NYHA class II - symptoms during more than usual physical activity
  - NYHA class III - symptoms during less than usual physical activity.
  - NYHA class IIIb - symptoms during minimal activity.
  - NYHA class IV - symptoms at rest

New classification not based on the severity of symptoms:

- Stage A: At high risk for HF but without structural heart disease or symptoms of HF
- Stage B: Structural heart disease but without symptoms of HF
- Stage C: Structural heart disease with prior or current symptoms of HF
- Stage D: Refractory HF requiring specialized interventions

Systolic Heart Failure-Prognosis

- Improved with modern therapy:
  - “The annualized mortality for heart failure has dropped from 18% to 20% to about 6% to 8% on average.”

- Francis GS, Tang WHW: JACC, 2006, 7, 1385-86

Congestion: The Essence of Heart Failure Syndrome

- Congestion after initial in-hospital therapy is associated with higher 60-day mortality.

Adapted from Dancey et al, JACC, 2004; 10:1097.
Importance of Congestion: Response of PCW but not Cardiac Output Predicts Mortality in Advanced Heart Failure

- PCW > 16 mmHg: Increased mortality compared to PCW < 16 mmHg
- Cardiac Index > 2.6 L/min-M²: Better prognosis than Cardiac Index < 2.6 L/min-M²
- P=0.001

Final hemodynamic measurement in 456 advanced HF patients after tailored vasodilator therapy. Fonarow. Circulation 1994;90:I-488

How is Congestion Sustained? The Cardio-Renal Syndrome in Heart Failure

- Increased morbidity and mortality
- Neurohormonal activation
- Development of diuretic & natriuretic resistance
- Diminished blood flow
- Impaired renal function
- Decreased renal perfusion

Prognostic Importance of GFR

- GFR a Marker of Cardiac Function in pts without intrinsic Renal disease

Diastolic Heart Failure: Prognosis

- Moderately severe heart failure
- The Charm Preserved Trial
- Candesartan Placebo (n=1514) (1509)
- Cardiovascular Death
  - 11.2% 11.3%
- Annual Mortality Rate
  - 3.8% 3.8%
**Diastolic and Systolic Heart Failure: Prognosis**

- Mortality and Morbidity — advanced heart failure
  - DHF: 60
  - SHF: 25
- EF %
  - 6-mo: 6
  - 6-mo: 11
- Mort %
  - In-hosp: 2
  - 2-mo: 3
- Readmission
  - 6-mo: 11
  - Mortality %: 53

(Adapted from: Danciu SC et al; AJC: 2006; 97, 256-259)

**Systolic Heart Failure: Sudden Cardiac Death**

- SCD
  - NYHA II: 64 %
  - NYHA III: 59 %
  - NYHA IV: 33 %
- CHF
  - NYHA II: 12 %
  - NYHA III: 26 %
  - NYHA IV: 56 %

**Diastolic Heart Failure: Sudden Cardiac Death**

- Sudden Cardiac Death
- Post-hoc analysis (Peace) trial
  - No <4000, LVEF > 40 %
  - SCD occurred in 1.5 % of patients during a median follow-up of 4.8 years. (mean EF 58 %)
- The independent predictors of SCD:
  - Digitalis use — HR 2.58
  - Diuretic use — HR 2.1
  - LVEF < 50 % - HR 2.08
  - Current angina-HR 1.51

**Diastolic and Systolic Heart Failure—Management Strategies**

- Diuretics are needed to relieve congestive symptoms in both systolic and diastolic heart failure
- Digitalis may be effective in selected patients in both systolic and diastolic heart failure
- Reduction in heart rate is beneficial in both systolic and diastolic heart failure.
Diastolic and Systolic Heart Failure-Management Strategies

