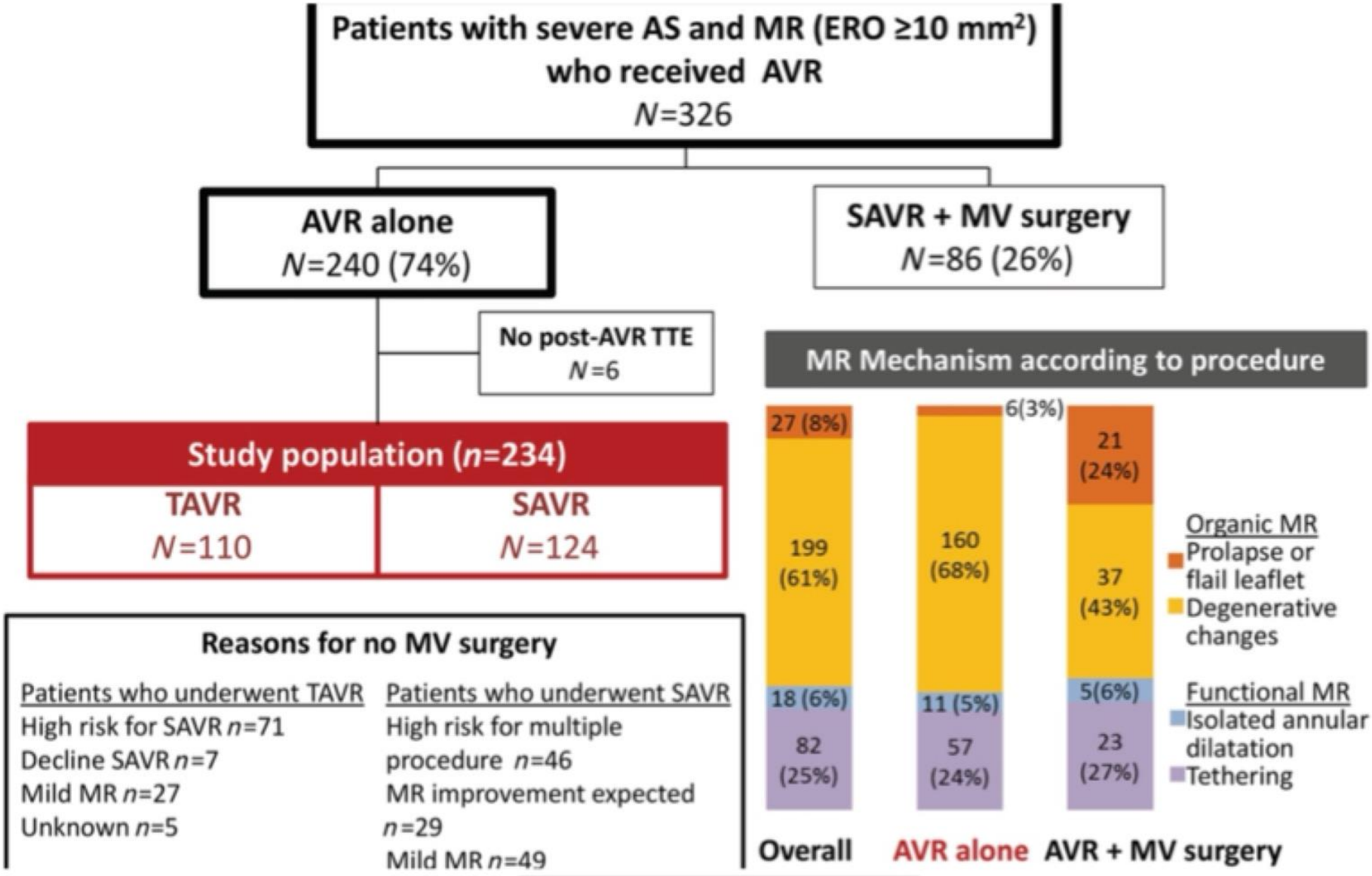

Patients with severe AS and MR (ERO ≥10 mm²) who received AVR
N=326
AVR alone
N=240 (74%)
SAVR + MV surgery
N=86 (26%)
No post-AVR TTE
N=6
Study population (n=234)
TAVR
N=110
SAVR
N=124
Reasons for no MV surgery
Patients who underwent TAVR
High risk for SAVR n=71
Decline SAVR n=7
Mild MR n=27
Unknown n=5
Patients who underwent SAVR
High risk for multiple procedure n=46
MR improvement expected n=29
Mild MR n=49
MR Mechanism according to procedure
27 (8%)
199 (61%)
18 (6%)
82 (25%)
6(3%)
160 (68%)
11 (5%)
57 (24%)
21 (24%)
37 (43%)
5(6%)
23 (27%)
Organic MR
Prolapse or flail leaflet
Degenerative changes
Functional MR
Isolated annular dilatation
Tethering
Overall
AVR alone
AVR + MV surgery

