Heart Failure with Preserved Ejection Fraction: Myths and Misconceptions

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  » Actelion, Novartis, AstraZeneca

• Honoraria/consulting:
  » ABIM, Pulmonary Hypertension Association, American Society of Echocardiography, Heart Failure Society of America, AstraZeneca, Bayer, Novartis, Merck
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• We pronounce HFpEF: “huff-puff”

Take home messages

• Don’t miss the diagnosis of HFpEF
  » Many patients go undiagnosed for years
  » Always think of HFpEF in the dyspneic patient

• Your HFpEF patients need help!
  » High risk for hospitalization and death
  » Symptomatic, depressed, debilitated
  » Complex cases in need of multidisciplinary care
  » Several clinical trials are available
HFpEF: A debilitating syndrome

- **TOPCAT trial** (spironolactone vs. placebo):
  - N=3445
  - At baseline:
    - Activity level very low (9.3 MET-hr/week)
    - Poor QOL similar to ESRD
    - 27% with moderate or greater depression


HFpEF: prevalence increasing

*GWTG-HF: N=110,621 patients hospitalized with HF
P<0.0001 for trend of increased HFpEF prevalence*

Oklay AA, Rich JD, Shah SJ. *Curr Heart Fail Rep* 2013
HFpEF: prevalence increasing

GWTG-HF: N=110,621 patients hospitalized with HF
P<0.0001 for trend of increased HFpEF prevalence

By 2020, 65% of hospitalized HF pts will have EF > 40%

HFpEF survival: poor

Dismal 35% survival at 5 years after HF hospitalization, regardless of LVEF
Northwestern HFpEF Program

- Funding: American Heart Association
- Nov 2007 to present, >1500 patients
- N=527 with detailed data in our database
- Daily EMR query to identify patients:
  - (1) Words “heart failure” in chart or
  - (2) BNP > 100 pg/ml or
  - (3) 2 or more doses of IV diuretics
    » If LVEF>50%, +Framingham criteria for HF:
    - Offered post-discharge follow-up in HFpEF clinic

Objective evidence of HFpEF

- Symptomatic:
  » NYHA class: 2.3±0.7 (49% class III or IV)
- Preserved LVEF, normal LV size:
  » LVEF: 61±7%, LVEDV index: 41±12 ml/m²
- Evidence of ↑LV filling pressures:
  » 72% with DD grade 2 or 3, 64% with ↑LAVi
  » Invasive PCWP: 23±9 mmHg
- Reduced ability to augment CO:
  » Peak VO₂: 14±5 ml/kg/min

Myth #1: Diagnosing HFpEF is difficult
Diagnosis of HFpEF?

• It’s not as complicated as you think:
  » 1. Signs and symptoms of CHF and
  » 2. LV ejection fraction > 45-50%
  » 3. Objective evidence of a cardiac problem
    – Elevated BNP or
    – Left atrial enlargement or
    – Elevated PCWP (> 15 mmHg) or
    – Elevated LV end-diastolic pressure (> 15 mmHg)
• That’s really it! That’s all you need!!

Diagnosis of HFpEF?

• Diastolic dysfunction (DD) on echo:
  » Not required for the diagnosis
  » Often uninterpreted or misinterpreted
  » Grade 2 (moderate) or grade 3 (severe) DD helpful but not required for diagnosis
  » Patients can have HFpEF with “normal” diastolic function or “mild” DD
• When in doubt: do a right heart cath!
Respiratory variation in PCWP

End-expiratory PCWP = 27 mmHg

Lung disease
Morbid obesity
Abnormal LA mechanics in HFpEF

Freed B...Shah SJ. Circ CV Imaging 2016

LA strain is a better predictor of outcomes compared to LV or RV longitudinal strain
Abnormal LA mechanics in HFpEF

- LV diastolic dysfunction
- LA fibrosis
- Atrial fibrillation
- Atrial myopathy

Chronic LA pressure and volume overload
- Pulmonary venous congestion
- Pulmonary vasoconstriction
- RV afterload
- RV failure

RV failure
Abnormal LA mechanics in HFpEF

- LV diastolic dysfunction
- LA fibrosis
- Atrial fibrillation
- Atrial myopathy
- Chronic LA pressure and volume overload
- Pulmonary venous congestion
- Pulmonary vasoconstriction
- RV afterload
- RV failure
- Reduced atrial emptying
- Decreased LV filling
- Decreased cardiac output
- Decreased peak VO₂

Exercise intolerance adverse outcomes
HFpEF: Global CV reserve dysfxn

HFpEF: evidence of impaired CV reserve at 20W exercise

A

B

C

Blue = Control
Green = HTN
Red = HFpEF

D

E

F

Effect of ↑ preload on LA strain

HFpEF vs. non-cardiac dyspnea

Appropriate augmentation of LA strain with leg raise
Lack of augmentation of LA strain with leg raise

NON-CARDIAC DYSPNEA
EARLY HFpEF
Effect of ↑ preload on LA strain

**HFpEF vs. non-cardiac dyspnea**

Obokata M, et al. *JACC Cardiovasc Imaging* 2013:
LA reservoir strain during passive leg raise differentiates HFpEF from HTN controls (AUROC 0.95), with diagnostic power beyond conventional echo parameters (E/e’, LV mass index, LA volume index)

