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Echo to Phenotype and Guide Therapy of HFpEF

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Echo is the key test for *HFpEF diagnosis*

HFpEF diagnostic toolbox

- Physical exam
- Biomarkers
- Echocardiography
- Invasive exercise hemodynamics
- Coronary evaluation
- Cardiac MRI
- Cardiopulmonary exercise test

Diagnosis of HFpEF?

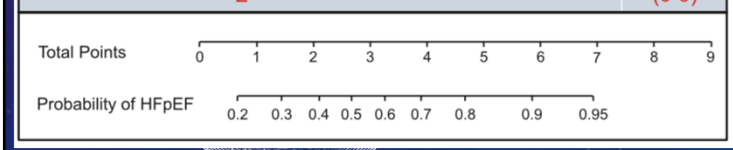
- It's not as complicated as you think:
  - ✓ Signs and symptoms of HF ***and***
  - ✓ LVEF ≥ 50% *and*
  - ✓ Objective evidence of a cardiac problem:
    - — Elevated BNP *or*
    - — LA enlargement *or*
    - — Elevated resting PCWP (≥ 15 mmHg) ***or***
    - — Elevated exercise PCWP (≥ 25 mmHg)

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 the diagnosis
    - — Patients can have HFpEF with "normal" diastolic function or "mild" DD *at rest*

H_2FPEF score

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)



- Dyspnea on exertion, normal EF
- HFpEF vs. non-cardiac dyspnea?
- Intermediate pre-test probability

Nomogram below table for probability of HFpEF based on score:

- A score of 4 or higher = 70% probability of HFpEF
- A score of 5 or higher = >80% probability of HFpEF
- **A score of 7 or higher = >95% probability of HFpEF**

Reddy YN…Borlaug BA. *Circulation* 2018

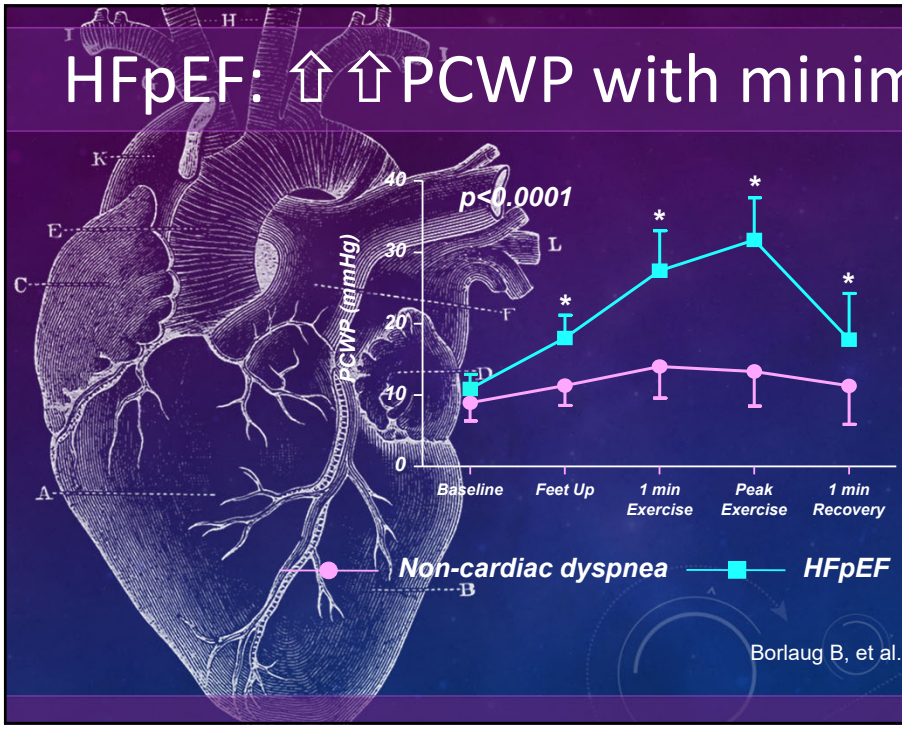
ESC HFA-PEFF score

MAJOR CRITERIA: 2 POINTS, MINOR CRITERIA: 1 POINT

	Functional	*Morphological*	*Biomarker*
MAJOR	Septal e' < 7, Lateral e' < 10, *or* E/e' (avg) ≥ 15	LAVI > 34 *or* LVMI > 149/122 (M/F) *and* RWT > 0.42	NTproBNP > 220/660 (SR/AF) *or* BNP > 80/240 (SR/AF) *SR = sinus rhythm / AF = a.fib
MINOR	E/e' (avg) 9-14, *or* TR vel > 2.8, *or* GLS < 16%	LAVI > 29-34, *or* LVMI > 115/95 (M/F), *or* RWT > 0.42, *or* LVWT > 12 mm	NTproBNP > 115-220 *or* BNP 35-80 in SR *or* NTproBNP > 365-660 *or* BNP 105-240 in AF

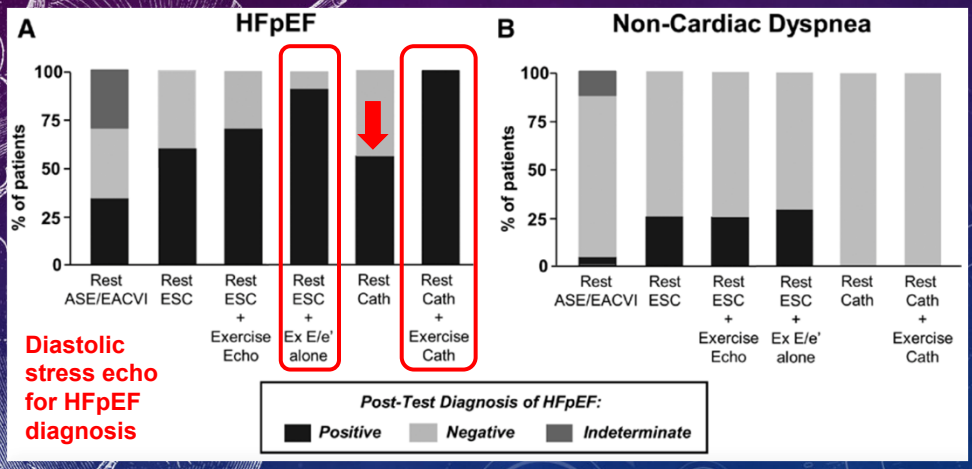
HFA-PEFF score ≥ 5 points: HFpEF
HFA-PEFF score 2-4 points: diastolic stress test *or* invasive hemodynamics
HFA-PEFF score < 2 points: No HFpEF

HFpEF: ⇧⇧PCWP with minimal exercise



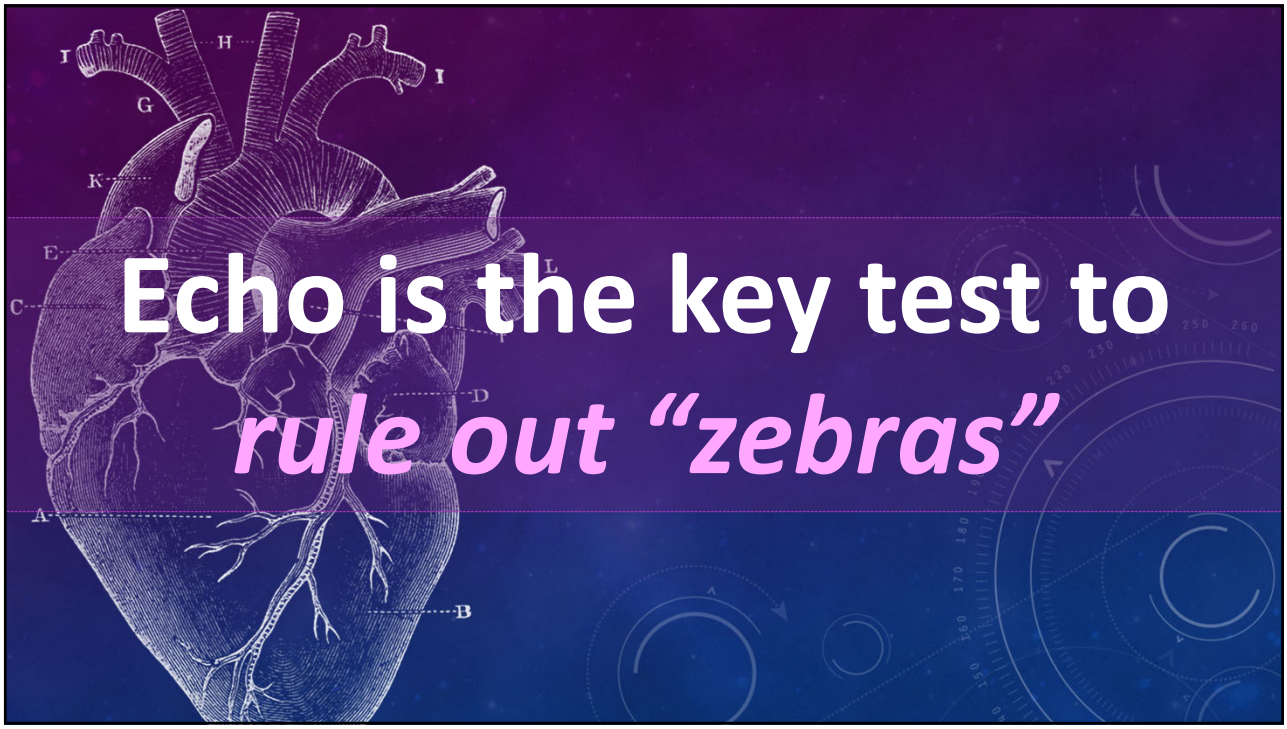
Borlaug B, et al. *Circ Heart Fail* 2010

"Perturb the system" for HFpEF Dx



Diastolic stress echo for HFpEF diagnosis

Obokata…Borlaug. *Circulation* 2017



Differential diagnosis of HFpEF

Etiology	Diagnostic tools	Treatment
Cardiac amyloidosis	Monoclonal proteins, radionuclide scintigraphy, biopsy	Tafamidis (for transthyretin amyloidosis) or chemotherapy (for light-chain amyloidosis); avoid neurohormonal antagonists
Hypertrophic cardiomyopathy	Echocardiography, cardiac MRI	β-Blockers, calcium-channel blockers or septal-reduction therapies (for obstructive cardiomyopathy); avoid vasodilators
Cardiac sarcoidosis	Cardiac MRI, FDG-PET, biopsy	Immunosuppressive agents
Constrictive pericarditis	Echocardiography, cardiac MRI or CT imaging, invasive haemodynamic measurements	Pericardiectomy
Valvular heart disease[a]	Echocardiography, invasive haemodynamic measurements with ventriculography	Surgical or percutaneous valve interventions
Coronary artery disease[a]	Invasive coronary angiography, stress imaging[b] or CT imaging	Revascularization, aspirin, statins, β-blockers and nitrates
High-output heart failure	Evaluate for arteriovenous shunts and liver disease	Treatments directed at the cause of high cardiac output (such as fistula ligation for shunts, liver transplantation for cirrhosis)
Myocarditis	Cardiac MRI, endomyocardial biopsy	Immunosuppressive agents for some types (such as giant cell myocarditis or eosinophilic myocarditis)
Toxins[a]	Assessment of clinical history, blood testing, endomyocardial biopsy	Removal of offending toxin (such as alcohol, cocaine, chemotherapy or radiation therapy, or heavy metals)