Pre-operative determinants of improvement in mitral regurgitation

Univariate logistic regression analyses to identify pre-operative variables associated with improvement in MR are listed in *Table 3*. In multivariable analysis, absence of atrial fibrillation at the index TTE (OR 2.09, 95% confidence interval [CI] 1.00–4.37; $P = 0.049$) in patients with organic MR (AUC = 0.61), and indexed AVA ≤ 0.40 cm^2 (OR 3.18, 95% CI 1.11–9.06; $P = 0.031$) in those with functional MR (AUC = 0.72), were the independent determinants of improvement in MR. Indexed AVA showed a significant interaction between organic and functional MR. In the overall cohort, mitral annulus diameter < 3 cm (the mean value, OR 1.74, 95% CI 1.02–2.97; $P = 0.041$) and QRS duration < 115 ms (the mean value, OR 1.73, 95% CI 1.00–2.98; $P = 0.049$) were independently associated with improvement in MR (AUC = 0.60). AR was not associated with improvement in MR. The prevalence and determinants of improvement in MR were similar when those with AR were excluded.

To our knowledge, the present study is the first to assess the impact of AVR on MR and the determinants for improvement in MR according to MR mechanism. MR improved after AVR in nearly 60% of patients with sAS and MR regardless of MR mechanism. Absence of atrial fibrillation at TTE in patients with organic MR, indexed AVA ≤ 0.40 cm^2 in those with functional MR, and QRS duration < 115 ms and mitral annulus diameter < 3 cm in the overall cohort were independent determinants of improvement in MR. Post-operative improvement was associated with reduced mortality during follow-up, notably in organic MR.

MAYO CLINIC

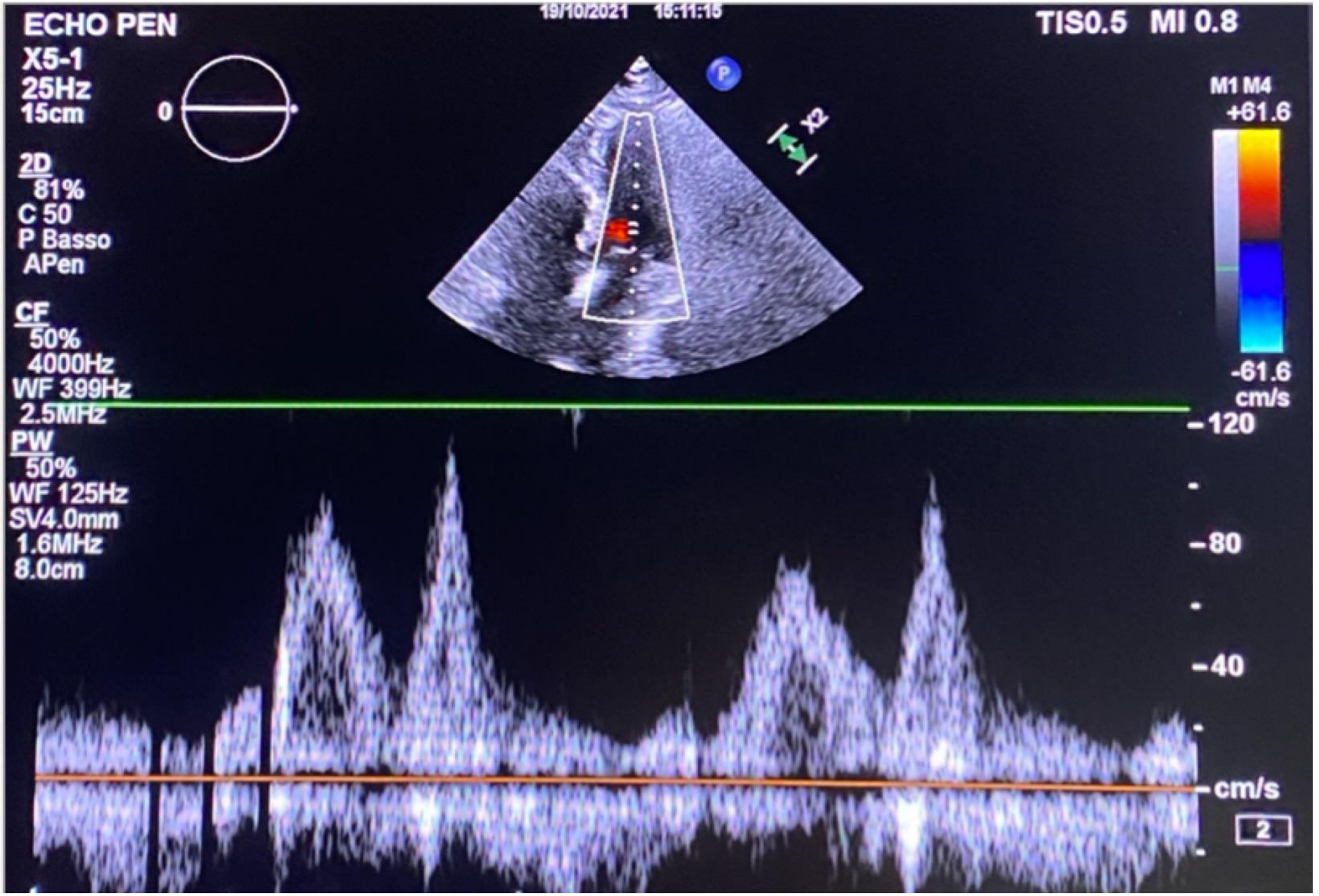
The Forgotten Victims of Diastolic Dysfunction