Volume challenge in a patient w/HFpEF

(PCWP (mmHg))

Baseline

Post-1L saline bolus

(No dynamic MR)
Exercise hemodynamics in a patient with severe HFpEF

Myth #2: A normal BNP rules out HFpEF as a diagnosis
BNP for the diagnosis of HFpEF

• BNP data in HFpEF limited
  » Most BNP and NT-proBNP data:
    – HF w/reduced EF or diastolic dysfunction
  » BNP < 100 pg/ml, NT-proBNP < 120 pg/ml:
    – Thought to have good negative predictive value

• Obesity:
  » Very common in HFpEF
  » Known to be associated with ↓BNP

Normal BNP in HFpEF

• Prospective study of HFpEF patients:
  » 159 confirmed HFpEF patients
  » All met Framingham criteria for HF
• All underwent cardiac catheterization and BNP measurement
  » PCWP > 15 mmHg or LVEDP > 15 mmHg in all patients

Anjan V...Shah SJ. Am J Cardiol 2012
Normal BNP in HFpEF

- 46/159 (29%) had BNP < 100 pg/ml
  - Younger
  - More obese
  - High PCWP in both groups: 25 mmHg vs. 27 mmHg
  - Better outcomes (HR 0.25 for CV hosp/death)
- BNP < 100 pg/ml:
  - Present in up to 1/3 of HFpEF
  - Associated with less severe HFpEF
    - BUT STILL SYMPTOMATIC, PCWP ~25 mmHg

NP system: deficient in HFpEF

- HFpEF: very high prevalence of obesity
- Adipose tissue: increased NP clearance
- Obesity: reduced NP production

Anjan V...Shah SJ. Am J Cardiol 2012
NP system: deficient in HFpEF

**Pleiotropic beneficial effects**

- Cardiac hypertrophy
- Cardiac fibrosis
- Cardiac dysfunction
- Endothelial dysfunction
- Lipolysis
- Metabolism
- Skeletal muscle performance
- Renal function

**Excluded from HFpEF clinical trials:**
- BMI 30-40 kg/m² excluded due to inability to tBNP levels
- BMI > 40 kg/m² excluded based on BMI cut-off

**Worse NYHA class**
- Reduced exercise capacity
- Worse quality of life

**NOS → NO → sGC → cGMP → PKG**

**NPRA/B → pGC → cGMP → PKG**
Myth #3: HFpEF is a single disease

The many faces of HFpEF
The many faces of HFpEF

HFpEF: not 1 single “disease”

Pathophysiologic contributors to HFpEF

- Diastolic dysfunction
- Longitudinal systolic dysfunction
- Chronotropic incompetence
- Autonomic dysfunction
- Endothelial dysfunction
- Extra-cardiac causes of volume overload
- Arterial stiffness
- Inflammation
- Abnormal V-A coupling
- Pulmonary hypertension / RV failure
- Skeletal muscle abnormalities

### Clinical categories of HFpEF

1. “Garden-variety” HFpEF (HTN, DM, obesity, CKD)
2. CAD-HFpEF
3. Right heart failure-HFpEF
4. A-fib predominant HFpEF
5. HCM-like HFpEF
6. High-output HFpEF
7. Valvular HFpEF (multiple 2+ lesions)
8. Rare causes of HFpEF (“zebras”)

Oktay AA, Shah SJ. *Curr Cardiol Rev* 2014

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**PROBLEM**: Categories not mutually exclusive; often difficult to classify a patient into a single group
3 types of HFpEF presentation

- ENVIRONMENT, DIET
- COMORBIDITIES
- GENETIC SUSCEPTIBILITY

- VULNERABLE HEART, VULNERABLE PATIENT

- HFpEF

- EXERCISE-INDUCED LA PRESSURE
- VOLUME OVERLOAD
- PULMONARY HTN, RV FAILURE

Shah SJ. JACC 2013

Risk profile, BNP vary by type of HFpEF presentation

- EXERCISE-INDUCED LV FILLING PRESSURE
- VOLUME OVERLOAD
- PULMONARY HYPERTENSION RV FAILURE

Clinical course

BNP LEVEL

Shah SJ. JACC 2013
Precision medicine: *Is it all about genomics?*
Cancer vs. heart failure

Optimal targeted approach

Cancer

- Tissue biopsy
- Imaging
- Phenotypic analysis
  - Tumor size, extent
  - Histologic analysis
- Gene expression

Targeted therapy

Sub-optimal one-size-fits-all approach

HF

- Imaging, ECG, PEX
- Phenotypic analysis
  - Quantify LVEF
  - Functional class
  - Fluid status
  - QRS duration

Non-targeted therapy
Phenomapping

deep phenotyping +

machine learning

for novel classification

of HFpEF
Phenomapping: *deep phenotyping + machine learning*

- Uses statistical learning algorithms to detect patterns in complex and varied phenotypic information
- Allows for characterization and discrimination to create discrete groups
- Advantageous for classification of heterogeneous diseases or clinical syndromes → improved targeting of Rx