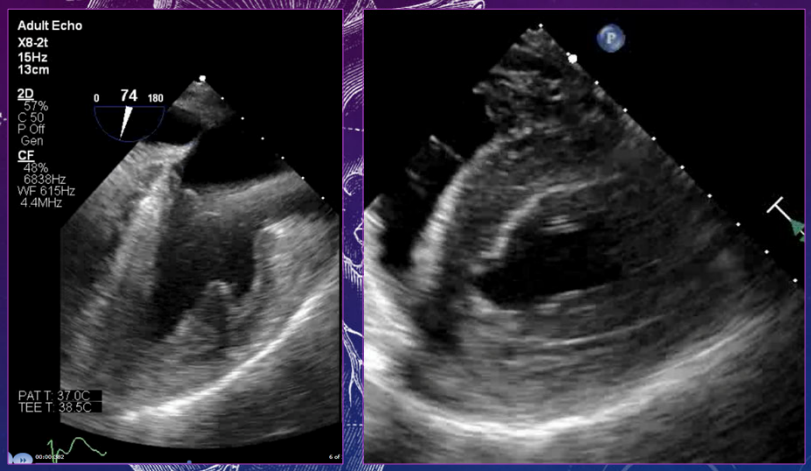
Borlaug BA.
Nat Rev Cardiol 2020

HFpEF: Rule out "zebras"

- Assessment of HFpEF:
  - ✓ A diagnostic mystery until proven otherwise
- Clues to possible zebras:
  - ✓ HFpEF in a younger patient (age < 55)
  - ✓ Low BP, lack of risk factors, or LVH without HTN
  - ✓ Definite HFpEF (e.g., HF hosp., ↑BNP) but low H2FPEF score
  - ✓ Kussmaul's sign: ↑JVP with inspiration
  - ✓ Persistent, low-level troponin elevation
  - ✓ Low prealbumin (=transthyretin)

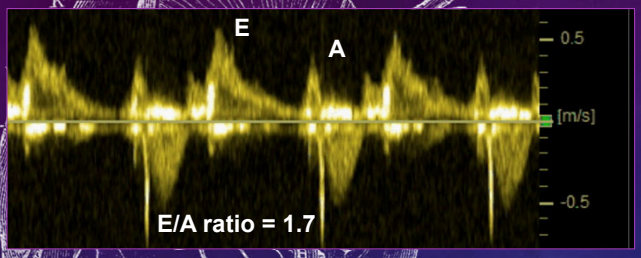
Oktay AA, Shah SJ. *Curr Cardiol Rev* 2014

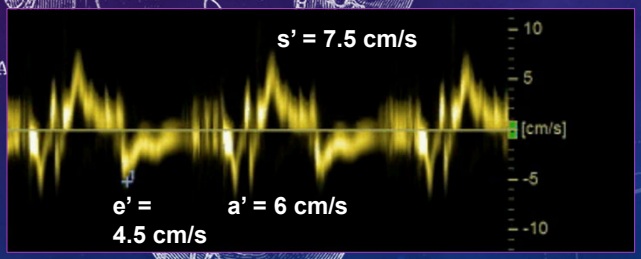
62-year-old man with HFpEF, AF

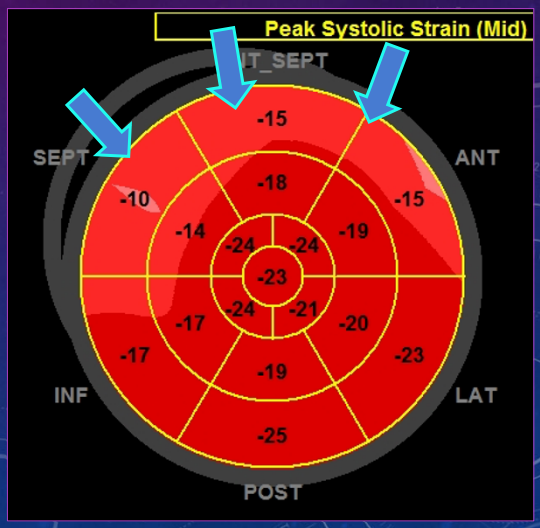


- **Previously healthy and active**
- **No other HFpEF risk factors**

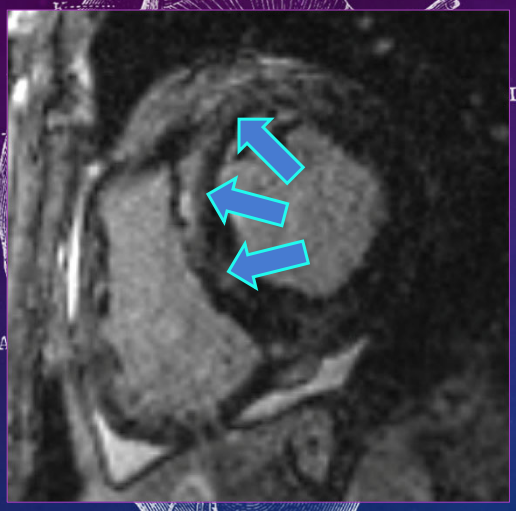
62-year-old man with HFpEF, AF







62-year-old man with HFpEF, AF



- **Cardiac MRI:** patchy +LGE especially in septum
- **Genetic testing:** *TNNT2* I79N pathogenic mutation, known cause of HCM with a restrictive cardiomyopathy pattern

HFpEF: Know your zebras

- Restrictive cardiomyopathy:
  - ✓ Sparkling myocardium
  - ✓ Severely decreased tissue Doppler s' and e'
  - ✓ Preserved radial fxn, reduced longitudinal fxn
- Constrictive pericarditis:
  - ✓ Septal bounce
  - ✓ Preserved e' velocity
  - ✓ Respiratory variation in mitral inflow
  - ✓ Preserved longitudinal fxn, reduced radial fxn

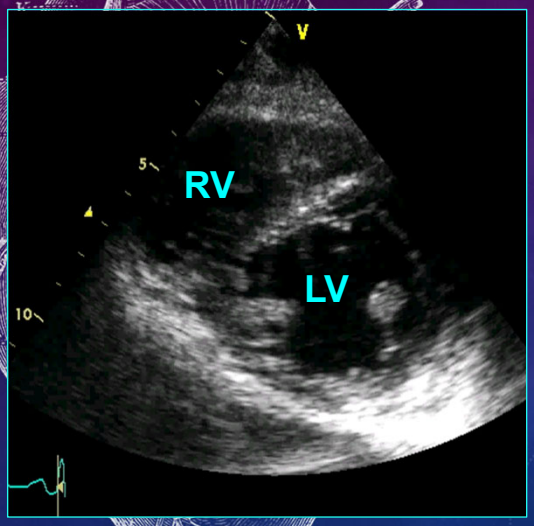
Oktay AA, Shah SJ.
Curr Cardiol Rev 2014

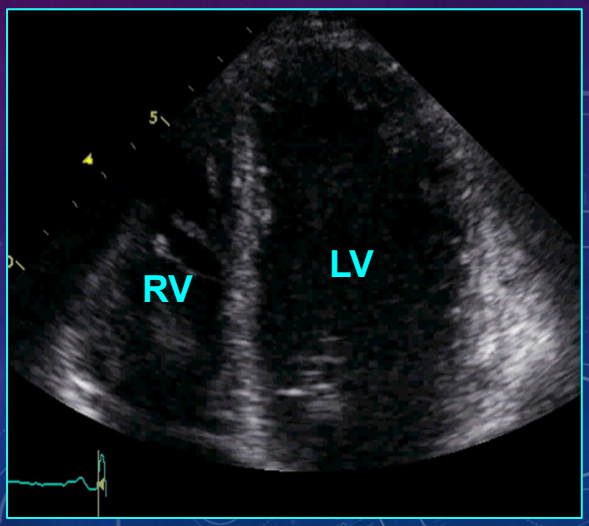
HFpEF: Know your zebras

Parameter	Restriction	Constriction
Tissue Doppler e' velocity	Severely reduced	Normal
Hepatic vein imaging	Flow reversal during *inspiration*	Flow reversal during *expiration*
Simultaneous LV/RV tracings	Concordance	Discordance

Oktay AA, Shah SJ.
Curr Cardiol Rev 2014

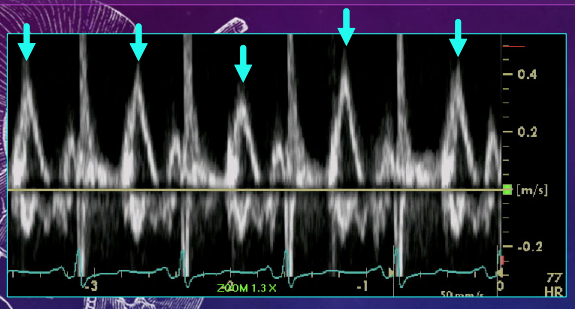
64-year-old man with “HFpEF”, ascites



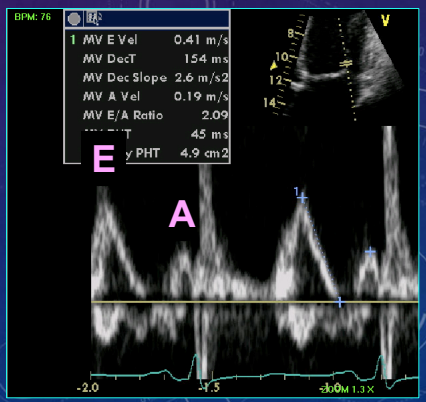


64-year-old man with “HFpEF”, ascites

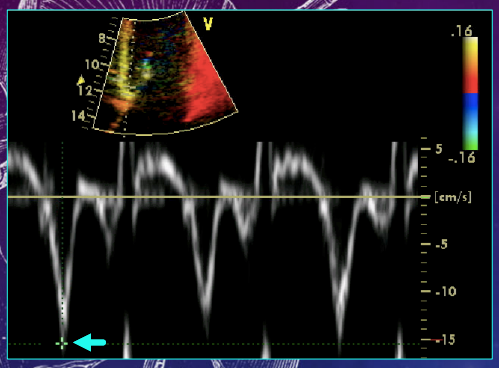
Respiratory variation in mitral inflow

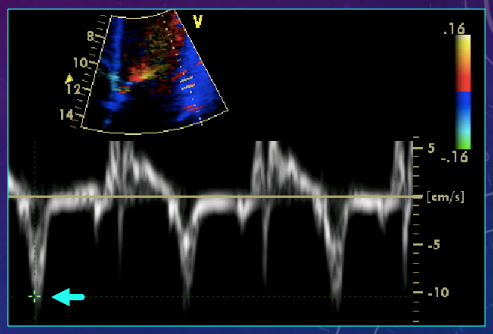


E/A: 2.1
DT: 154 ms
(Grade 3 DD)