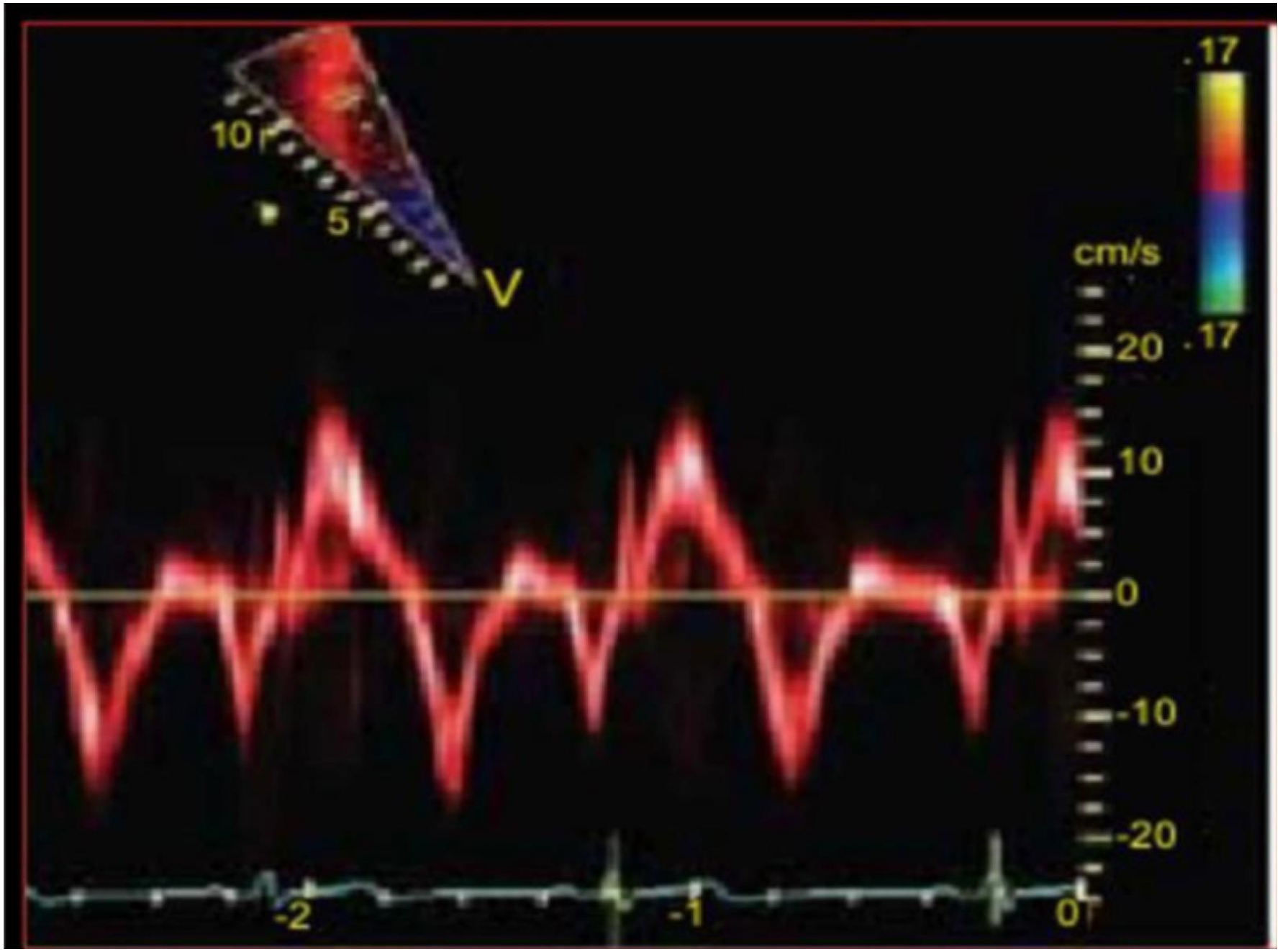
HFpEF continues to be Underrecognized

Typical Patient I see

- 70 year old woman w FC II-III dyspnea
- Here for 3rd opinion, variably told she was "deconditioned", "obese", and "depressed"
- HTN, metabolic syndrome, no HF admit
- BMI 35, no JVD, normal BNP
- Echo:
  - EF 60%,
  - LAVI 28, E/e' 11, RVSP 32

ESC algorithm says "no HFpEF"