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**Heart Failure**

**Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction**

Sanjiv J. Shah, MD; Daniel H. Katz, MD; Senthil Selvaraj, MD, MA; Michael A. Burke, MD; Clyde W. Yancy, MD, MSc; Mihaei Gheorghiade, MD; Robert O. Bonow, MD; Chiang-Ching Huang, PhD; Rahul C. Deo, MD, PhD

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**Editorial**

**Using “Big Data” to Dissect Clinical Heterogeneity**

Russ B. Altman, MD, PhD; Euan A. Ashley, MRCP, DPhil

Experienced practitioners recognize that patients with a shared diagnosis often fall into subsets that “look” the same and often respond to similar treatment strategies. Individual data points that are impossible for an individual clinician to analyze fully. HFrEF represents a challenging clinical problem with few effective treatments. Unlike heart failure
Phenomapping of HFpEF

Pheno-group classification:
- Added prognostic value over MAGGIC risk score and BNP
- Replicated prospectively in 107 additional HFpEF patients
HFpEF pheno-groups: clinical

**Pheno-group #1**
- Youngest
- Least comorbidities (except 51% obese)
- Lowest BNP (median 72 pg/ml)

**Pheno-group #2**
- Highest BMI (mean 37 kg/m²)
- Highest fasting glucose
- Most diabetes
- Most sleep apnea
- Most anti-HTN medications
- Mid-range BNP (median 188 pg/ml)
### HFpEF pheno-groups: clinical

<table>
<thead>
<tr>
<th>Pheno-group #1</th>
<th>Pheno-group #2</th>
<th>Pheno-group #3</th>
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<tbody>
<tr>
<td>Youngest</td>
<td>Highest BMI (mean 37 kg/m²)</td>
<td>Oldest</td>
</tr>
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<td>Highest fasting glucose</td>
<td>Lowest BMI</td>
</tr>
<tr>
<td>Lowest BNP (median 72 pg/ml)</td>
<td>Most diabetes</td>
<td>Worst renal function (53% with CKD)</td>
</tr>
<tr>
<td></td>
<td>Most sleep apnea</td>
<td>Most electrical remodeling, AF</td>
</tr>
<tr>
<td></td>
<td>Most anti-HTN medications</td>
<td>Highest BNP (median 607 pg/ml)</td>
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### HFpEF pheno-groups: echo + invasive

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<tr>
<td>PCWP 20±6 mmHg</td>
<td>PCWP 25±8 mmHg</td>
<td>PCWP 24±9 mmHg</td>
</tr>
<tr>
<td>Least cardiac remodeling/dysfunction</td>
<td>Lowest e’ velocity</td>
<td>Most cardiac remodeling/dysfunction (especially RV dysfunction)</td>
</tr>
</tbody>
</table>
Future directions

• Proteomic/RNA-seq evaluation to look for clues to underlying molecular differences
• Further analysis of phenomapping in TOPCAT, RELAX, NEAT, PARAMOUNT HFpEF clinical trials
  » Does Rx response differ by pheno-group assignment?
• Prospective application of phenomapping to HFpEF clinical trials
• Development of animal models that mimic the 3 HFpEF pheno-groups (e.g., db/db mouse for pheno-group #2)

Future directions

• Deep learning: neural network with multiple layers of nodes (feature identification and feature learning; processing in stages): mimics the human brain
Future directions

- History/Physical
- Labs
- ECG
- Echo

Assign Pheno-group

- Deep learning to identify features (phenotypes)
- Statistical learning to assign pheno-groups

Rx

- Late \( I_{Na} \) inhibitors
- sGC stimulators
- \( I_f \) inhibitors
- SERCA2a agonist
- Neprilysin inhibitors

Clinical Trials

Myth #5:
There are no proven treatments for HFpEF
State-of-the-art in 2016: Treatment of HFpEF
Why have treatments failed?

- Multiple potential risk factors
- Confusion about how to diagnose HFpEF
- Poor recognition of presence/prognosis
- Heterogeneity of HFpEF syndrome
  » Several pathophysiologic mechanisms
- Care by multiple different providers
- Comorbidity burden is high
  » Cause of death often not related to progressive heart failure (competing risk)
Rx Step #1: Prevent HFpEF before it even occurs

Stages of heart failure

Stage A
- High risk for development of HF
- HTN, CAD, DM, obesity

Stage B
- Asymptomatic HF
  (abnormal cardiac structure/function)

Stage C
- Symptomatic HF

Stage D
- End-stage, refractory HF

How can we prevent Stage B (and Stage C) heart failure?

HFpEF can be prevented...