64-year-old man with “HFpEF”, ascites

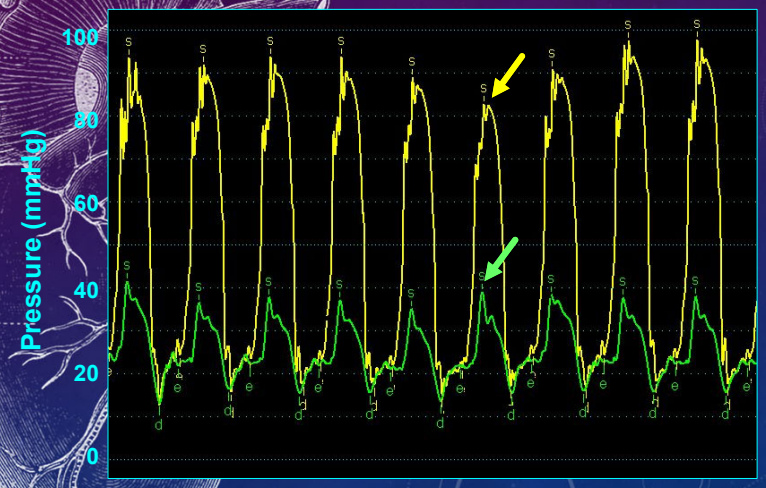




Septal e’ = 15 cm/s **Lateral e’ = 10 cm/s**

Annulus paradoxus: Preserved e’ despite grade 3 DD
Annulus reversus: Septal e’ > lateral e’

64-year-old man with “HFpEF”, ascites

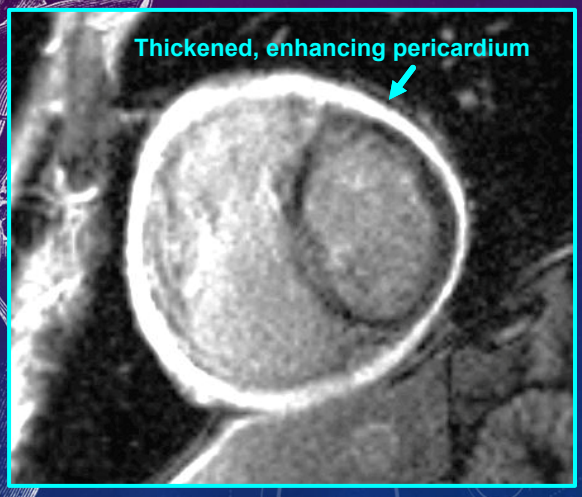


RV-LV discordance during inspiration

64-year-old man with “HFpEF”, ascites

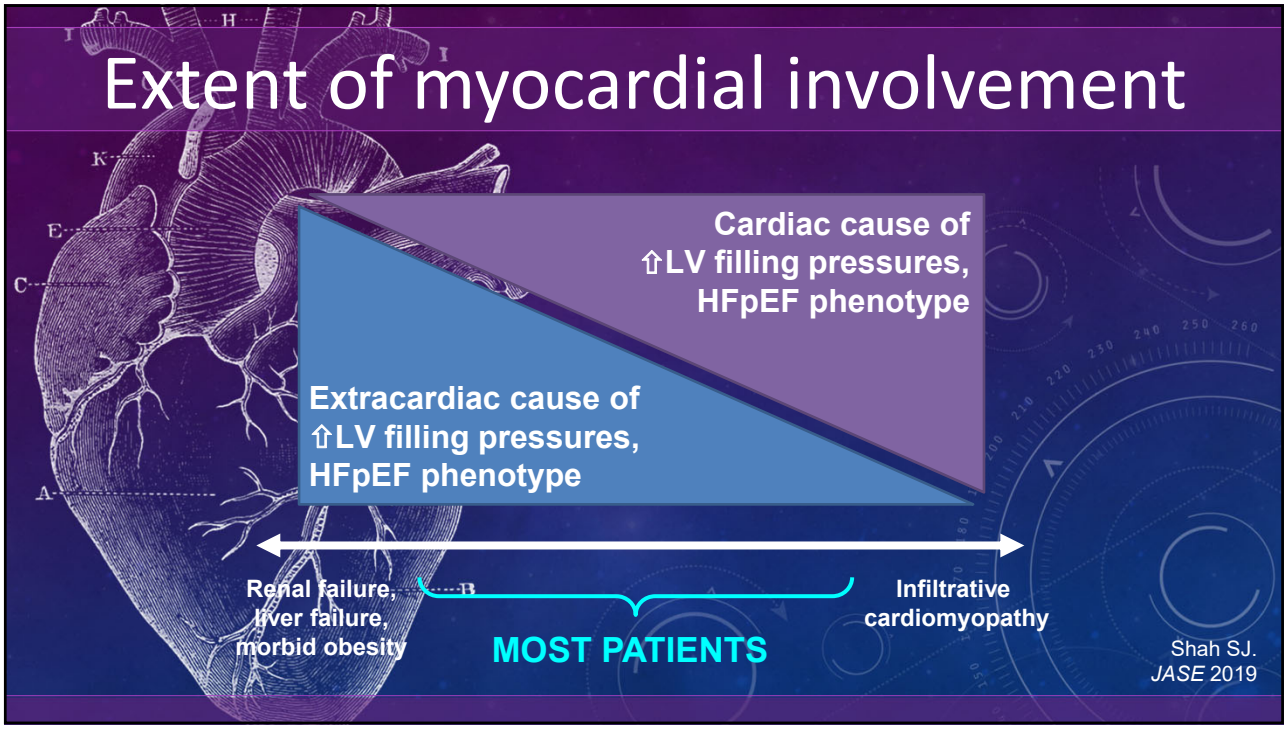
Cardiac MRI with contrast

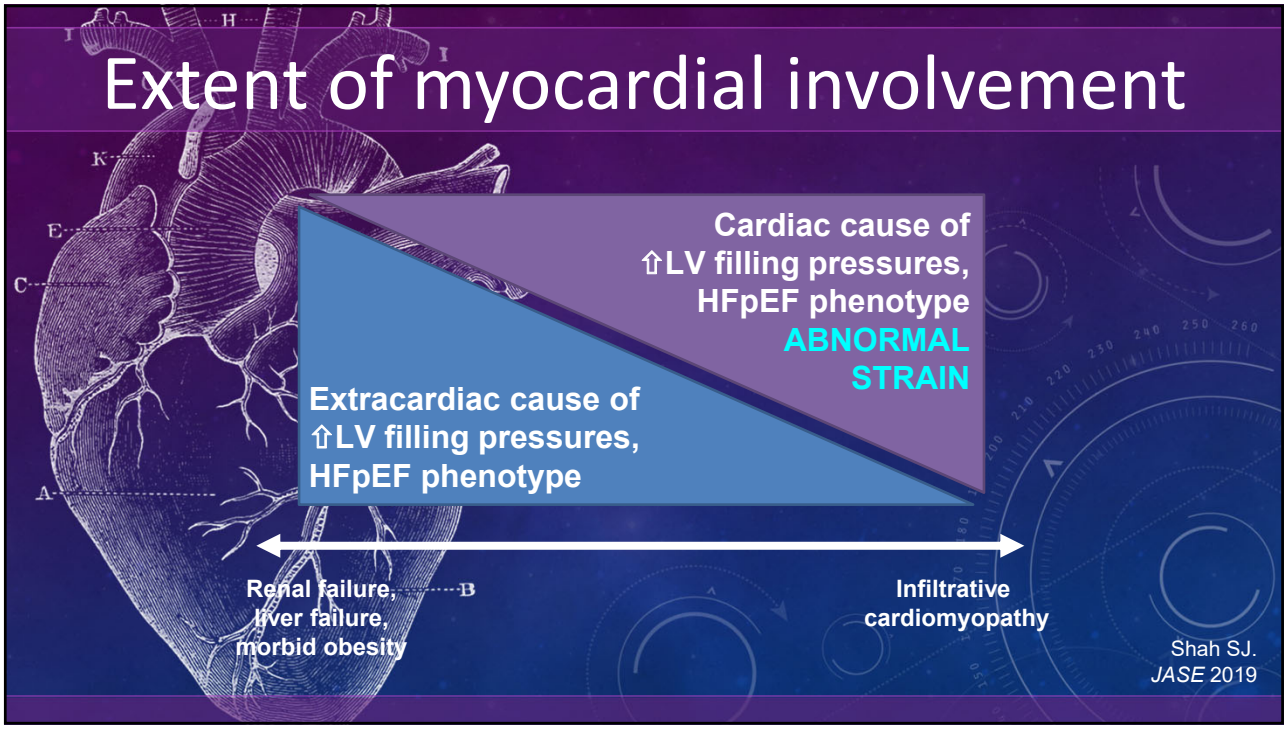
Final diagnosis: Constrictive pericarditis

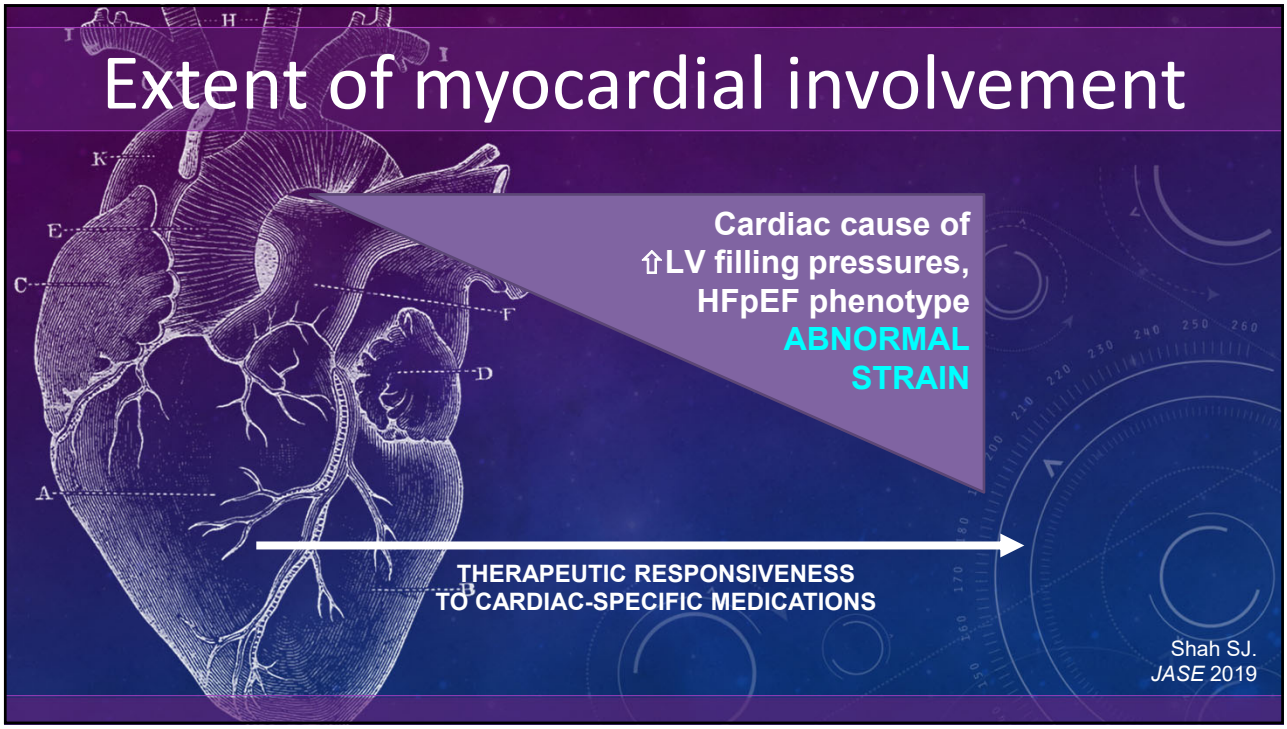


Echo is the key test for *HFpEF subtyping*

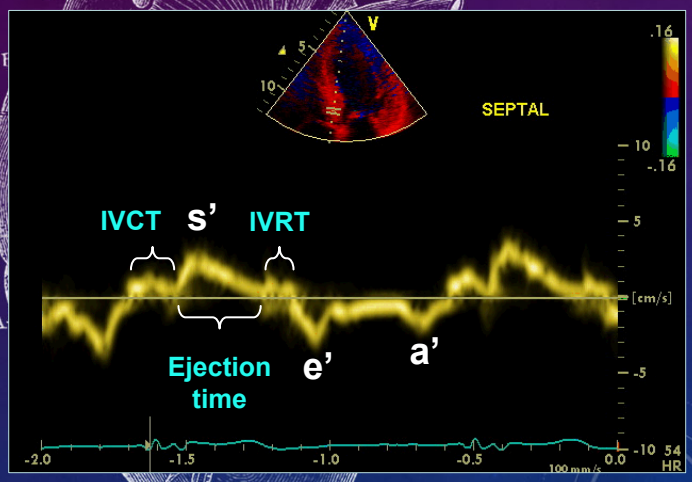

HFpEF


Extent of myocardial involvement
Cardiac cause of
⇧LV filling pressures,
HFpEF phenotype
Extracardiac cause of
⇧LV filling pressures,
HFpEF phenotype
Renal failure,
liver failure,
morbid obesity
MOST PATIENTS
Infiltrative
cardiomyopathy
Shah SJ.
JASE 2019


