CASE PRESENTATION

• DF is an 84 year old woman with DM and HBP who presents with 1 yr DOE and fatigue, worse over p 1 month.
• On the Saturday after Thanksgiving, she presents in the ED with acute SOB, coughing up pink frothy sputum.
• BP 190/100 mmHg, HR 110/min, & reg. JVP ↑. Bilateral rales 50% up. No peripheral edema.
• EKG: HR 102/min, LVH, ST ↓ 2,3,AVF, V5-6. Similar to previous EKGs but HR higher and STs worse.

CASE PRESENTATION

• Troponin WNL but BNP 854, BUN/Cr 54/1.8.
• CXR- Acute pulmonary edema
• Echo: LVH w NBVSF, EF 66%, mild MR and TR, aortic sclerosis, MAC, PA systolic 48 mmHg.
• Home meds: HCTZ, atenolol, metformin
• Dx? Rx?


• 47 patients with signs and sx of CHF, normal EF, ↑LVEDP
• 10 patients without CV disease as controls
• Patients with diastolic heart failure had prolonged τ (59 ±14 vs 35±10 msec) and increased passive stiffness
Diastolic Heart Failure — Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle. NEJM 5/6/04
Michael R. Zile, M.D., Catalin F. Baicu, Ph.D., and William H. Gaasch, M.D.

PATIENTS
10 CONTROLS

CHARACTERISTICS, RX & OUTCOMES OF PTS W PRESERVED SYSTOLIC FX HOSP FOR CHF: THE OPTIMIZE REGISTRY

• 60-90 DAY FOLLOW UP OF 20,118 PTS W CHF & LV SYSTOLIC DYSFUNCTION (EF <40%) VS 21,149 PTS WITH PRESERVED SYSTOLIC FUNCTION.
• PTS WITH PRESERVED SYSTOLIC FUNCTION HAD SIMILAR MORTALITY (9.5% VS 9.8%) AND REHOSPITALIZATION RATE (29.2% VS 29.9%) AS PTS W LV SYSTOLIC DYSFUNCTION.

FONAROW ET AL. JACC 2007:50:768-777

SYSTOLIC AND DIASTOLIC HEART FAILURE IN THE COMMUNITY

• OLMSTED COUNTY, MAYO CLINIC: 9/10/03 TO 10/27/05, 556 CHF PATIENTS
• 308 (55%) HAD NORMAL LV EF AND 242 (44%) HAD ISOLATED DIAST DYS WITH NORMAL LV EF
• AT 6 MONTHS, MORTALITY WAS 16% FOR BOTH PRESERVED AND REDUCED EF CHF.
• EF AND DIAST DYS WERE INDEPENDENT PREDICTORS OF BNP ELEVATION.

BURSI F, WESTON SA, REDFIELD MM et al. JACC NOV 8, 2006

The Pathogenesis of Acute Pulmonary Edema Associated with Hypertension
Bowman Gray School of Medicine, Winston-Salem, NC


Purpose

• To determine if patients hospitalized with acute pulmonary edema in association with hypertension have transient left ventricular systolic dysfunction or MR which is no longer present when LVEF is subsequently evaluated after treatment
• If so, then isolated diastolic dysfunction may be a less common cause of heart failure than has been recently observed

• N Engl J Med 2001;344:17-22
Results

- 38 patients (14 men, 24 women); mean age 67 years, all with acute pulmonary edema studied during the acute episode and 1-3 days later
- Mean SPB was 200 ± 28 mmHg during the initial echo exam and was reduced to 139 ± 17 mmHg (P< 0.05) at follow-up
- EF was similar during the acute episode (0.50 ± 0.15) and after treatment (0.5 ± 0.13)


Results

- No difference in the LV regional wall-motion index between the acute episode and after treatment
- No patient had severe mitral regurgitation during the acute episode


Conclusion

“In patients with hypertensive pulmonary edema, a normal EF after treatment suggests that the edema was due to the exacerbation of diastolic dysfunction… not to transient systolic dysfunction or mitral regurgitation”.


LV Diastolic Dysfunction

- IMPAIRED LV FILLING DUE TO INCREASED CHAMBER STIFFNESS AND/OR DECREASED RELAXATION
- OCCURS MORE COMMONLY IN WOMEN AND THE ELDERLY
- RESPONSIBLE FOR 50% OF CHF IN ADULTS
- PROGNOSIS SIMILAR TO SYSTOLIC HEART FAILURE
- MANY PATIENTS HAVE BOTH LV SYSTOLIC AND DIASTOLIC DYSFUNCTION
Causes of Diastolic Heart Failure:
Increased Resistance to Diastolic Filling

- Myocardial:
  a. impaired relaxation
  b. ↑ passive stiffness (fibrosis, amyloid, hemosiderin, etc)
- Endocardial
- Epi / Pericardial
- Other: Volume overload of the contra-lateral ventricle; Extrinsic compression by tumor, coronary microcirculation