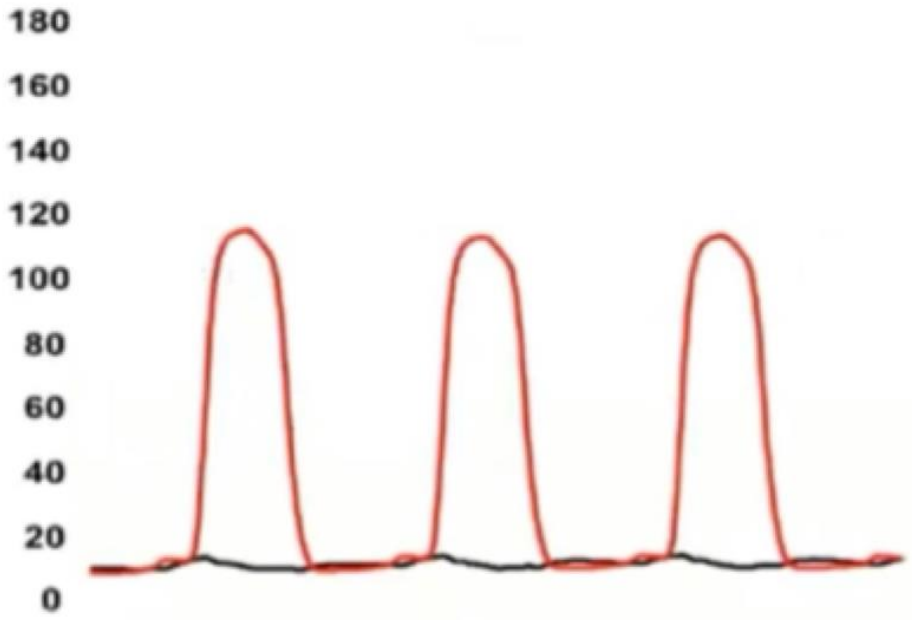

ECHO PEN
19/10/2021 15:11:15
TIS0.5 MI 0.8
X5-1
25Hz
15cm
0
P
X2
M1 M4
+61.6
-61.6
cm/s
2D
81%
C 50
P Basso
APen
CF
50%
4000Hz
WF 399Hz
2.5MHz
PW
50%
WF 125Hz
SV4.0mm
1.6MHz
8.0cm
120
80
40
cm/s
2


10
5
V
.17
cm/s
20
10
0
-10
-20
.17
-2
-1
0

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

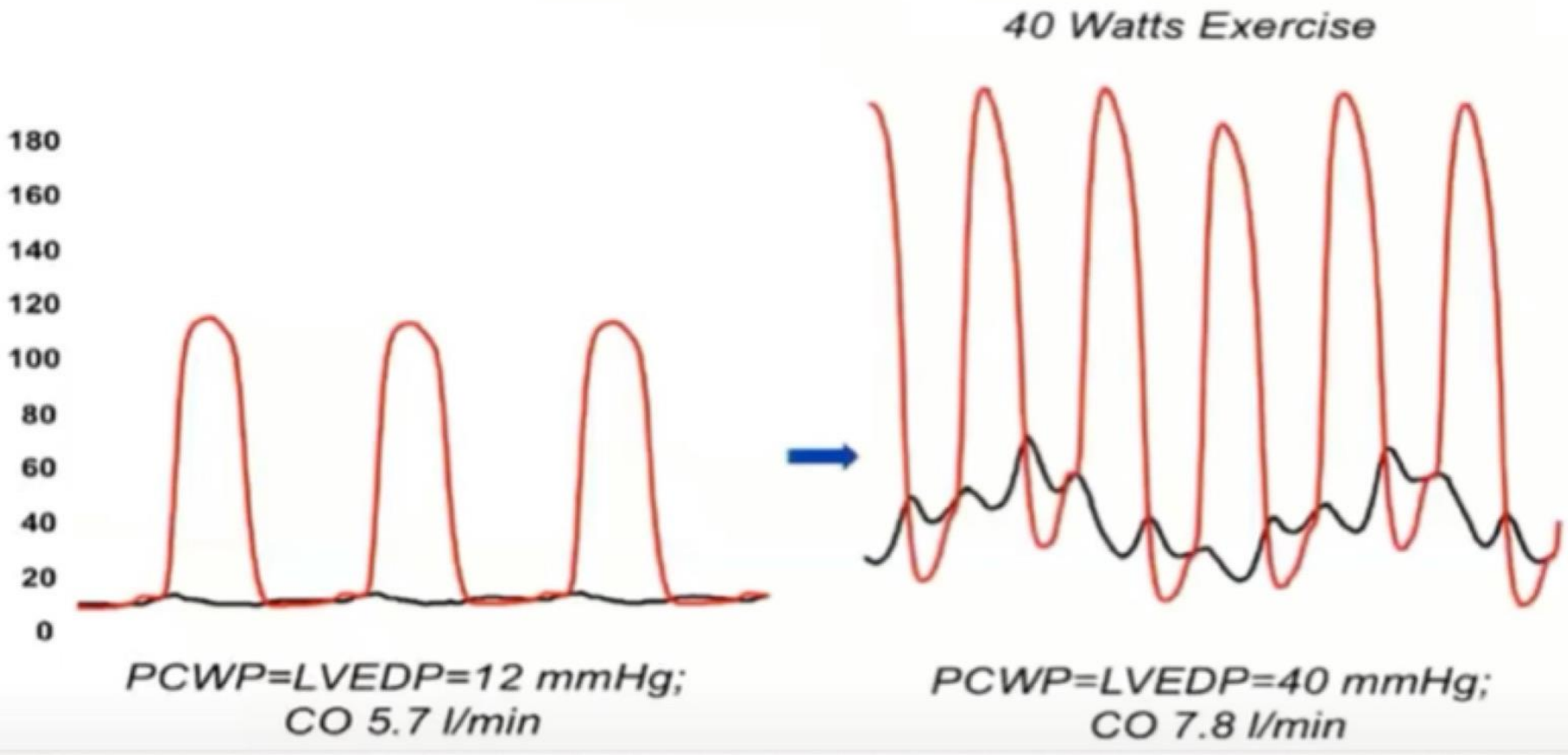
Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Referred for invasive hemodynamic assessment