**HYVET trial**
indapamide resulted in 64% reduction in HF hosp. compared to placebo

Beckett NS, et al. NEJM 2008

**ALLHAT-HFpEF:** chlorthalidone best for HFpEF prevention

Rx Step #2: Before treating, remember the zebras

HFpEF: Know your zebras

- Assessment of HFpEF: a diagnostic mystery until proven otherwise
- Careful history, physical examination
- Clues to zebras:
  » Kussmaul’s sign: ↑JVP with inspiration
  » ↓Voltage ECG with ↑LV wall thickness
  » Careful evaluation of echo is essential

Oktay AA, Shah SJ. Curr Cardiol Rev 2014
50-year-old woman with SOB

Low voltage, pseudoinfarct pattern

ECG findings
ECG findings

50-year-old woman with SOB

Thick LV, “texture” of myocardium consistent with infiltrative cardiomyopathy
50-year-old woman with SOB

High E velocity, elevated E/A ratio, reduced E', ↓E deceleration time

Grade III (severe) LV diastolic dysfunction due to cardiac amyloidosis

Global longitudinal strain (GLS)

Apical 4-chamber
Apical 2-chamber
Apical 3-chamber
Global longitudinal strain (GLS)

Apical 4-chamber

Apical 2-chamber

"Cherry on top"

Apical 3-chamber

Pop quiz:
Can you identify the cause of LVH in these 4 patients with HFpEF?
A

\[ E = 78 \text{ cm/s} \]
\[ A = 12 \text{ cm/s} \]
\[ E/A = 6.5 \]

B

\[ E = 90 \text{ cm/s} \]
\[ A = 26 \text{ cm/s} \]
\[ E/A = 3.5 \]

C

\[ E = 158 \text{ cm/s} \]
\[ A = 28 \text{ cm/s} \]
\[ E/A = 5.6 \]

D

\[ E = 82 \text{ cm/s} \]
\[ A = 92 \text{ cm/s} \]
\[ E/A = 0.9 \]
A: $s' = 2.9 \text{ cm/s}$  
$e' = 2.2 \text{ cm/s}$  
$a' = 2.4 \text{ cm/s}$

B: $s' = 5.1 \text{ cm/s}$  
$e' = 6.0 \text{ cm/s}$  
$a' = 1.8 \text{ cm/s}$

C: $s' = 9.9 \text{ cm/s}$  
$e' = 7.1 \text{ cm/s}$  
$a' = 10.1 \text{ cm/s}$

D: $s' = 5.8 \text{ cm/s}$  
$e' = 6.0 \text{ cm/s}$  
$a' = 4.1 \text{ cm/s}$

**Peak Systolic Strain**

A:  
B:  
C:  
D:  

Click here for tips
Typical echo findings in cardiac amyloidosis

Loss of longitudinal cardiac function

Typical echo findings

Severely reduced longitudinal tissue velocities

“5-5-5 sign”
64-year-old man with chronic ascites

[Image of echocardiogram with RV and LV labels]

64-year-old man with chronic ascites

[Diagram showing pressure in mmHg]

Pressure (mmHg)
64-year-old man with chronic ascites

Zebras can be treated!

- **Cardiac amyloid:** *not a death sentence*
  - Primary (AL) amyloidosis:
    - Stem cell transplantation *or*
    - Cardiac transplant followed by stem cell tx
  - Familial or wild-type TTR amyloidosis:
    - Several novel drugs in pipeline (TTR stabilizers, RNA interference, RNA anti-sense molecules)
    - Heart-liver transplant

- **Constrictive pericarditis:**
  - Pericardial stripping can be curative
Primary (AL) cardiac amyloid: improved survival with stem-cell tx

- Northwestern (N=26)
  - Chemo + HSCT: N=19
  - Chemo only: N=7
- Historical controls (N=24)
  - Dubrey et al. Heart 1997

Rx Step #3:
Treat comorbidities, BP, fluid overload
HFpEF treatment algorithm

- Diagnose HFpEF accurately
  » Remember that HFpEF is extremely common
  » Make sure you’re not dealing with a “zebra”
  » Low threshold for cardiac catheterization, CAD eval
- Treat the underlying cause of HFpEF
- Treat BP, fluid overload
- Treat comorbidities aggressively
- CHF education, chronic disease management

Carvedilol
Bumetanide
Chlorthalidone
Lisinopril
Spironolactone

HFpEF “poly-pill”
Step #4:
Tailor treatment to the type of HFpEF

EXERCISE-INDUCED
↑LA PRESSURE

- Exercise training
- Structure diet/weight loss
- Nitrates/nitrites?
- Ivabradine?
- Late Na+ current inhibitors (e.g., ranolazine)?
Interatrial shunt device for HFpEF

Creation of L-to-R shunt = ↓↓LAp at rest/exercise = ↓↓symptoms in HFpEF


InterAtrial Shunt Device: Concept

Transcatheter implant to create a small permanent interatrial shunt (Qp:Qs ratio 1.2-1.3)
IASD deployment

Fluoroscopic + TEE/ICE guidance
Venous access (16F)
Standard transseptal puncture mid fossa

LA legs deployed  Post-deployment
REDUCE LAP-HF trial


REDUCE LAP-HF trial

Two 66-year-old women with HFpEF: Who should get the IASD?
Two 66-year-old women with HFpEF: Who should get the IASD?