Extent of myocardial involvement
Cardiac cause of ⇧LV filling pressures, HFpEF phenotype ABNORMAL STRAIN
Extracardiac cause of ⇧LV filling pressures, HFpEF phenotype
Renal failure, liver failure, morbid obesity
Infiltrative cardiomyopathy
Shah SJ. JASE 2019


Extent of myocardial involvement
Cardiac cause of ⇧LV filling pressures, HFpEF phenotype ABNORMAL STRAIN
THERAPEUTIC RESPONSIVENESS TO CARDIAC-SPECIFIC MEDICATIONS
Shah SJ. JASE 2019

Use TDI to evaluate myocardium



Signs of a sick myocardium:

- Low s', e', a' velocities
- Short ejection time
- Prolonged isovolumic contraction and relaxation times

Phenotyping HFpEF: beyond EF

Argulian E, et al. *Circ Res* 2018

Heart failure

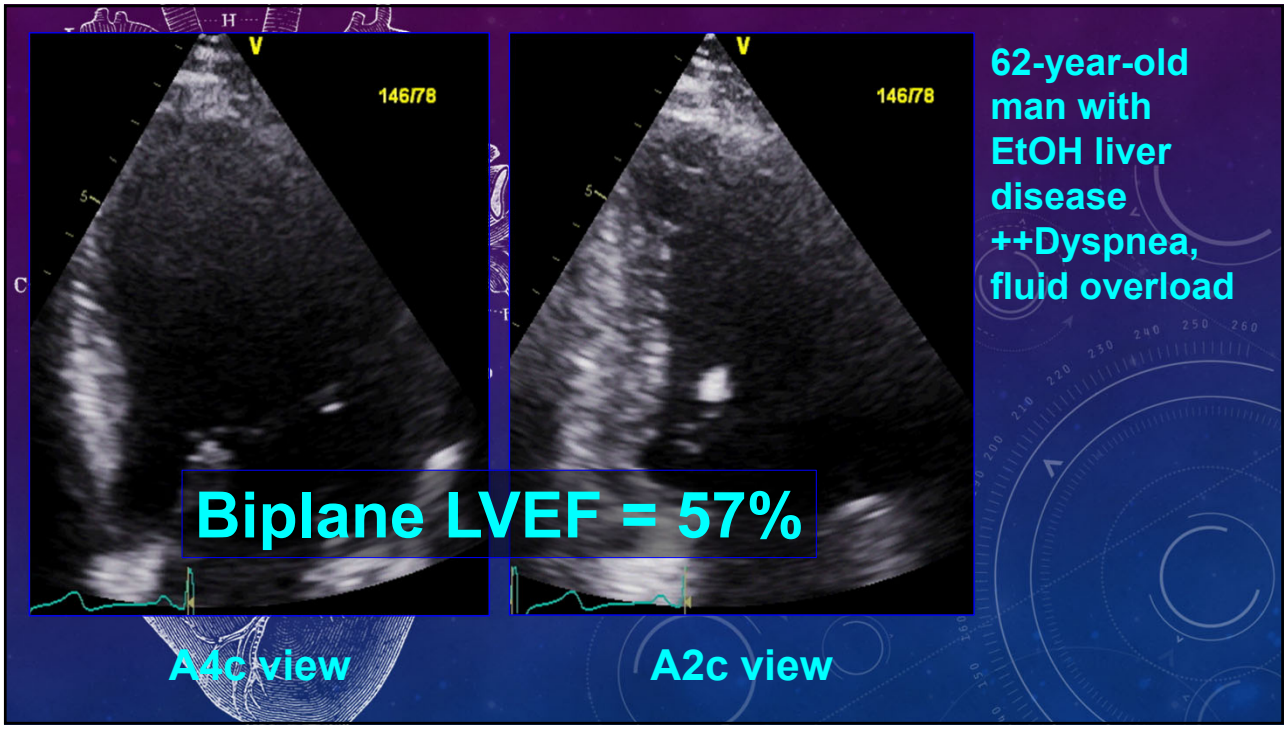
Preserved LVEF

HFpEF with reduced longitudinal strain

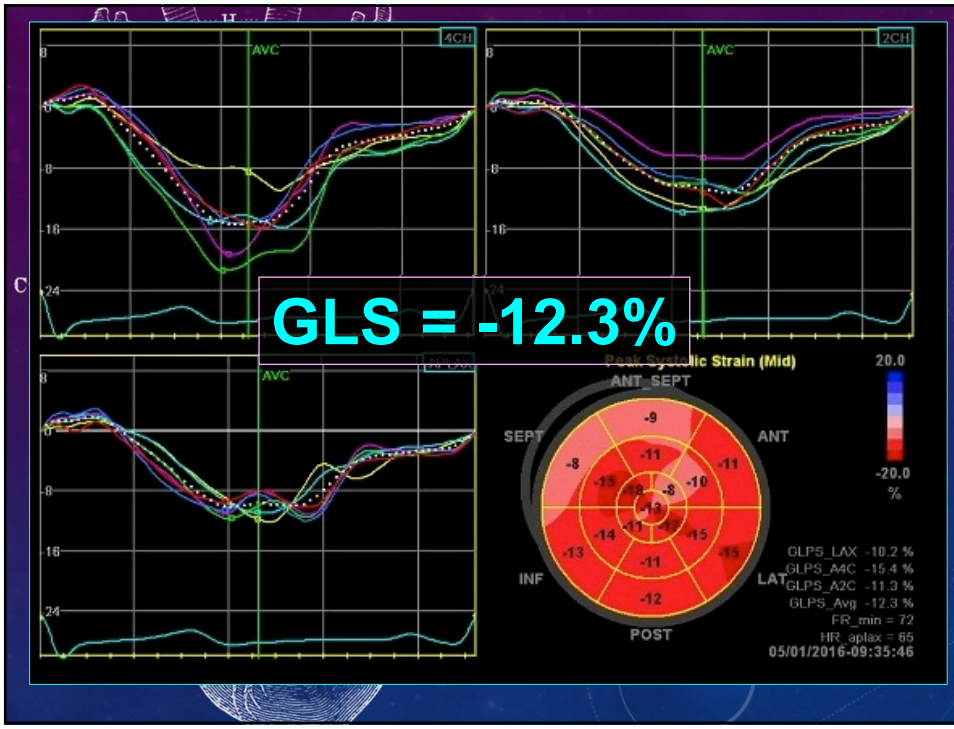
- Contractile dysfunction
- Myocardial fibrosis
- Infiltrative cardiomyopathy
- Microvascular dysfunction
- Maladaptive hypertrophy

HFpEF with preserved longitudinal strain

- Primary LA dysfunction
- Vascular stiffening
- Abnormal V-A coupling
- Extra-cardiac volume overload
- RV dysfunction



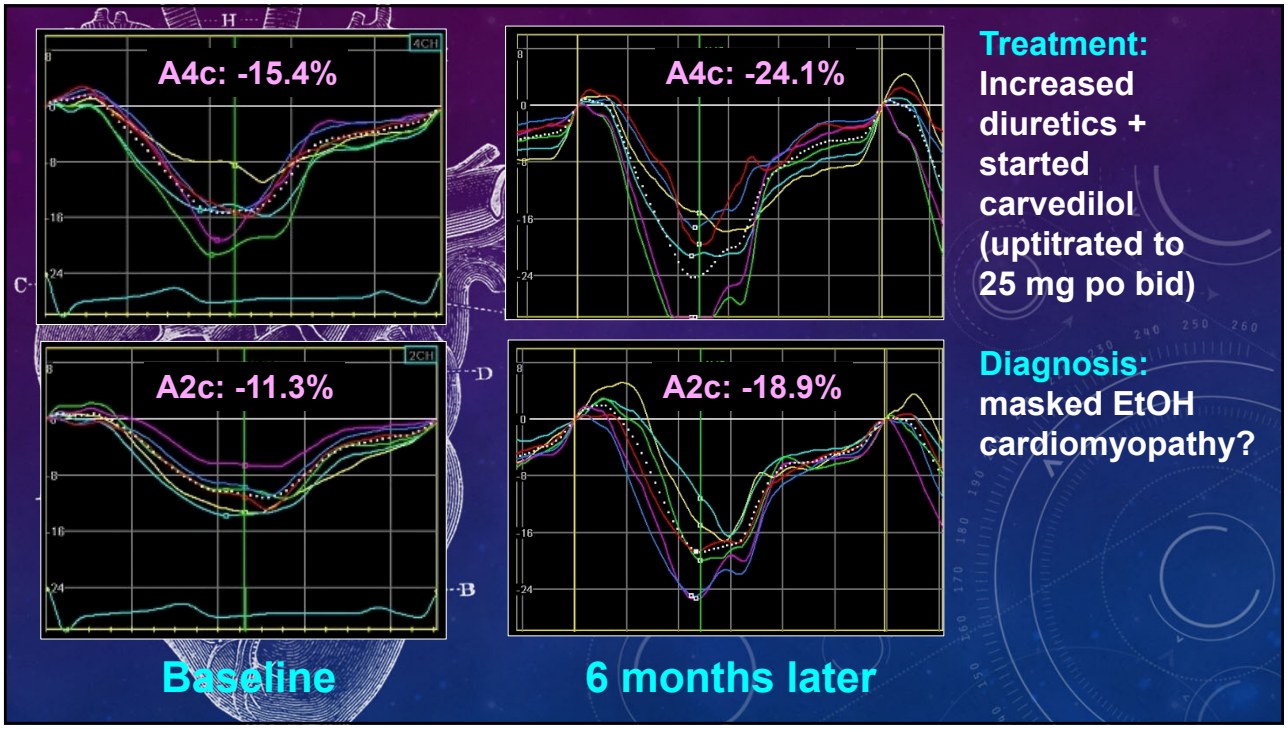
62-year-old man with EtOH liver disease ++Dyspnea, fluid overload



LV GLS (global longitudinal strain)

Ref. ranges
(absolute values):

