Diastolic Heart Failure:  
Update in 2008

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CASE PRESENTATION

• DF, 84 year old woman with DM & HBP, 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 edema.
• EKG: ST 102/min, LVH, ST↓ 2,3,AVF, V5-6. Similar to previous EKGs but HR higher and STs worse.
CASE PRESENTATION

• TnI 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?
Progression of Cardiovascular Disease
Focus on Heart Failure

- Smoking
- Dyslipidemia
- Diabetes

- HTN
- Obesity
- Diabetes

- LVH
- Normal LV structure and function
- LV Remodeling
- Subclinical LV Dysfunction

- MI
- Systolic Dysfunction
- Diastolic Dysfunction

- Heart Failure

- Death

- Clinical Heart failure

Years

- Possible pathway of progression

Adapted from Levy D. J Am Coll Cardiol 1993
DIASTOLIC PRESSURE-VOLUME RELATIONS OF THE LEFT VENTRICLE

PRESSURE

VOLUME

Stiff

Normal

A  B  C

• 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

47 PATIENTS
10 CONTROLS
CLINICAL PRESENTATION, MANAGEMENT, AND IN-HOSP OUTCOMES OF PATIENTS w ACUTE DECOMPENSATED HF & PRESERVED EF

- Data from >100,000 hospitalizations of the Acute Decompensated Heart Failure Registry (ADHERE).
- CHF w preserved systolic function (PSF) present in 50.4% of pts.
- CHF pts w PSF were older, women, and hypertensive; less likely to have prior MI, or be on ACEI or ARB.
- In-hospital mortality was 2.8% with PSF, 3.9% w depressed EF.

Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. For ADHERE. JACC 2006;47:76-84
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
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 heart failure:
Increased resistance to diastolic filling

- **Myocardial**
  - **Impaired relaxation**
    - Epicardial or microvascular ischemia
    - Cardiomyopathies
    - Hypothyroidism
    - Myocyte hypertrophy
    - Aging
Diastolic Dysfunction in Angina Pectoris

Before Angina  |  During Angina  |  Recovery from Angina

ECG

LV Pressure (mmHg)

Time
Diastolic Function During Tachycardia: Normal Heart
Diastolic Function During Tachycardia: Coronary Disease
Causes of diastolic CHF: Increased resistance to diastolic filling

- **Myocardial**
  - Impaired relaxation
    - Epicardial or microvascular ischemia
    - Cardiomyopathies
    - Aging
    - Hypothyroidism
    - Myocyte hypertrophy
Effects of Angiotensin II on Intracellular Calcium and Contracture in Metabolically Inhibited Cardiomyocytes.¹

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Accepted for publication: January 14, 1990

ABSTRACT
Angiotensin II (AII) is known to potentiate ischemic contraction during ischemia, but the mechanisms involved are not completely established. We examined the effects of AII on intracellular calcium concentration ([Ca²⁺]i) and cell contracture caused by metabolic inhibition in isolated adult rabbit ventricular myocytes. [Ca²⁺]i was assessed by flow cytometry using the Ca²⁺-sensitive fluorescent probe, Fura-2. After 30 min of exposure to 2% fetal serum (FS2%) and 5% glucose, there was a significant increase in myocyte [Ca²⁺]i. This increase was slightly augmented by the presence of 100 mM LiCl. In the presence of partial Na⁺/K⁺ ATPase pump inhibitor (KCl = 0.6 mM), there was a more significant increase in [Ca²⁺]i associated with exposure to OH· AII vs. OH alone. Similar results were obtained with OH plus 2 mM glibenclamide, and the effect of AII was inhibited by 10 μM 1Hbenzimidazole-5-carboxylic acid (BAPTA). Myocytes exposed to 2 mM OH and 0 glucose gradually developed contractures over a 60 min period. Addition of 100 mM AII significantly (P < 0.01) enhanced loss of cell shape and morphology during 60 min of OH exposure. Partial inhibition of the Na⁺/Ca²⁺ exchange by exposure to 0.6 mM KCl had no effect on contracture observed in the absence of OH, but augmented the harmful effect of AII on cell contracture caused by OH exposure. This effect of AII was completely reversed by the addition of 10 μM tetracaine, a Na⁺/H⁺ exchange inhibitor. We conclude that AII directly enhances cell injury during OH exposure in isolated adult ventricular myocytes. We postulate that this effect of AII is mediated by stimulation of Na⁺/H⁺ exchange with resultant increased [Na⁺] and subsequent Ca²⁺ loading, possibly via reverse Na⁺/Ca²⁺ exchange.

ACE inhibition has now been widely shown to be clinically beneficial in a number of cardiac conditions, including patients with asymptomatic left ventricular dysfunction. It is suggested that ACE may therefore directly enhance ischemic myocardial injury by augmenting Na⁺ overload and increased Na⁺/H⁺ exchange which would then lead...
CHARM STUDY

- Candesartan in Heart failure - Assessment of Reduction in Mortality and morbidity
CHARM-Preserved
Patient disposition

3025 patients randomised
NYHA II-IV
LVEF >40%

2 patients with no data

Candesartan
n=1514
Lost to follow-up
n=2
Completed Study
n=1512

Placebo
n=1509
Lost to follow-up
n=1
Completed Study
n=1508

Median follow-up, 37 months

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

Number at risk
Candesartan 1514 1458 1377 833 182
Placebo 1509 1441 1359 824 195

Yusuf et al, Lancet 2003
CHARM-Preserved
Investigator-reported CHF hospitalisations

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
DIASTOLIC STIFFNESS IN THE FAILING DIABETIC HEART: Importance of Fibrosis, Advanced Glycation End Products, and Myocyte Resting Tension

- 90 pts hospitalized w worsening CHF; 20 had CAD at cath, and were excluded
- LV bx in 28 pts (16 w DM) w HFNEF (>50%)
- LV bx in 36 pts (10 w DM) w HFREF (<45%)
- Histology for AGE, Collagen volume fraction
- Force measurements in isolated cardiomyocytes
- LV pressure volume analysis

Paulus Lab, Amsterdam: Circulation 2008:117;43-51
DIASTOLIC STIFFNESS IN THE FAILING DIABETIC HEART

Van Heerebeek,…Paulus, W. Circulation 2008:117;43-51
DIASTOLIC STIFFNESS IN THE FAILING DIABETIC HEART

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DIASTOLIC STIFFNESS IN THE FAILING DIABETIC HEART

• CONCLUSION: DIASTOLIC STIFFNESS IS INCREASED IN THE LV OF DIABETICS, PRIMARILY DUE TO INCREASED RESTING TENSION IN INDIVIDUAL MYOCYTES

Van Heerebeek,…Paulus, W. Circulation 2008:117;43-51
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

MANY WAYS TO GET FROM A TO C!!

ISCHEMIA, FIBROSIS, AMYLOID, LVH, ↓SERCA, TnI, ETC
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???