- RAP: 12 mmHg
- PCWP: 29 mmHg
- CI: 3.4 L/min/m²
- PVR: 1.8 WU

- RAP: 24 mmHg
- PCWP: 28 mmHg
- CI: 2.1 L/min/m²
- PVR: 3.8 WU

REDUCE LAP-HF I randomized trial

- A randomized study to evaluate the Corvia Medical IASD® System II to REDUCE Elevated Left Atrial Pressure in Patients with HF
- Enrollment began Q1 2016
- Symptomatic HF with LVEF > 40%
- 1-mo. mechanistic endpoint (exercise PCWP)
- Planned enrollment: n=60, goal implant in n=40 (20 in each arm)
- Crossover allowed at 1 year
VOLUME OVERLOAD

- Elevated Cr during diuresis? Consider hemoconcentration
- Spironolactone
  - Hemodynamic monitoring for tailored diuretic therapy
  - Neprilysin inhibition? (PARAGON-HF trial)
  - sGC stimulator therapy? (SOCRATES trial)
  - Serelaxin for acute HF? (RELAX-AHF2 trial)

Spironolactone

- Great for volume overload, RV failure
- ALDO-DHF and RAAM-PEF:
  » Mineralocorticoid receptor antagonists probably don’t work in exercise-induced DD
- TOPCAT (N=3445):
  » Spironolactone vs. placebo for HFpEF
  » More volume overloaded than ALDO-DHF
  » ↓ hospitalization but missed 1° endpoint
  » In Americas, spironolactone = better outcomes
**1. Outcome**
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

Placebo vs Spironolactone:
- **HR = 0.89 (0.77 – 1.04)**
- **p=0.138**

Placebo Rates:
- **Primary Outcome, by region**
  - **Americas N=1767 (51%)**
    - US: N=1151
    - Canada: N=326
    - Brazil: N=167
    - Argentina: N=123
    - **12.6 per 100 pt-yr**
  - **Russia/Georgia N=1678 (49%)**
    - Russia: N=1066
    - Rep Georgia: N=612
    - **2.3 per 100 pt-yr**
Placebo vs. Spiro by Region

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)

Russia, Rep Georgia
HR=1.10 (0.79-1.51)

Interaction p=0.122

Placebo: 280/881 (31.8%)
Spiro: 242/886 (27.3%)

Placebo: 71/842 (8.4%)
Spiro: 78/836 (9.3%)

CHAMPION TRIAL

LA pressure = improved outcomes in HFpEF

Adamson PB, et al. Circulation Heart Failure 2014
PULMONARY HYPERTENSION
RV FAILURE

- Aggressive diuresis, ultrafiltration often needed
- May need to discontinue systemic vasodilators
- Midodrine for low BP during diuresis (if not contraindicated)
- Digoxin to RV inotropy
- PDE5 inhibition if PADP-PCWP gradient > 5 mmHg
- Hemodynamic sensor for careful titration of diuretics

HFpEF treatment pearls

1. “Garden-variety”-HFpEF: Rx BP, DM, obesity, refer for clinical trial; If AF → trial of cardioversion
2. CAD-HFpEF: Rx like HF w/reduced EF (BB, ACE-I/ARB, revasc)
3. Right heart failure-HFpEF: diuresis / ultrafiltration, digoxin, sildenafil?
4. HCM-HFpEF: verapamil, diltiazem, long-acting metoprolol
5. High-output HFpEF: Rx underlying cause; diuretics/UF
6. Valvular HFpEF: Rx valve disease if possible
7. Rare causes of HFpEF: clinical trial, Rx underlying cause
Myth #6: HFpEF clinical trials are doomed

HFpEF survival: poor

Dismal 35% survival at 5 years after HF hospitalization, regardless of LVEF
HFpEF survival: poor

HFpEF survival: comparable to T4 non-small cell lung cancer, stage 3B or worse

Current HFpEF clinical trials

- PARAGON-HF: *neprilysin inhibition*
- SOCRATES-Preserved: *sGC stimulator*
- REDUCE-LAP: *interatrial shunt device*
- INDIE-HF: *inhaled nitrites*
- KNO₃CK-OUT: *oral nitrites*
- LIBERTY-HCM: *late I_{Na⁺} inhibitor*
- ATTR-ACT: *transthyretin stabilizer*
- ENDEAVOUR: *transthyretin RNAi*
cGMP-PKG pathway in HFpEF

NOS → NO → sGC → cGMP → PKG

NATRIURETIC PEPTIDES → NPRA/B → pGC → cGMP → PKG

Pleiotropic beneficial effects

↓Cardiac hypertrophy
↓Cardiac fibrosis
↓Cardiac dysfunction
↓Endothelial dysfunction
  ◦ Lipolysis
  ◦ Metabolism
  ◦ Skeletal muscle performance
  ◦ Renal function

Nitrates
Nitrites
sGC stimulators
PDE5 inhibitors

↑Natriuretic Peptides
  ◦ Neprilysin inhibitors
  ◦ ANP, BNP
  ◦ PDE9 inhibitors

Pleiotropic beneficial effects

↓Cardiac hypertrophy
↓Cardiac fibrosis
↓Cardiac dysfunction
↓Endothelial dysfunction
  ◦ Lipolysis
  ◦ Metabolism
  ◦ Skeletal muscle performance
  ◦ Renal function
NP system