- **Normal > 18%**
- **Borderline 16-18%**
- **Abnormal < 16%**

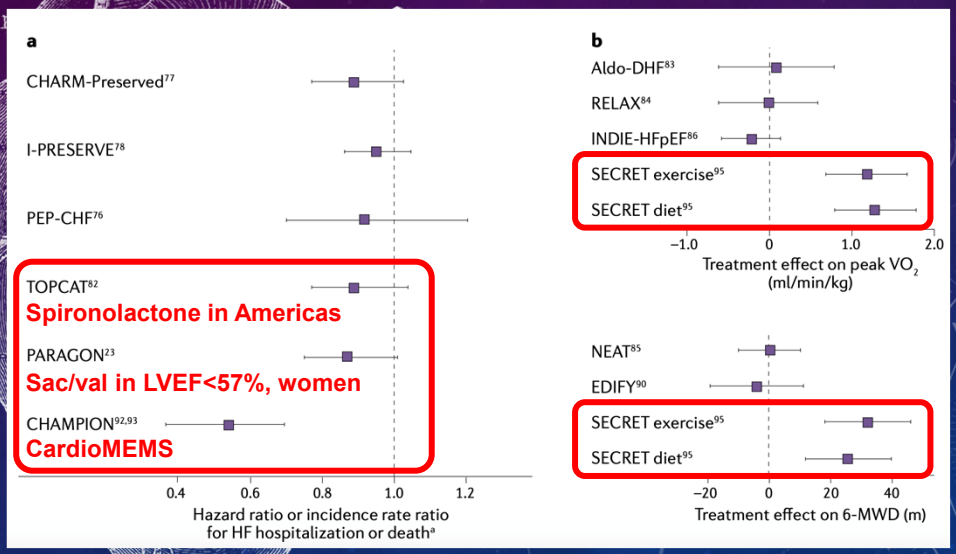


Treatment: Increased diuretics + started carvedilol (uptitrated to 25 mg po bid)

Diagnosis: masked EtOH cardiomyopathy?

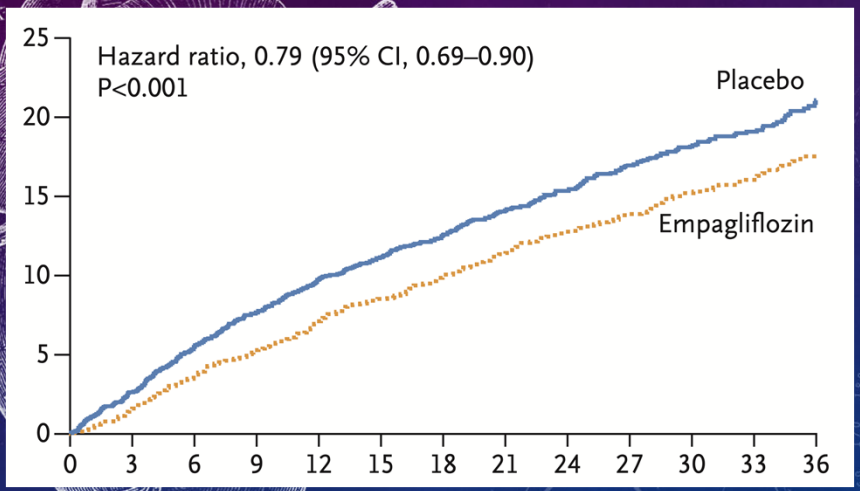
Echo is the key test for *targeted Rx in HFpEF*

Limited HFpEF treatment landscape



Borlaug BA. *Nat Rev Cardiol* 2020

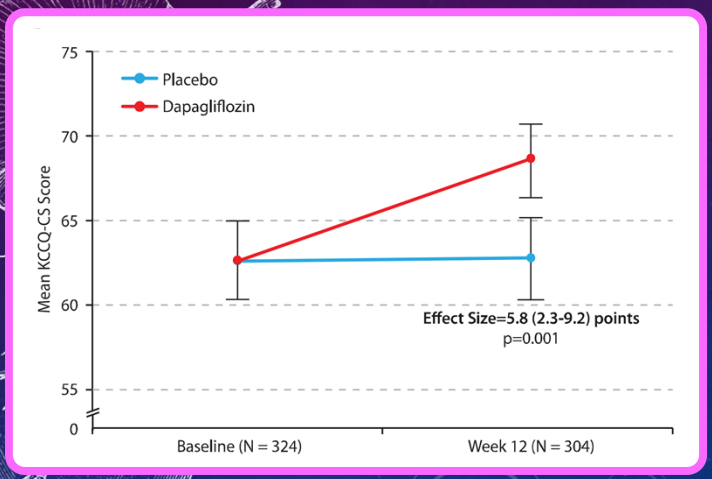
SGLT2i in HFpEF: EMPEROR-Preserved



- N=5988
- Empagliflozin vs. placebo
- HF with LVEF > 40%
- (n=4005 [67%] with LVEF ≥ 50%)
- Primary outcome driven by HF hospitalizations
- +1.32-point improvement in KCCQ vs. placebo at 52 weeks

Anker S, et al. *NEJM* 2021

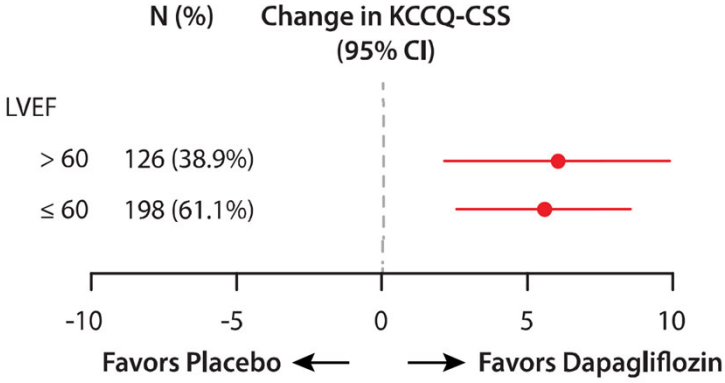
SGLT2i in HFpEF: PRESERVED-HF KCCQ



- N=324
- Dapagliflozin vs. placebo
- HF with LVEF ≥ 45%
- +5.8-point improvement in KCCQ vs. placebo

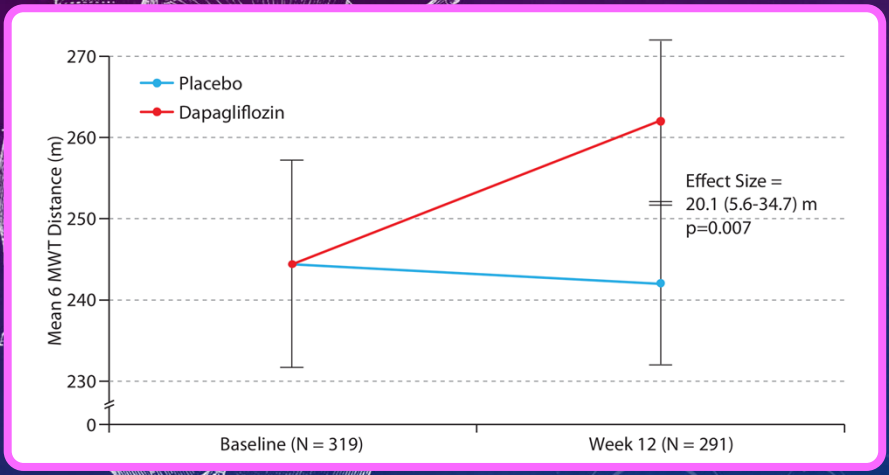
Nassif M…Kosiborod M. *Nature Medicine* 2021

SGLT2i in HFpEF: PRESERVED-HF KCCQ



Nassif M…Kosiborod M. *Nature Medicine* 2021

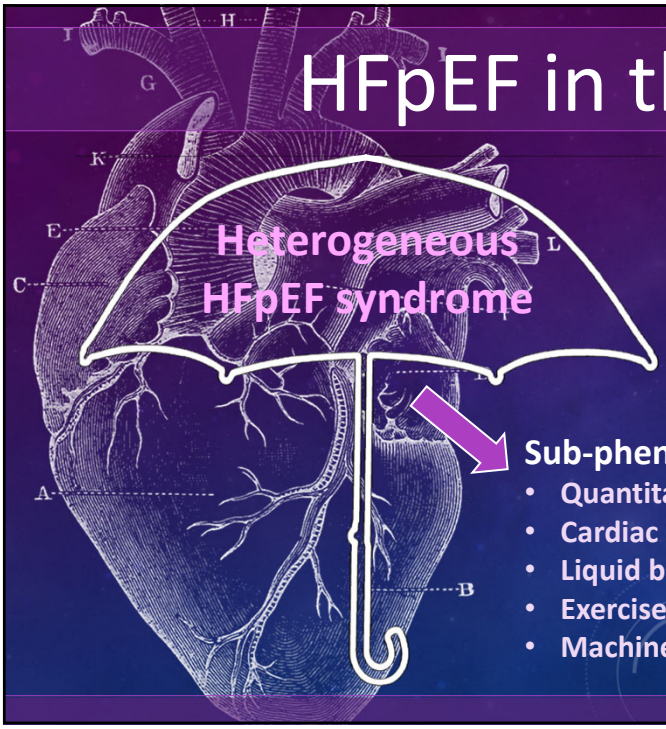
SGLT2i in HFpEF: PRESERVED-HF 6MWT



- N=324
- Dapagliflozin vs. placebo
- HF with LVEF ≥ 45%
- +5.8-point improvement in KCCQ vs. placebo
- +20.1-meter improvement in 6MWT distance vs. placebo

Nassif M…Kosiborod M. *Nature Medicine* 2021

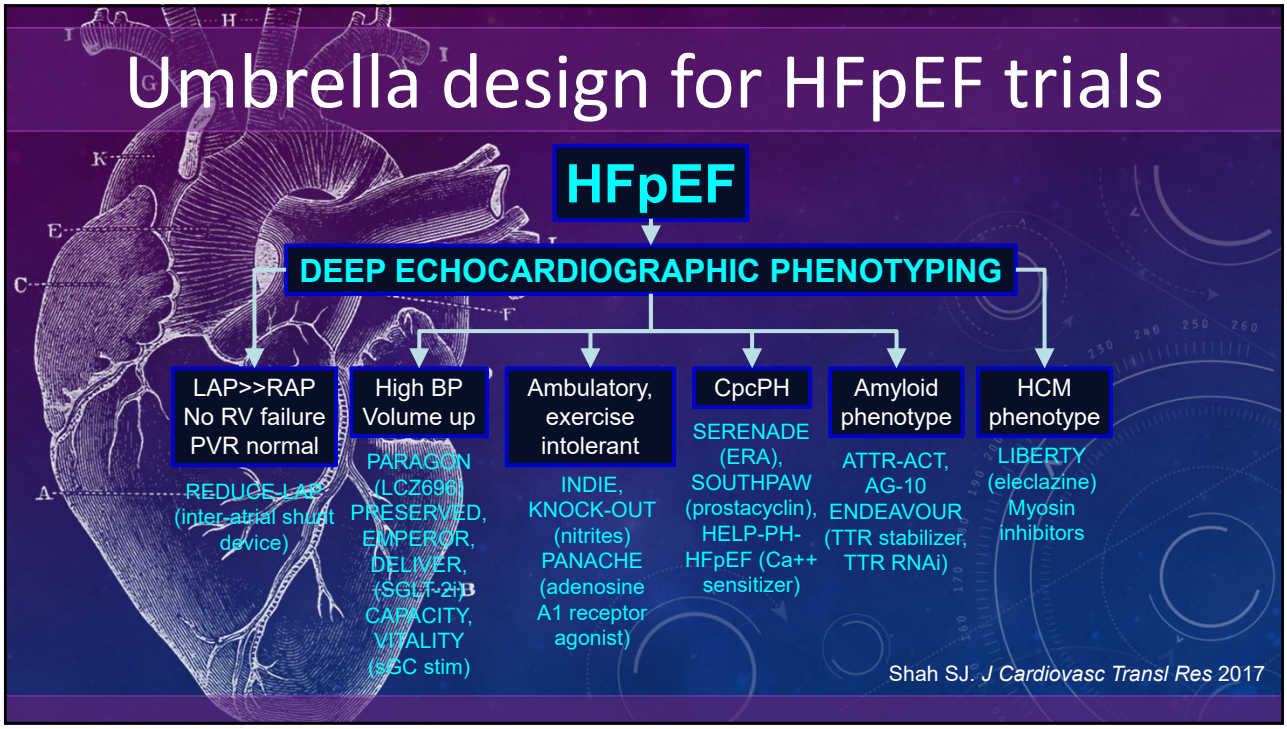
HFpEF in the future



Heterogeneous HFpEF syndrome

Sub-phenotyping:
- Quantitative imaging
- Cardiac biopsy
- Liquid biopsy
- Exercise phenotyping
- Machine learning