- ACEIs / ARBs:
  - Decrease mortality and morbidity in systolic heart failure
  - Decrease morbidity not mortality in diastolic heart failure
  - (CHARM-PRESERVED, PEPC-CHF)
  - I-PRESERVE ARB in diastolic heart failure-no benefit
- Beta-blocker therapy:
  - Decrease mortality and morbidity in systolic heart failure
  - Unproven benefit in diastolic heart failure
  - Hydralazine-nitrate
  - Decrease mortality and morbidity in systolic heart failure
  - Unproven benefit in diastolic heart failure

CHARM-Preserved
Primary outcome, CV death or CHF hospitalisation

- Candesartan 1514 1458 1377 833 182
- Placebo 1509 1441 1359 824 195

HR 0.89 (95% CI 0.77-1.03), p=0.118
Adjusted HR 0.86, p=0.051

CHARM-Preserved
Investigator-reported CHF hospitalisations

- Patients hospitalised
  - Placebo
  - Candesartan
  - p=0.017

- Hospitalisations
  - Placebo
  - Candesartan
  - p=0.014

Death or CV Hosp.
Diastolic and Systolic Heart Failure-Management Strategies

- Aldosterone antagonists:
  - Decrease mortality and morbidity in symptomatic patients with systolic heart failure
  - Unproven benefit in diastolic heart failure
  - TOPCAT trial is ongoing (4500 pts, LVEF > 45%, age > 50, CV death/CHF hospitalization)
- Exogenous BNP:
  - Decrease morbidity in decompensated systolic heart failure
  - Unproven benefit in diastolic heart failure

Proven Outcomes for Systolic Heart Failure Therapies

- Improve Survival
  - ACE inhibitor
  - ARB
  - Beta blocker
  - Aldosterone receptor antagonist (III/IV and post MI with LVSD)
  - Hydralazine/long-acting nitrates
  - CRT
- Reduce Hospitalization
  - ACE inhibitor
  - ARB
  - Beta blocker
  - Aldosterone receptor antagonist
  - Hydralazine/long-acting nitrates
  - Digoxin
  - CRT

Prevalence of Inter- or Intraventricular Conduction Delay (QRS >120 ms)

General HF Population  
Moderate to Severe HF Population

QRS prolongation associated with:
- Mortality
- Mechanical dysynchrony (worsening HF)

CARE HF OVERVIEW

- n=813
  - NYHA III,IV
  - EF < 35%
  - Isc. & non-isc
  - QRS > 120

Follow Up  
Follow Up  
Follow Up

Baseline  
Randomization Stratification  
Implant  
Opt  
Resynchronization Therapy

< 5 days 0 < 5 working days one month three months 18 months

Time Post Randomization

NEJM 2005;352
Cardiac Resynchronization Therapy
Summary of Major Mortality & Morbidity Trials

- NYHA class III, IV
- EF ≤ 35%
- Optimal Medical Rx
- Ventricular Dysynchrony (QRS≥120-130 ms)

CRT Reduces:
- All-cause mortality or hospitalization by 20%
- All-cause mortality or CV hosp. by 30-37%
- All-cause mortality or HF hosp. by 35-40%
- All-cause mortality by 36% [CARE-HF]

CRT-D Reduces:
- All-cause mortality by 36% [COMPANION]


Cardiac Resynchronization Therapy
Summary of Major Trials

- NYHA class III, IV
- EF ≤ 35%
- Ventricular Dysynchrony (QRS≥120-130 ms)
- Optimal Medical Rx

CRT Improves:
- Exercise Capacity (6MWD:+50 m; VO₂: +0.8-2.0 ml/kg/min)
- Quality of Life (17 points)
- Symptoms
- Cardiac structure and function


Management of Diastolic Heart Failure: My Approach

- Identification of Modifiable Risk:
  - OSA
  - Ischemia
  - Metabolic Syndrome (hypertension, insulin resistance, obesity)
  - Thyroid Abnormalities
  - Atrial fibrillation
  - Optimizing ventricular rate: do not overdue AV nodal blockade
  - Renal Failure
Management of Diastolic Heart Failure: My Approach