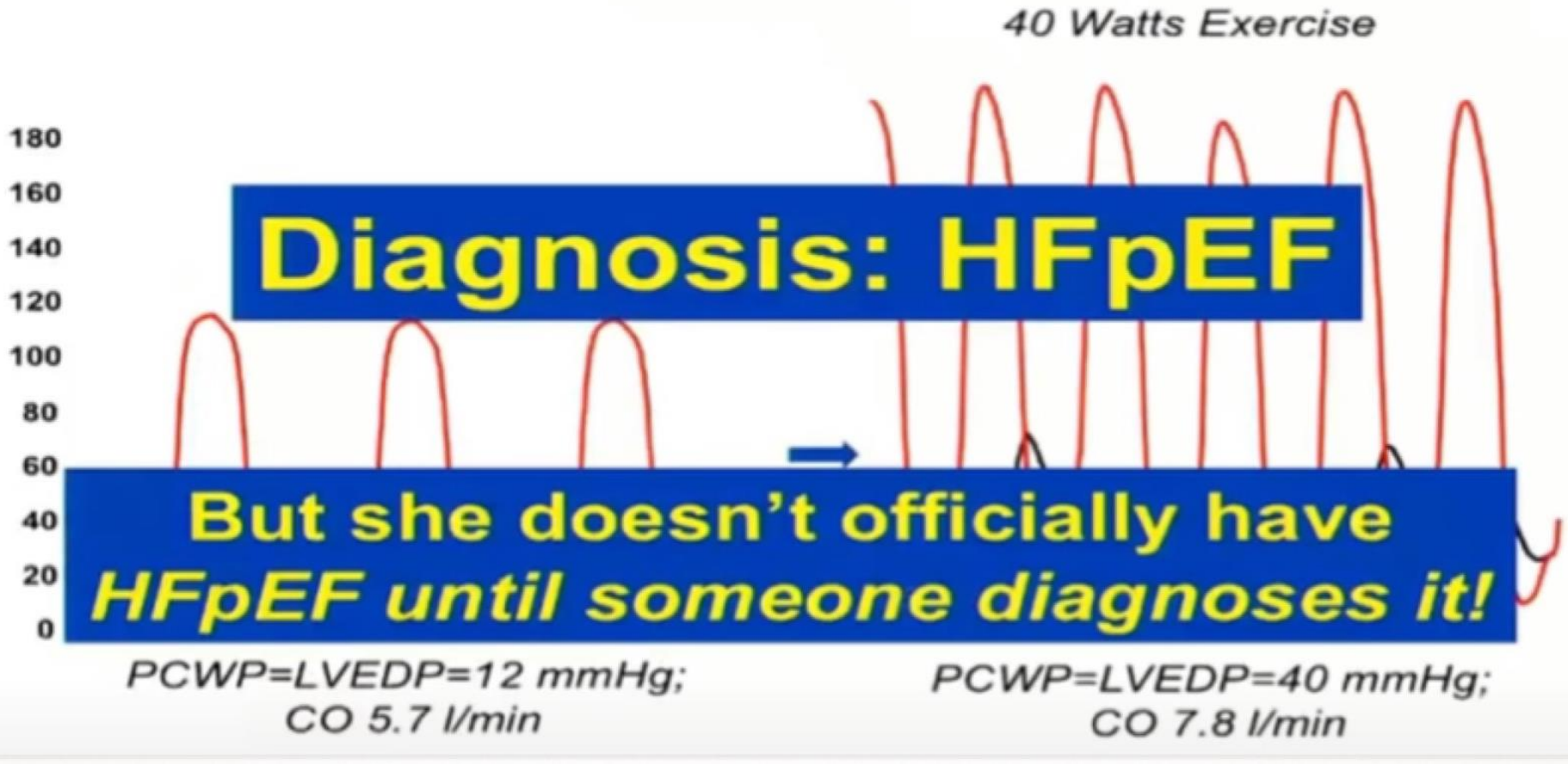


PCWP=LVEDP=12 mmHg;
CO 5.7 l/min

Referred for invasive hemodynamic assessment



Referred for invasive hemodynamic assessment



A New Tool to Increase Awareness: The H_2FPEF Score

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)