Causes of diastolic heart failure:
Increased resistance to diastolic filling

- Myocardial
  - Impaired relaxation
    • Epicardial or microvascular ischemia
    • Cardiomyopathies
    • Hypothyroidism
    • Myocyte hypertrophy
    • Aging
Causes of diastolic CHF:
- Increased resistance to diastolic filling
  - Myocardial
    - Impaired relaxation
      - Epicardial or microvascular ischemia
      - Cardiomyopathies
      - Aging
      - Hypothyroidism
      - Myocyte hypertrophy

CHARM STUDY
- Candesartan in Heart failure - Assessment of Reduction in Mortality and morbidity

CHARM STUDIES
3 component trials comparing candesartan to placebo

<table>
<thead>
<tr>
<th>CHARM Alternative</th>
<th>CHARM Added</th>
<th>CHARM Preserved</th>
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<tbody>
<tr>
<td>n=2028</td>
<td>n=2548</td>
<td>n=3025</td>
</tr>
<tr>
<td>LVEF ≤40%</td>
<td>LVEF ≤40%</td>
<td>LVEF &gt;40%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>ACE inhibitor</td>
<td>ACE inhibitor treated/not treated</td>
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<tr>
<td>intolerant</td>
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</table>

Primary outcome: CV death or CHF hospitalisations

Yusuf et al, Lancet 2003

CHARM-Preserved
Patient disposition

3025 patients randomised
NYHA II-IV
LVEF >40%

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<thead>
<tr>
<th>Candesartan</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>n=1514</td>
<td>n=1509</td>
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<tr>
<td>Lost to follow-up</td>
<td>n=2</td>
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<tr>
<td>Completed Study</td>
<td>n=1512</td>
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</table>

Median follow-up, 37 months

Yusuf et al, Lancet 2003
CHARM-Preserved
Primary outcome, CV death or CHF hospitalisation

![Graph showing HR 0.89 (95% CI 0.77-1.03), p=0.118, Adjusted HR 0.86, p=0.051]

<table>
<thead>
<tr>
<th></th>
<th>Candesartan</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Number at risk</td>
<td>1514</td>
<td>1509</td>
</tr>
<tr>
<td>1</td>
<td>1458</td>
<td>1441</td>
</tr>
<tr>
<td>2</td>
<td>1377</td>
<td>1359</td>
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<tr>
<td>3</td>
<td>833</td>
<td>824</td>
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<tr>
<td>3.5</td>
<td>182</td>
<td>195</td>
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</tbody>
</table>

Yusuf et al, Lancet 2003

CHARM-Preserved
Investigator-reported CHF hospitalisations

![Graph showing Patients (%) and Number of episodes]

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes</td>
<td>700</td>
<td>600</td>
</tr>
<tr>
<td>Patients hospitalised</td>
<td>500</td>
<td>400</td>
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</tbody>
</table>

Yusuf et al, Lancet 2003

DIASTOLIC HEART FAILURE: CURRENT TRIALS

- I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function)
  - 4100 pts (LVEF>45%, age>60) irbesartan vs pbo
  - Primary endpoint- Death & CV hospitalization
- TOPCAT (Aldosterone Antagonism for Heart Failure and Preserved Systolic Function)
  - 4500 pts (LVEF>45%, age>50) spironolactone versus pbo
  - 4 year – CV mortality / HF hospitalization

High Prevalence of Cardiac Parvovirus B19 Infection in Patients with Isolated LV Diastolic Dysfunction

- 70 pts admitted with CHF and preserved LVEF in Berlin, Germany
- Echo, R & L heart cath, Bx and tissue exam for cardiotropic viruses.
- Of those with confirmed Diast Dys, 84% had parvovirus 19, and strong assoc with coronary endothelial dysfunction.

Tschope et al. Circulation 2005;111:879-886

Statin Therapy May Be Associated With Lower Mortality in Patients with Diastolic Heart Failure.

- Observational study: 137 Pts with CHF and EF >50% followed for 21 months. 68 received statins, 69 did not.
- Initial LDL 153 for statin group, fell to 101.
  For non-statin group, LDL was 98

Hidekatsu Fukuta, David Sane, Steffen Brucks, William C. Little. Circulation July 19, 2005

Kaplan-Meier survival and survival without cardiovascular (CV) hospitalization in propensity-matched patients grouped by statin therapy

BACK TO OUR CASE

• PATIENT DF, 84 YO WOMAN IN ACUTE PULMONARY EDEMA
• DX: DIASTOLIC HEART FAILURE
• MULTIPLE CAUSES: HBP, LVH, MYOCARDIAL ISCHEMIA, DM & ACUTE VOL FROM THANKSGIVING.
• RX....................

Therapy for Diastolic Heart Failure

• Relieve VOL; diuresis, fluid/Na+ restriction, dialysis
• Decrease HR; beta-blockade, verapamil, diltiazem. In AF, digoxin, AV ablation + pacer
• Relieve ischemia; revascularization, med Rx
• Regress LVH; treat HBP aggressively, ARBs
• Renin-angiotensin blockade; ACEI, ARBs
• Reduce fibrosis; aldosterone antagonists?
• Statins???