• Hypervolemia:
  – Dietary salt, water restriction
  – Diuretics (bumex, torsemide when right heart failure is present and aldactone)
• Disease Progression:
  – AngII-receptor blocker (especially when LVH is present)
  – Renal Failure
  – Restrictive cardiomyopathy suspected (Family Hx):
    • Workup including dMRI, SPEP/UPEP, consider EBx
  – Hypertrophic Cardiomyopathy suspected (Family Hx):
    • LV outflow obstruction; Heart failure
    • Exercise : Programmed Cardiac Rehabilitation

Advanced Heart Failure Therapies: Role of Inotropes?

• 36 patients discharged home on continuous outpatient inotropic support (inotrope dependent)
• Mean LVEF 19%, mean PCWP 27 mmHg at baseline
• 3 week LOS prior to discharge on COSI

Diastolic and Systolic Heart Failure - Management Strategies

• Cardiac Resynchronization and/or ICD:
  • Decrease mortality and morbidity in
  • refractory systolic heart failure
  • Not indicated in diastolic heart failure
• Implantable LVAD:
  • May improve short term survival in
  • selected refractory systolic heart failure patients
  • Unproven benefit in diastolic heart failure
• Cardiac Transplantation
  • May be of benefit in both systolic and diastolic heart failure

Success with Orthotopic Heart Transplantation

R Hershberger et al, J. Card Fail 2003
Cardiac Transplantation

- **Current Indications**
  - Severe symptoms despite optimal medical and device Rx
  - MVO2< 14 ml/kg-min
  - Worsening renal function, diuretic resistance
  - Inotrope dependence

- **Contra-indications**
  - Physiologically aged
  - Psychosocial hurdles (patient and family/support)
  - Irreversible liver disease
  - Severe IDDM, PVD, CVA
  - Increased Pulmonary Vascular Resistance *
  - Severe chronic lung dz
  - Systemic Disease (primary amyloid)

Mechanical Circulatory Support (MCS):

- **Indications**
  - Cardiogenic Shock post AMI
  - Postoperative Low Output Syndrome-failure to wean on pump
  - Bridge to Transplant (BTT)
  - Destination Therapy (DT)

HeartMate II vs HeartMate XVE LVAD

- Pulsatile-flow LVAD (HM XVE)
  - Provides excellent hemodynamic support
  - Best used in large patients
  - Large percutaneous lead

- Continuous-flow LVAD (HM II)
  - 1/4 weight
  - Quiet
  - 40% smaller lead
  - One moving part
  - Long term durability

HeartMate II Bridge to Transplant Clinical Trial

Outcomes (n=133)

- 79% (105) Transplantation, Recovery or Ongoing
  - 51% (68) Transplanted
  - 26% (34) Ongoing support > 180 days *
  - 2% (3) Cardiac recovery, device explanted
  - Average Duration of Support = 168+/−148 days

*Median Duration of Support for ongoing patients = 307 days (range 223-600 d)
HeartMate II Clinical Trial

Functional Status - NYHA Class I or II

- Percent of patients
- NYHA II
- NYHA I
- 63%
- 83% 87%
- 0%*
- n=133                    104                       78                       46

* All were NYHA Class IV at Baseline

HeartMate II Clinical Trial

Reduction in Adverse Events compared to previous generation HeartMate XVE

- Nearly 90% reduction in percutaneous lead infection
- Nearly 40% reduction in bleeding requiring surgery
- More than 50% reduction in stroke
- Nearly 60% reduction in non-stroke neurological events

The Future is Bright: What to Look for in the Next Decade

- Myocardial Recovery of End-Stage Heart Failure (non-ischemic) with mechanical circulatory support
- Embryonic and non-embryonic (e.g., cardiac) stem cell trials
- Trials of therapies that target cardiac metabolism and cardiac energetics