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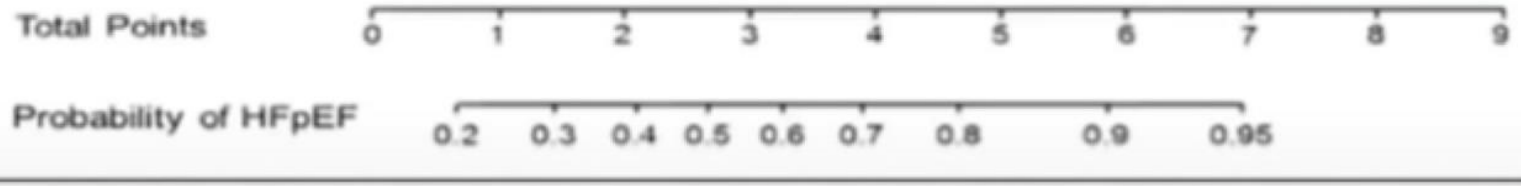
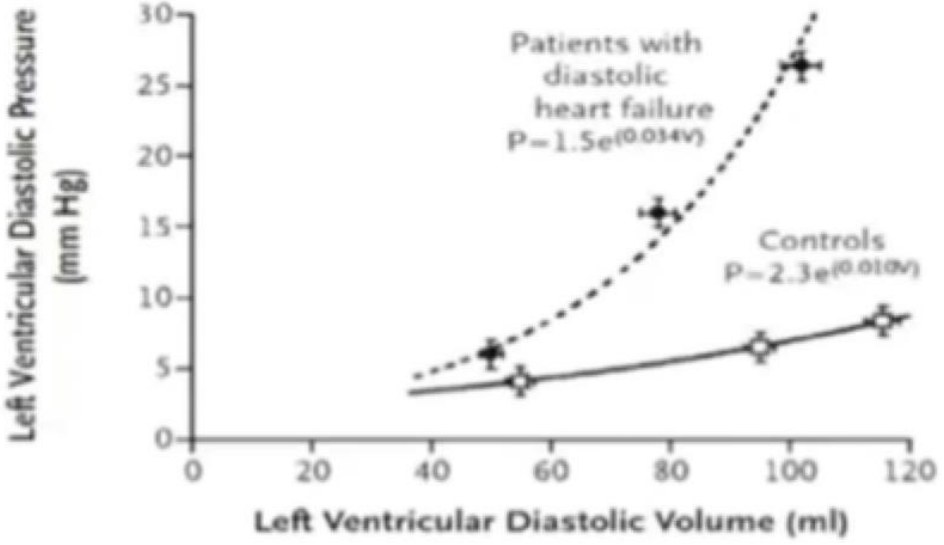
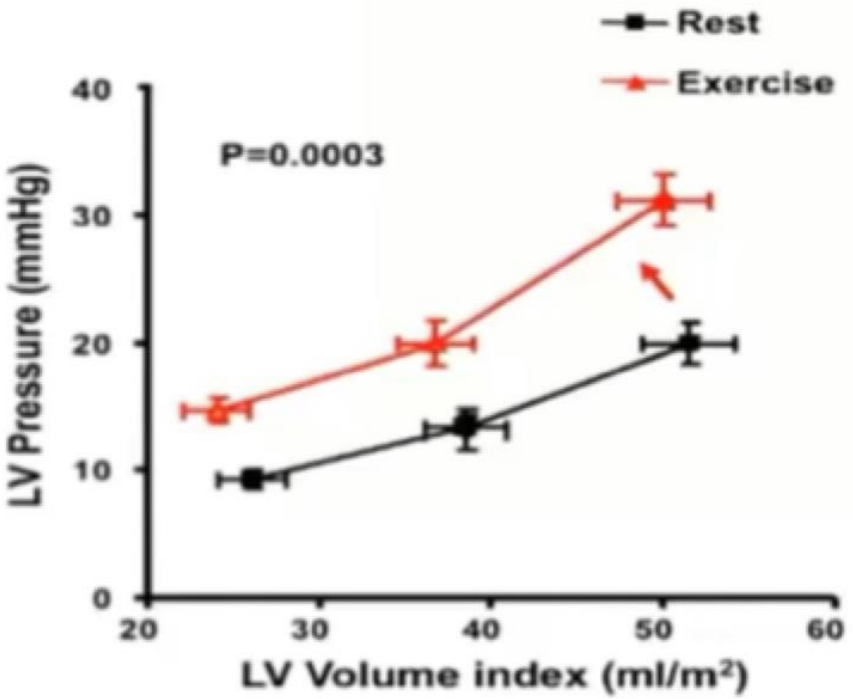
H_2FPEF score			Sum (0-9)