Physiological response

NP system

Pathophysiological response

Ang II

AT₁ receptor

Inactive fragments

Vasodilation

BP

Sympathetic tone

Aldosterone

Fibrosis

Hypertrophy

Natriuresis

HF symptoms/progression

Vasoconstriction

BP

Sympathetic tone

Aldosterone

Fibrosis

Hypertrophy

Endothelial Dysfunction

Oxidative Stress

Inflammation

sGC Insufficiency

Myocardial Dysfunction

Impaired Relaxation, Diastolic Stiffening, Energy Wastage

Vascular Dysfunction

Disturbed Endothelium-Dependent Vasotone Regulation

Endothelial NO Synthase (eNOS)

sGC: soluble Guanylate Cyclase

NO: Nitric Oxide

cGMP: cyclic Guanosine Monophosphate

Endothelial Dysfunction

sGC Stimulators

sGC Insufficiency

Myocardial Dysfunction

Vascular Dysfunction

Impaired Relaxation, Diastolic Stiffening, Energy Wastage

Disturbed Endothelium-Dependent Vasotone Regulation

sGC: soluble Guanylate Cyclase

NO: Nitric Oxide

cGMP: cyclic Guanosine Monophosphate
**Hypothesis**

Dr. A. Sauer, Dr. S. Shah, Northwestern

- Soluble guanylate cyclase stimulators will:
  - Increase cGMP \( \rightarrow \) improve calcium handling
  - Decrease heterogeneity of APD-CaT delay

**Rationale for testing NITRITES in HFpEF**

1. **Nitrites are very different than nitrates**
2. Endothelial dysfunction plays a central role in HFpEF
3. Nitrites improve endothelial function
4. Nitrates may actually *worsen* endothelial function via increased ROS
5. Unlike nitrates, there is strong preliminary data for nitrites in HFpEF (both oral and inhaled forms)
**ISMN and Nitrite are very different**

<table>
<thead>
<tr>
<th></th>
<th>Isosorbide mononitrate (ISMN)</th>
<th>Nitrite</th>
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<tr>
<td><strong>Activation</strong></td>
<td>P450 enzymes in the endoplasmic reticulum</td>
<td>Heme-containing proteins, XO, others</td>
</tr>
<tr>
<td><strong>NO elaboration</strong></td>
<td>Tonic - Throughout the day</td>
<td>Intermittent - Coupled to tissue hypoxia, exercise</td>
</tr>
<tr>
<td><strong>Tolerance</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Endothelial Dysfunction</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>↑ROS</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**“Matchmaking” for optimizing HFpEF clinical trials**

<table>
<thead>
<tr>
<th></th>
<th>Exercise-induced Diastolic Dysfunction</th>
<th>Volume Overload</th>
<th>Pulmonary Hypertension RV Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THEORETICAL “MATCHED” THERAPIES</strong></td>
<td>Ivabradine</td>
<td>Aldosterone blocker</td>
<td>PDE5 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Exercise training</td>
<td>Neprilysin inhibitor</td>
<td>Hemodynamic sensor</td>
</tr>
</tbody>
</table>

Shah SJ. JACC 2013
“Matchmaking” for optimizing HFpEF clinical trials

EXERCISE-INDUCED DIASTOLIC DYSFUNCTION ↔ VOLUME OVERLOAD ↔ PULMONARY HYPERTENSION RV FAILURE

THEORETICAL “MATCHED” THERAPIES

- Ivabradine
- Interatrial shunt device
- Exercise training
- Inorganic nitrates

- Aldosterone blocker
- Neprilysin inhibitor

- PDE5 inhibitor
- sGC stimulator

- Hemodynamic sensor

Shah SJ. JACC 2013

STOP!
1. Make sure you didn’t miss dx of HFpEF

2. Don’t forget the zebras

3. Categorize by type of HFpEF presentation and tailor treatment

4. There are treatment options for HFpEF!

5. Enroll in HFpEF clinical trials

---

**HFpEF: to “huff and puff”**

**huff and puff**

1. to breathe very hard; to pant as one exerts effort. John came up the stairs huffing and puffing. He huffed and puffed and finally got up the steep hill.

**huff and puff**

1. to breathe noisily, usually because you have been doing physical exercise. They’re so out of breath that they start huffing and puffing if they have to run further than twenty yards.
2. (informal) to complain noisily about something but not be able to do anything about it. They huffed and puffed about the price, but eventually they paid up.

---

Stop! STOP!
huff and puff

Fig. to breathe very hard; to pant as one exerts effort. John came up the stairs huffing and puffing. He huffed and puffed and finally got up the steep hill.

See also: and, huff, puff


huff and puff

1. to breathe noisily, usually because you have been doing physical exercise. They're so out of breath they start huffing and puffing if they have to run further than twenty yards.

2. (informal) to complain noisily about something but not be able to do anything about it. They huffed and puffed about the price, but eventually they paid up.

See also: and, huff, puff


huff and puff

1. to breathe in a noisy manner. He was on the top of the hill long before I came up huffing and puffing behind him.

2. to complain. The owners will huff and puff about their financial problems and then not do anything to solve them.

See also: and, huff, puff


---

Need help with HFpEF?