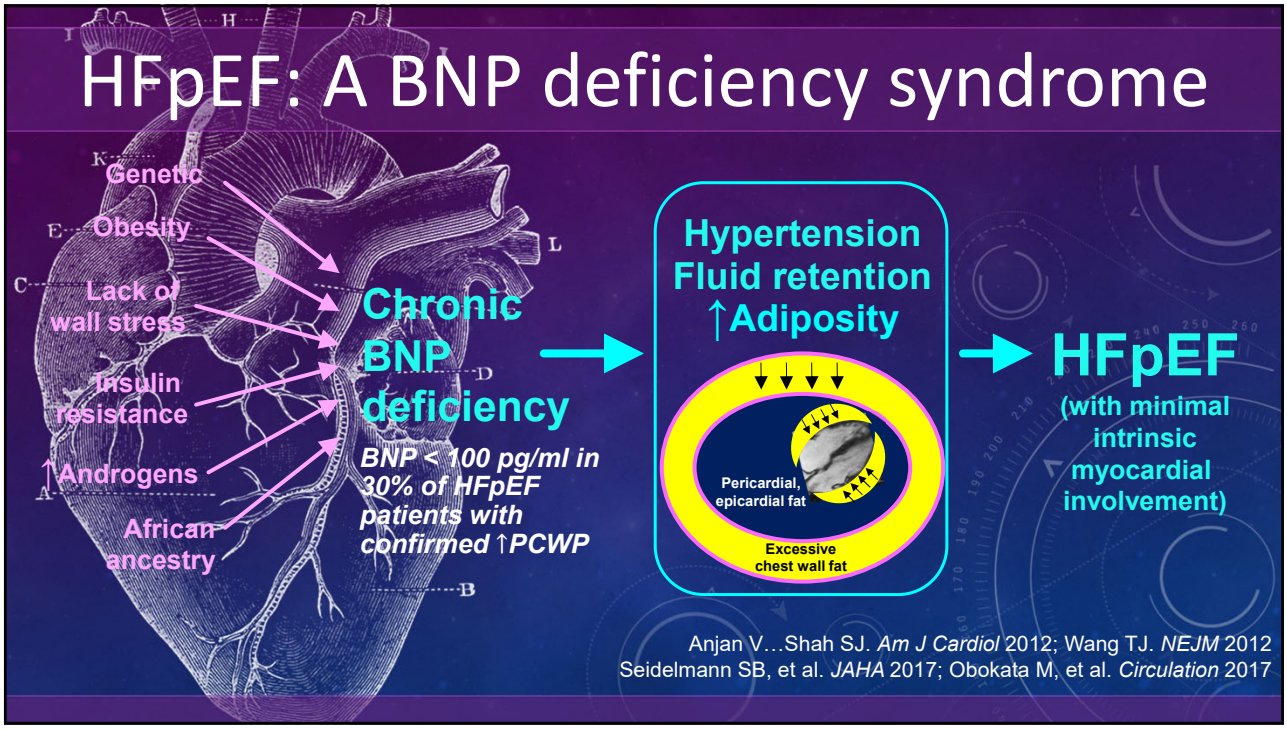
Phenotype-specific treatment



Obese, BNP-deficient

HFpEF subtype

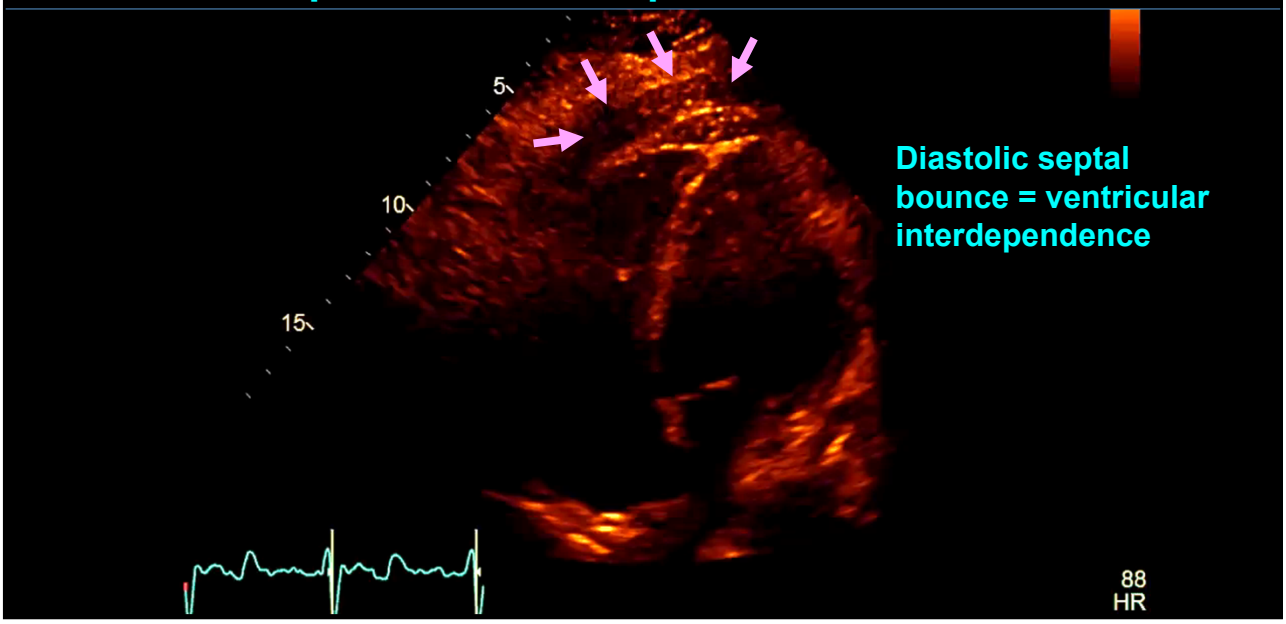
HFpEF: A BNP deficiency syndrome



Anjan V…Shah SJ. *Am J Cardiol* 2012; Wang TJ. *NEJM* 2012
Seidelmann SB, et al. *JAHA* 2017; Obokata M, et al. *Circulation* 2017

74-year-old woman with BMI 46 kg/m^2 with HFpEF, BNP = 28 pg/ml

Severe pericardial and epicardial fat over the RV



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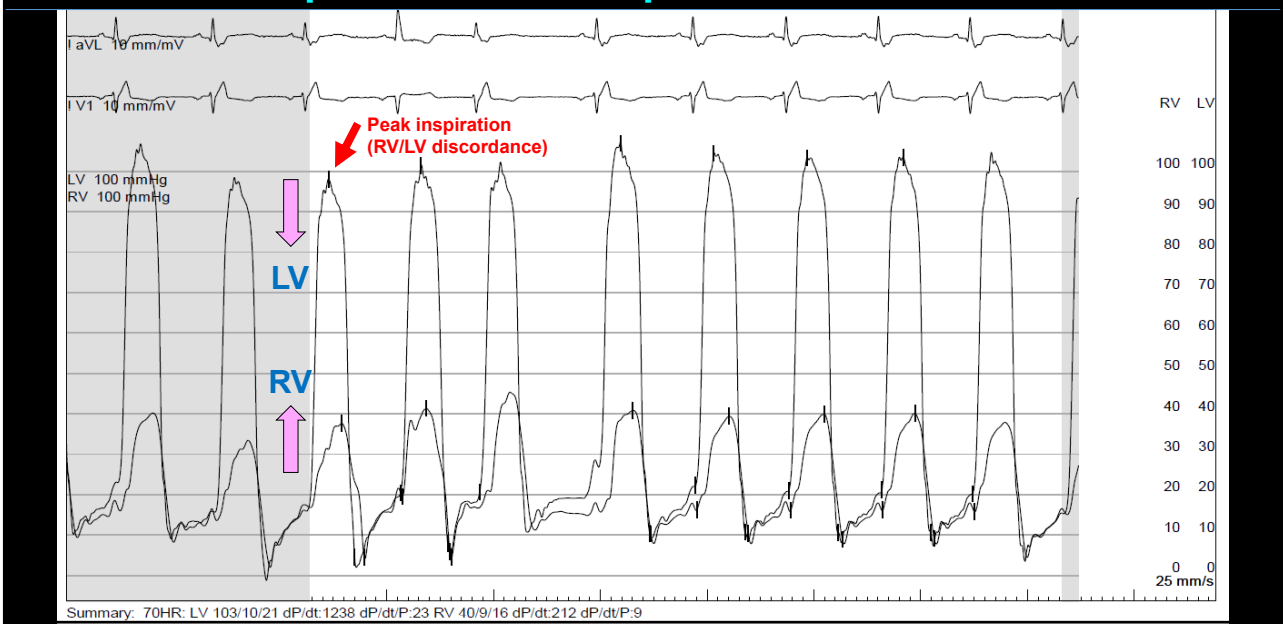
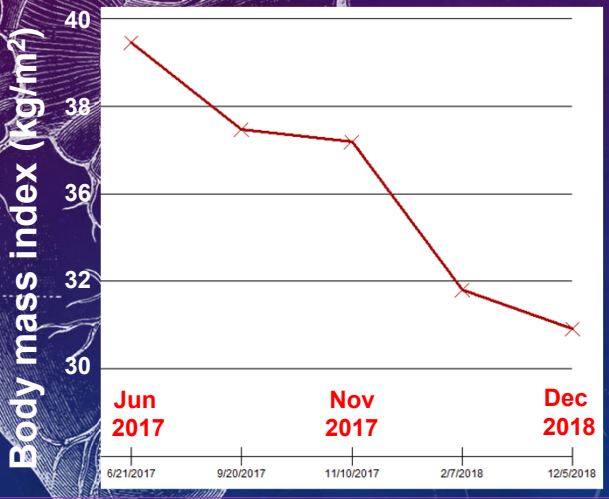