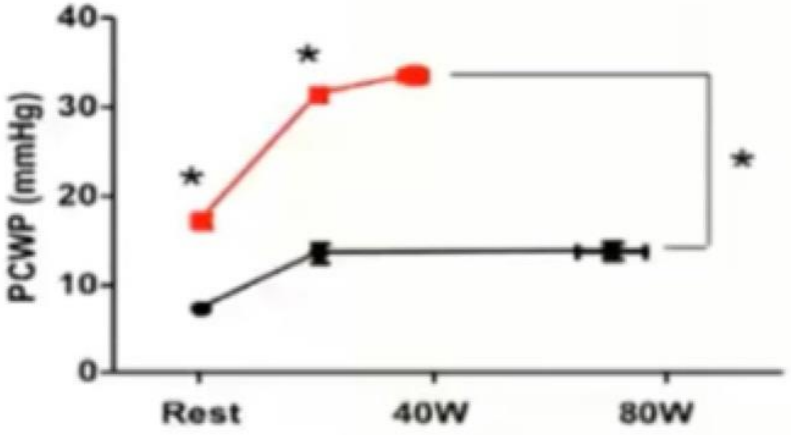


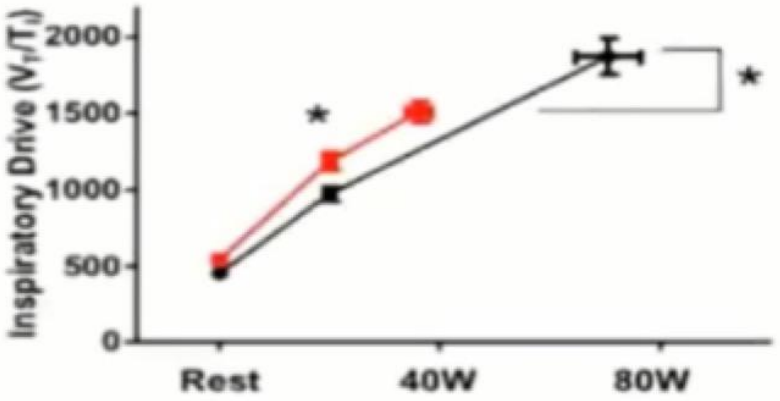
What is root cause of HFpEF?

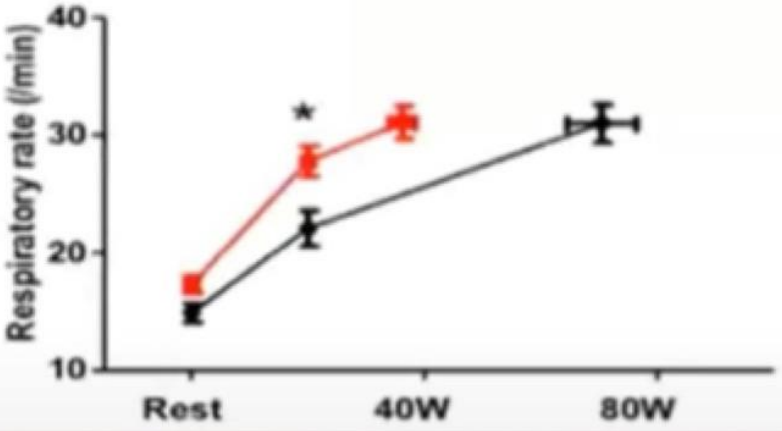


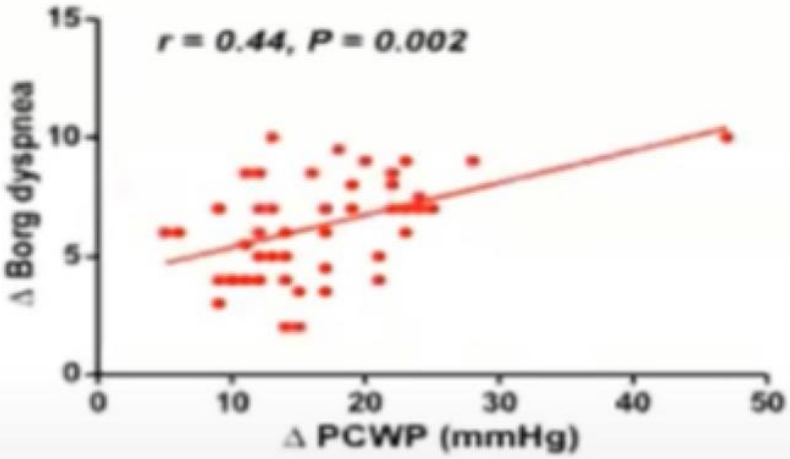


Why are High LVFP Bad?







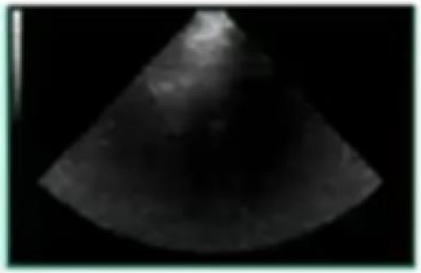


Scala di Borg modificata per la valutazione della dispnea (M-Borg)

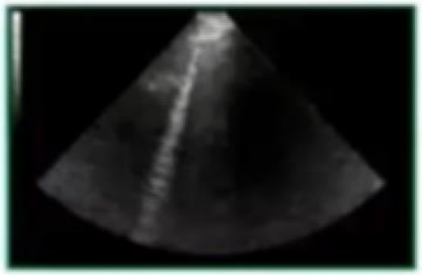
0	Nessuna
0,5	Molto molto lieve
1	Molto lieve
2	Lieve
3	Moderata
4	Piuttosto intensa
5	Intensa
6	
7	Molto intensa
8	
9	Molto molto intensa
10	Insopportabile

What happens in the lungs when ↑PCWP in HFpEF?