- Email me:
  » sanjiv.shah@northwestern.edu
Case #1:
63-year-old woman with long-standing rheumatoid arthritis presents with dyspnea, LE edema, fatigue

Meds: furosemide, hydroxychloroquine, NSAIDs PRN

PEX: BP 108/62, HR 84, RR 12
JVP 12 cm, clear lungs, RRR nl S1 S2
3/6 holosystolic murmur LSB, 1+ LE edema
Case #1

Normal LVEF = 60%  
PASP = 55 mmHg

E/A ratio = 2:1  
LV filling pressures: indeterminate

Pulmonary vein S/D ratio = 0.7

Septal e’ = 5 cm/s  
Lateral e’ = 7 cm/s
Case #2: Hemodynamics

- Dip-and-plateau in RV pressure tracing
- Concordant RV and LV pressure tracings
VACUOLIZATION OF MYOCYTES

MYELIN FIGURES
PAH vs PVH: Practical tips on echo

Normal LVEF + ↑PASP?
Think PVH (HFpEF) until proven otherwise
PAH vs PVH: Practical tips on echo

Normal LVEF + ↑PASP? 
Think PVH (HFpEF) until proven otherwise

Left atrial enlargement 
(LA size > RA size)

PAH vs PVH: Practical tips on echo

Normal LVEF + ↑PASP? 
Think PVH (HFpEF) until proven otherwise

Left atrial enlargement 
(LA size > RA size)

Interatrial septum bows 
from left to right
PAH vs PVH: Practical tips on echo

Normal LVEF + ↑PASP? Think PVH (HFpEF) until proven otherwise

Left atrial enlargement (LA size > RA size)
Interatrial septum bows from left to right
Grade 2+ diastolic dysfunction (↑E/A ratio)

Decreased lateral e’
Elevated lateral E/e’
PAH vs PVH: Practical tips on echo

- Normal LVEF + PASP?
  - Think PVH (HFpEF) until proven otherwise

- Left atrial enlargement (LA size > RA size)
- Interatrial septum bows from left to right
- Grade 2+ diastolic dysfunction (E/A ratio)
- Decreased lateral e’
- Elevated lateral E/e’

Respiratory variation in PCWP

- PW 10/12 (7)
- Respiratory variation in PCWP
Respiratory variation in PCWP

End-expiratory PCWP = 27 mmHg

Lung disease
Morbid obesity
Case #2:
62-year-old woman with HTN, DM2, CKD presents with DOE

PEX: BP 148/52, HR 88, RR 12
JVP 10 cm, clear lungs,
RRR; nl S1 S2; No S3, +S4;
soft systolic murmur
trace LE edema

BNP 90 pg/ml (normal < 100 pg/ml)

HFpEF: Global CV reserve dysfxn

HFpEF: evidence of impaired CV reserve at 20W exercise
Case #2: Diastolic stress echo

Diastolic stress echocardiography

- Useful test to determine whether or not patients have exercise-induced DD
- E/e’ estimates LV filling pressures at rest and with exercise
- Based on published studies, an E/e’ > 13 (using the septal E’ velocity) can be used to diagnose exercise-induced DD
- Okay to wait until heart rate < 90 bpm

Effect of ↑preload on LA strain

*HFpEF vs. non-cardiac dyspnea*

Exercise hemodynamics

**Typical left-sided HF**
(pulmonary venous hypertension)
Volume challenge in a patient w/HFpEF

PCWP (mmHg)

Baseline  Post-1L saline bolus

(No dynamic MR)

Exercise hemodynamics in a patient with severe HFpEF

PCWP

REST  AFTER 1 MIN. OF EXERCISE

(No dynamic MR)
Additional treatment pearls for HFpEF

Pulmonary vasodilators in PH-HFpEF

- **Theoretical risk of increasing PCWP**
- PDE5 inhibitors:
  » Most promising; but trials = mixed results
- sGC stimulators:
  » DILATE-1: single dose oral riociguat
  » Failed to decrease invasive PA pressure
  » $\uparrow$SV, $\downarrow$BP, decreased RV end-diastolic area

## Sildenafil in HFpEF: RCTs

<table>
<thead>
<tr>
<th>Guazzi et al</th>
<th>RELAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of PH required</td>
<td>Evidence of PH not required</td>
</tr>
<tr>
<td>N=44</td>
<td>N=216</td>
</tr>
<tr>
<td>PASP 53 mm Hg</td>
<td>PASP 41 mm Hg</td>
</tr>
<tr>
<td>Mean PADP-PCWP: 9 mmHg</td>
<td>Hemodynamic testing not done</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>6 month follow-up</td>
</tr>
<tr>
<td>Primary outcome: hemodynamics, RV performance, QOL</td>
<td>Primary outcome: peak VO$_2$</td>
</tr>
<tr>
<td>Positive trial</td>
<td>Negative trial</td>
</tr>
</tbody>
</table>

Redfield M, et al. JAMA 2013

## Treatment of uncontrolled HTN

- **Look for secondary causes**
- **BAD drugs**: Atenolol, prazosin, clonidine
  - These drugs won’t control BP very well: Diltiazem, verapamil, metoprolol
- **GOOD drugs**: Carvedilol, ACE-I/ARB, thiazide, aldo-blockers
  - Dihydropyridine CCBs are effective, but cause edema
Treatment of uncontrolled HTN

- **Remember!** Volume overload = higher BP in older pts with stiff arteries, so diurese
- **Remember!** Non-cardiac meds can exacerbated BP (avoid NSAIDs, look for other offending drugs)
- Most patients don’t require newer expensive drugs (e.g., tekturna, nebivolol)