Obese HFpEF phenotype: weight loss Rx

Effect of dramatic weight loss (pharmacological)



- 68-year-old woman with HFpEF, NYHA class III treated with a GLP1-RA in June 2017
- By Dec 2018, off of all diuretics and anti-hypertensive Rx, NYHA class I symptoms

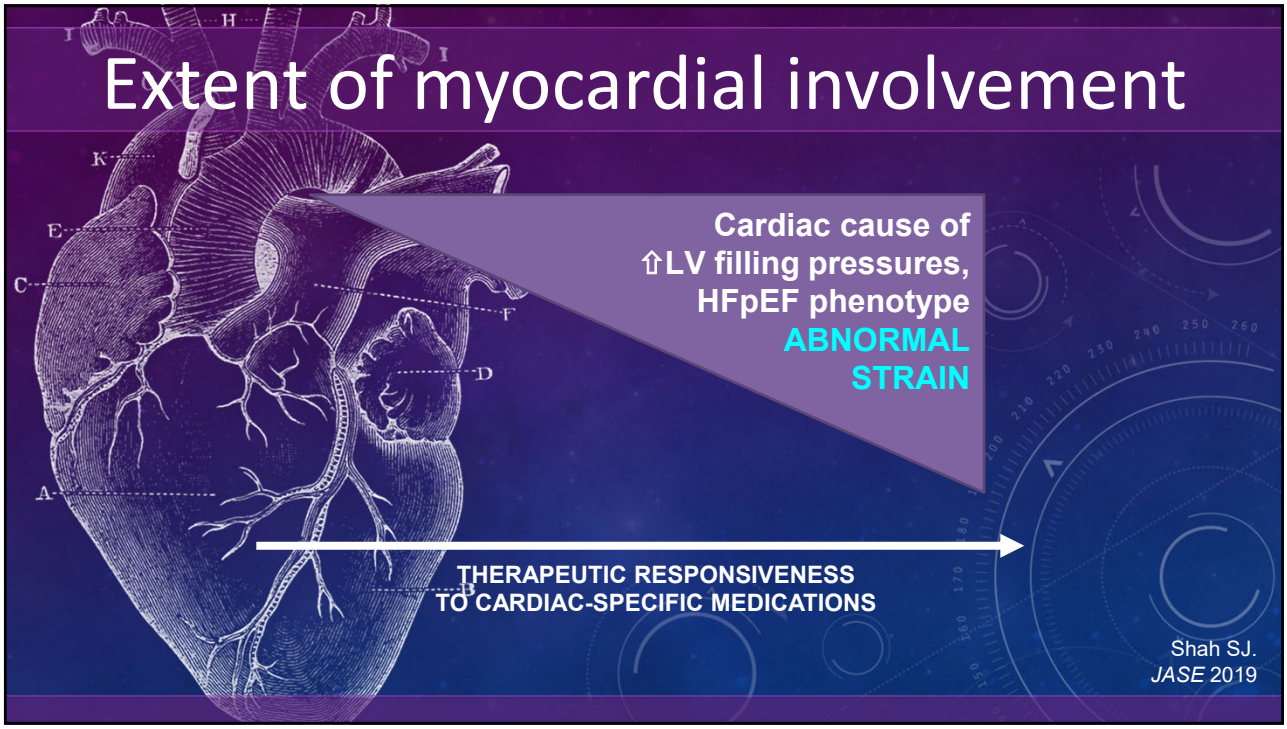
Rx of obese, BNP-deficient HFpEF

- Pharmacological or surgical weight loss:
  - ✓ GLP-1 receptor agonists, bariatric surgery
- Treatment of pericardial constraint:
  - ✓ Pericardiotomy
- Augmenting BNP and/or its downstream effects:
  - ✓ ANP mimetic
  - ✓ Neprilysin inhibition
  - ✓ PDE9 inhibition

Myocardial-predominant

HFpEF subtype

Extent of myocardial involvement

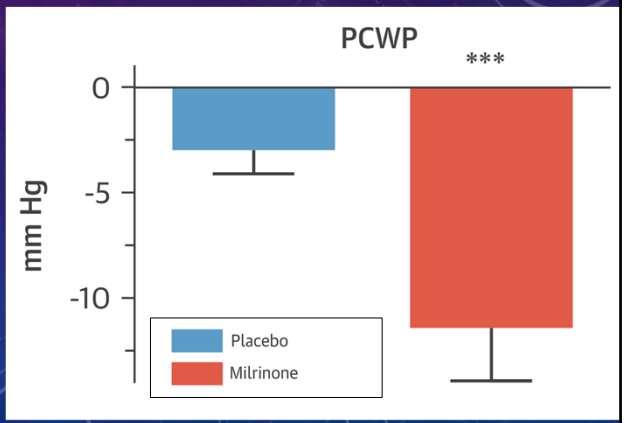


Shah SJ.
JASE 2019

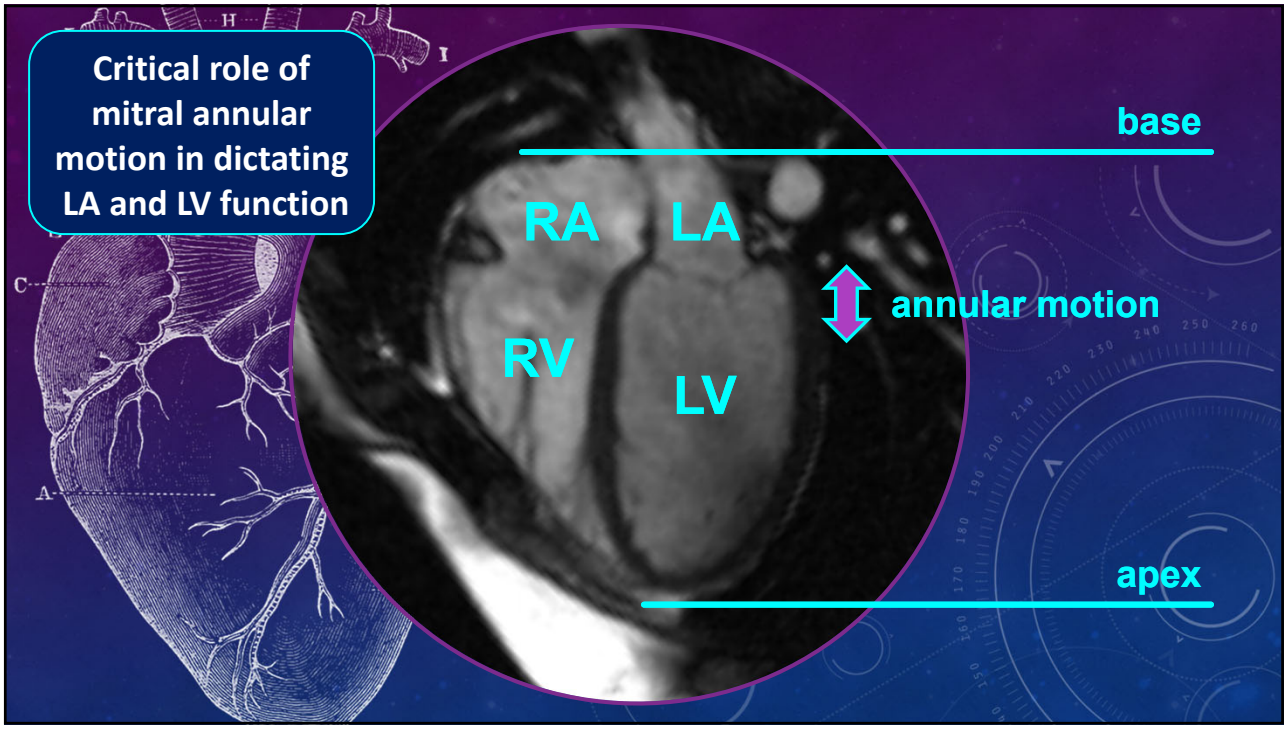
Treatment of "myocardial" HFpEF

- Neprilysin inhibition (PARAGON, LVEF < 57%)
- Spironolactone (LVEF < 60%)
- Targeting the NP-PDE9-cGMP-PKG or MRA system
- Anti-fibrotic therapy (PIROUETTE, REGRESS-HFpEF)
- Myosin modulation
- Inotropes

Change in peak exercise hemodynamics after 20-min infusion in HFpEF patients (n=10 placebo vs. n=10 milrinone)