Inpatient diuresis pearls

- Loop diuretics are secreted from proximal tubule → lumen
  » Worse renal function = need higher dose
  » Normal renal function = need higher frequency
- If using a continuous infusion:
  » Remember to start with bolus and always re-bolus before increasing dose/rate of gtt
- In patients who are on chronic loop diuretics or who have “diuretic braking” effect:
  » Add thiazide and/or aldo-blocker
Inpatient diuresis pearls

- Remember! ↑creatinine during IV diuresis ≠ worsening renal failure in all cases
- Consider hemoconcentration if:
  » The patient is improving clinically
  » Hematocrit, albumin, total protein going up
  » BP is stable
- In these cases, don’t give back fluids & continue to diurese if still hypervolemic
  » Do echo to look at IVC or right heart cath to determine volume status if in doubt

Loop diuretics

- Bumetanide, torsemide better absorbed (and higher bioavailability) than furosemide
- Use higher doses in patients w/CKD
- Once euvolemic, minimize the dose to prevent adverse effects
- Teach patients self-titration
Chlorthalidone

- ALLHAT: may be beneficial in HFpEF
- Helpful for augmenting diuresis with loop diuretics
- Start at a low dose (e.g., 12.5 or 15 mg PO QD) and titrate carefully, especially in the elderly

Beta-blockers

- Trials (ELANDD, J-DHF) have been disappointing
- Use vasodilating beta-blockers (e.g., carvedilol) if you use them
  » COHERE registry showed that carvedilol improves outcomes in HF regardless of underlying LVEF
- Watch for chronotropic incompetence
  » Use cardiopulmonary exercise test to look for this
- Watch for restrictive cardiomyopathy-type physiology (dependence on HR to augment CO)
ACE-I/ARB

- Trials have been disappointing in terms of hard endpoints
- Might improve exercise tolerance
- Might work well in CAD-HFpEF
- Bottom line:
  » Most patients are on these drugs for comorbidities

Treat HFpEF by treating comorbidities

- >90% of patients with HFpEF have HTN, CAD, diabetes, and/or CKD
- Sleep disordered breathing and COPD very common in HFpEF
- Comorbidities drive morbidity and mortality in HFpEF

HFpEF: Importance of CAD

- Downplayed as a risk factor for HFpEF
- But prevalence up to 50% in HFpEF
- Consider coronary angiography in all pts.
- Lower EF? ↑likely to have CAD
- When investigated systematically, CAD associated with worse outcomes
- Rx CAD: may alleviate HFpEF

Shah SJ, Curr Treat Options Cardiovasc Med 2010

CAD: worse outcomes in HFpEF

<table>
<thead>
<tr>
<th>Freedom from HF Hospitalization</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Graph](no CAD vs CAD)</td>
<td>![Graph](no CAD vs CAD)</td>
</tr>
<tr>
<td>Hazard Ratio = 1.7 (95% CI 1.0-2.7)</td>
<td>Hazard Ratio = 3.2 (95% CI 1.5-6.6)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, obesity, HTN, hyperlipidemia, diabetes, CKD, logBNP, S', E/E', and baseline wall motion abnormality*

Gupta D., Shah SJ. ASE 2011
Confirmed diagnosis of HFpEF
Signs and symptoms of HF
LVEF > 50%

Yes

No

Known CAD?
Prior MI, CABG, or PCI; or coronary stenosis > 50%.

Yes

No

Relative contraindication to coronary angiography (e.g., significant CKD)?

Yes

No

Desire to locate ischemia and/or quantify ischemic burden to assist in planning coronary revascularization?

Yes

No

Perform right and left heart catheterization with coronary angiography

HFpEF + CAD
HFpEF, no CAD

Go to treatment section

HFpEF diagnosis equivocal

Consider right and left heart catheterization to confirm diagnosis of HFpEF (r. LVEF, filling pressures and/or R & cardiac output). Perform coronary angiography if not contraindicated.

HFpEF + CAD
HFpEF, no CAD
No HFpEF

Go to treatment section

Treatment of HFpEF + CAD:
1. Consider revascularization based on current guidelines for CAD and HFpEF.
2. Statins: all patients unless contraindicated
3. Aspirin: all patients unless contraindicated
4. CCB (or equivalent antihypertensives): if indicated by current guidelines (e.g., recent PCI or ACS)
5. ACE inhibitor: consider in all patients unless contraindicated
6. ARB: if ACE inhibitor contraindicated
7. B-blocker: perform exercise testing to evaluate for CI. If CI, first consider percutaneous revascularization, then start B-blocker. If no CI, treat with vasodilating B-blocker.*
8. Angina: consider revascularization if angina is not controlled by above medications. Also consider nitrates, calcium channel blockers.*
9. Optimal BP management: if BP is not controlled by ACE inhibitor/ARB + vasodilating B-blockers, optimize fluid status (hypervolemia may exacerbate hypertension in patients with increased arterial stiffness), add thiazides, consider spironolactone
10. Lifestyle modification: diet, exercise, cardiac rehabilitation, smoking cessation, weight loss (consider bariatric surgery in morbid obesity). Treat obstructive sleep apnea
11. Enroll in HFpEF clinical trial

Shah SJ. Curr Treat Options Cardiovasc Med 2010