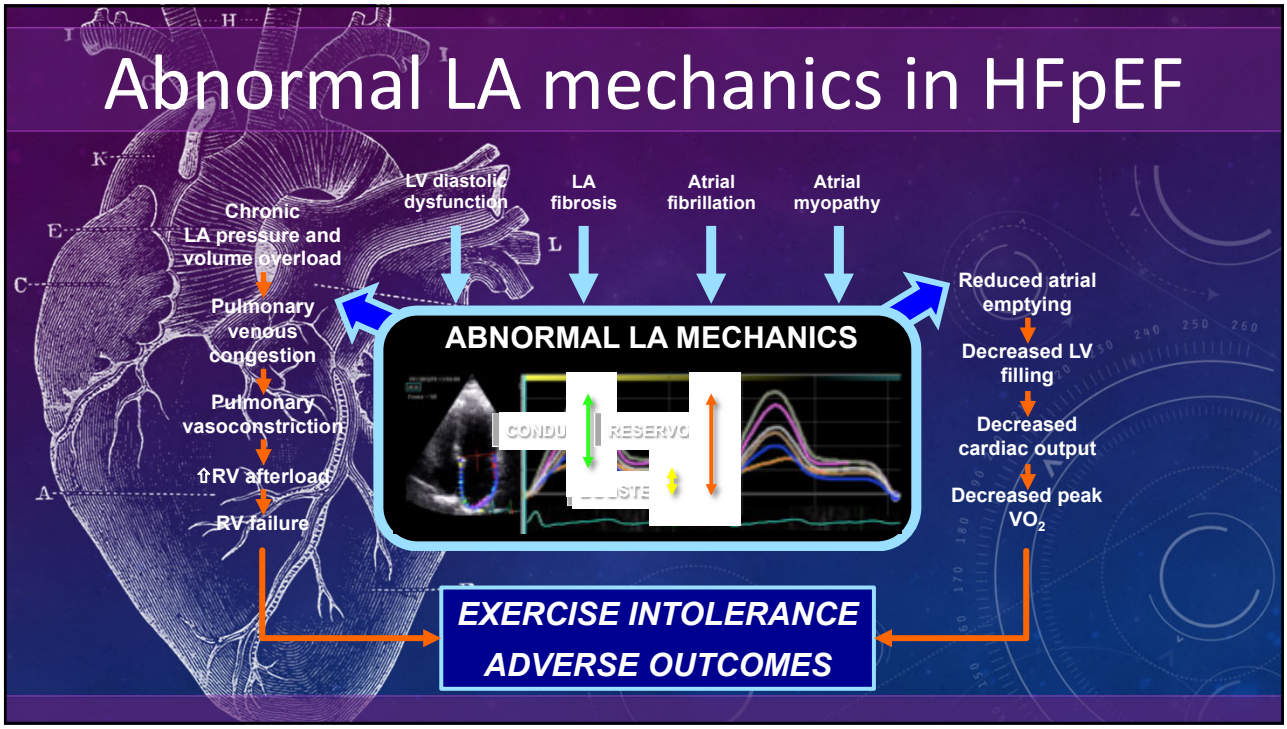
Kaye D, et al. *JACC* 2016



Left atrial myopathy

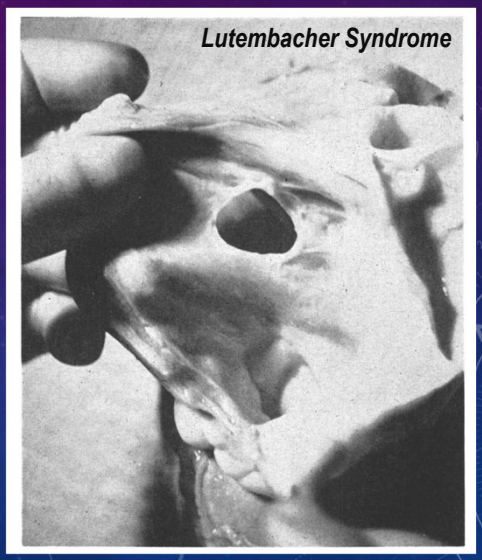
HFpEF subtype

Abnormal LA mechanics in HFpEF



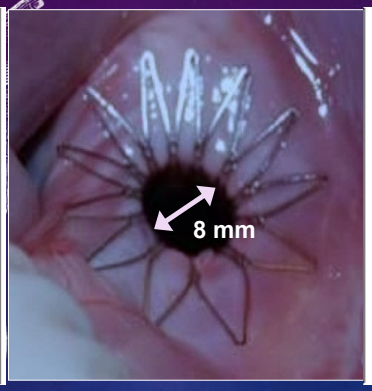
ASD in the setting of mitral stenosis

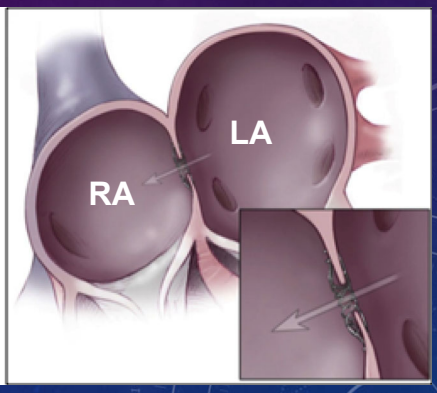
- Congenital ASD in the setting of mitral stenosis
  - Decompression of high LA pressure
  - Large reservoir: right atrium, great veins, hepatic veins



Scherlis & Cowley. *Ann Intern Med* 1955

InterAtrial Shunt Device

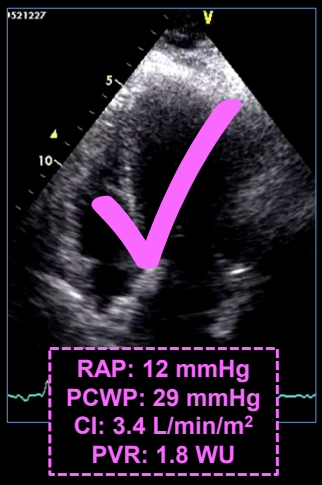




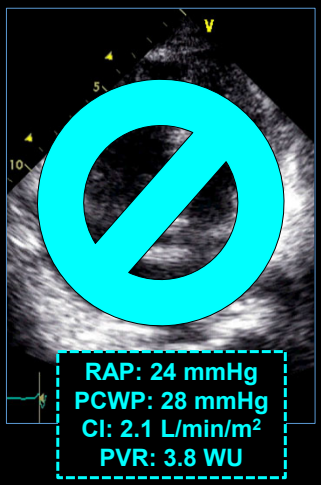
IASD proposed mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA → RA (Qp:Qs 1.2-1.3)

Feldman T…Shah SJ. *Circ Heart Fail* 2016

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

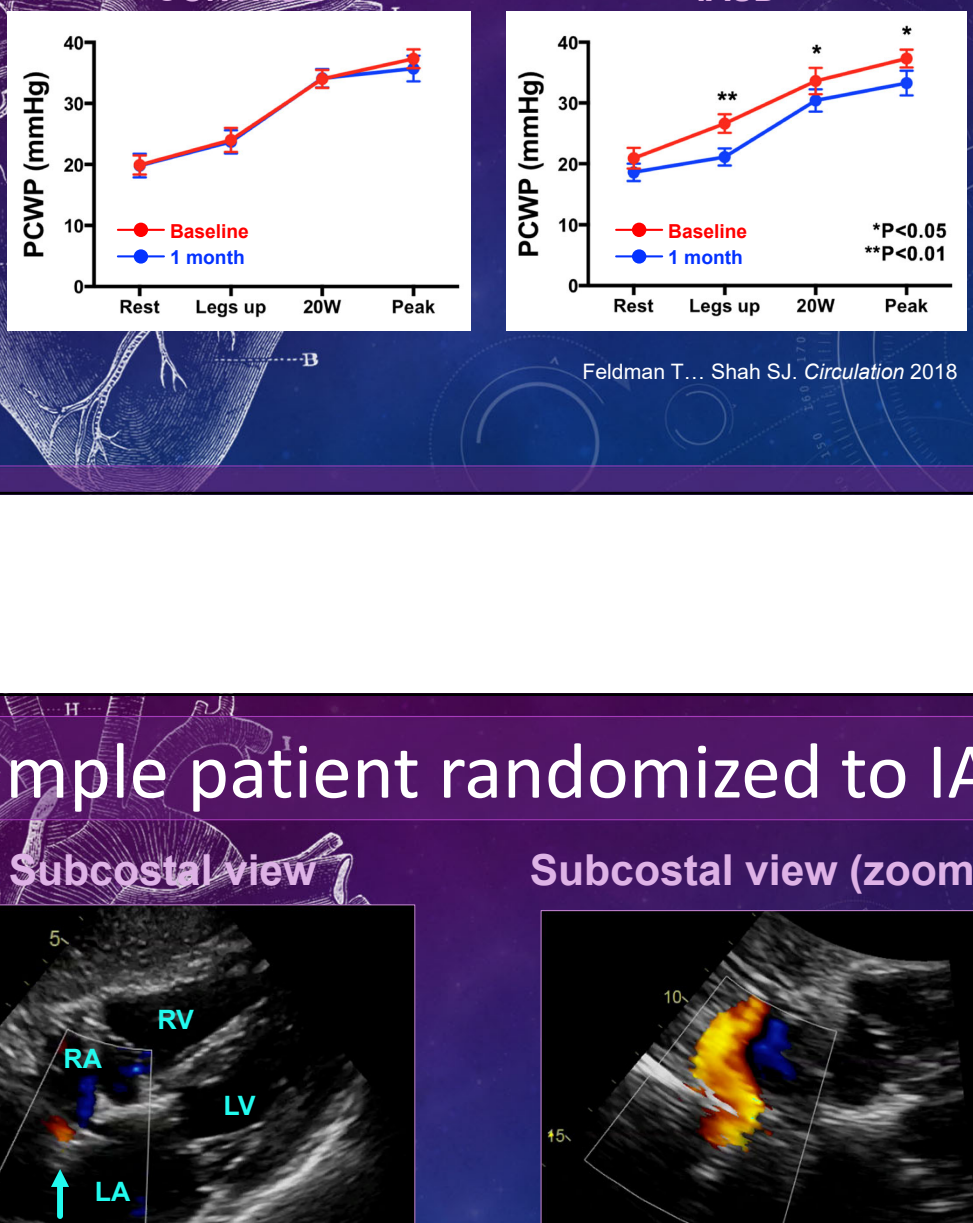


RAP: 12 mmHg
PCWP: 29 mmHg
CI: 3.4 L/min/m²
PVR: 1.8 WU



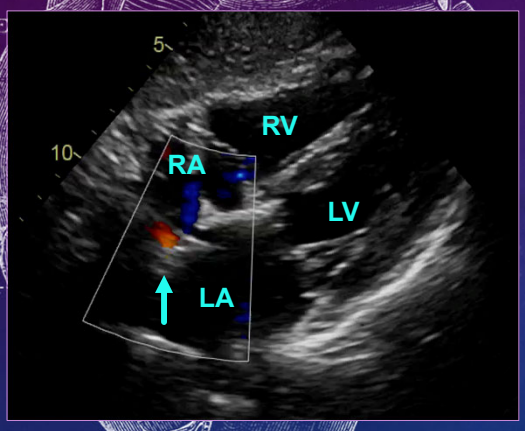
RAP: 24 mmHg
PCWP: 28 mmHg
CI: 2.1 L/min/m²
PVR: 3.8 WU

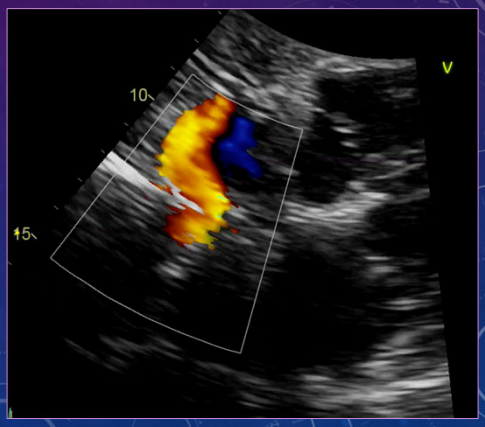
REDUCE LAP-HF I RCT



Feldman T… Shah SJ. *Circulation* 2018

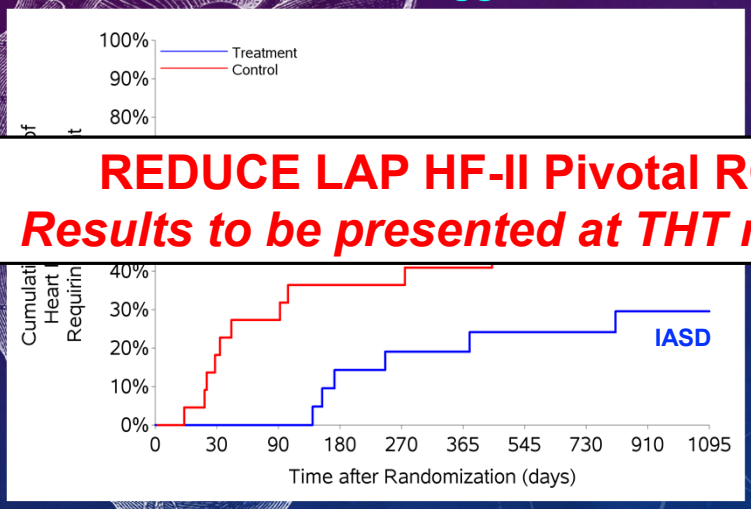
Example patient randomized to IASD





REDUCE LAP-HF I RCT: 3-yr. outcome

Results suggest durable efficacy



Test	Chi-Square	P-value
Log-Rank	5.1851	0.034
Wilcoxon	5.1354	0.028

REDUCE LAP HF-II Pivotal RCT (n=626):
Results to be presented at THT meeting Feb 1st

Unpublished data

Take home points

- Echo is the cornerstone for diagnosis and management of HFpEF
  - ✓ *Don't just look at LVEF and diastology, use a "holistic approach" during echo evaluation of HFpEF*
- Echo for diagnosis of HFpEF: use the H2FPEF or HFA-PEFF scores, and diastolic stress echo
- Use echo to rule out "zebras"
- Use echo to sub-phenotype HFpEF to guide targeted treatment and enroll in clinical trials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