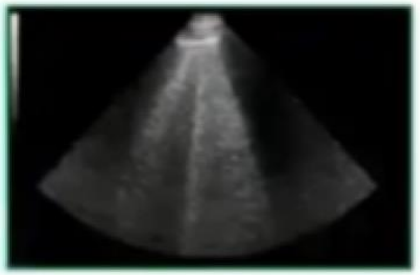
Lung US: sensitive for extravascular lung water



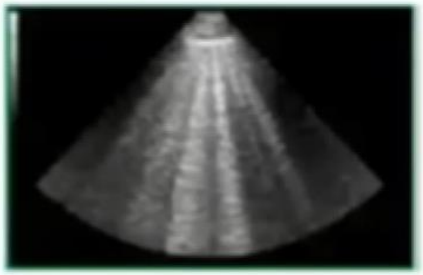
Normal Lung



B-lines -Mild



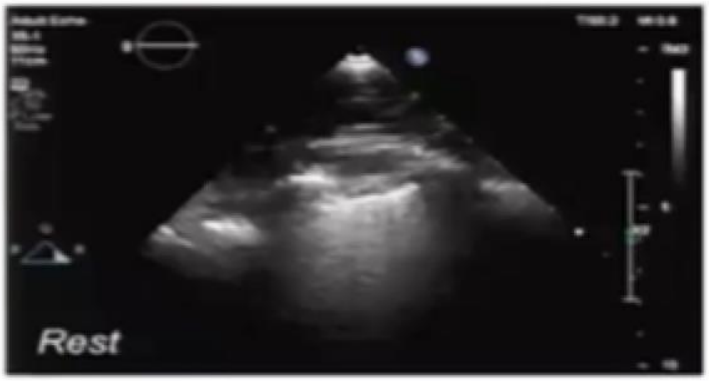
Moderate

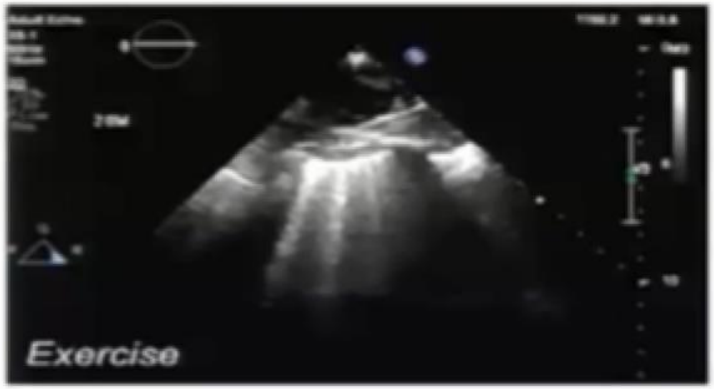


Severe

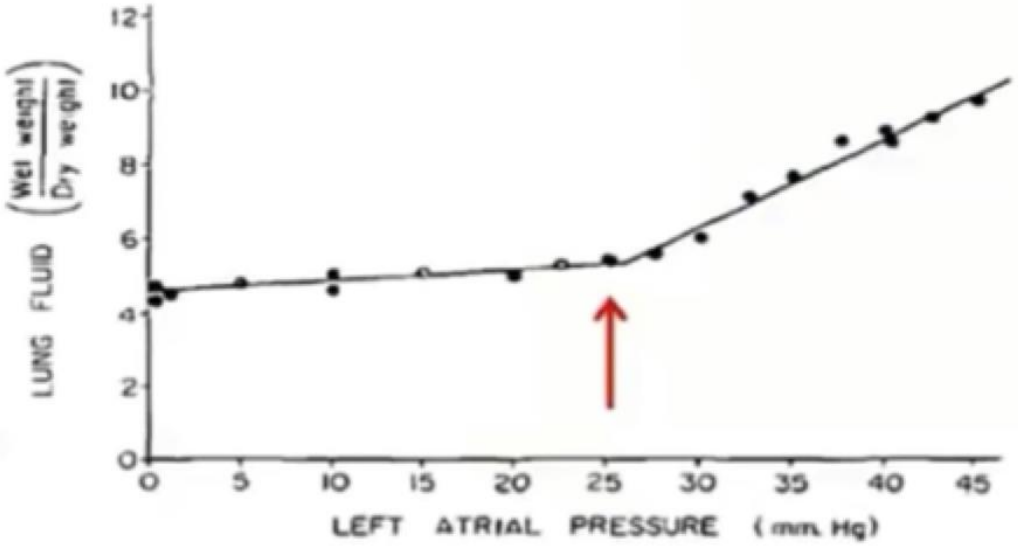
- 51 HFpEF patients prospective simultaneous echo, cath, blood sampling—rest & submax exercise
  - Simultaneous lung US

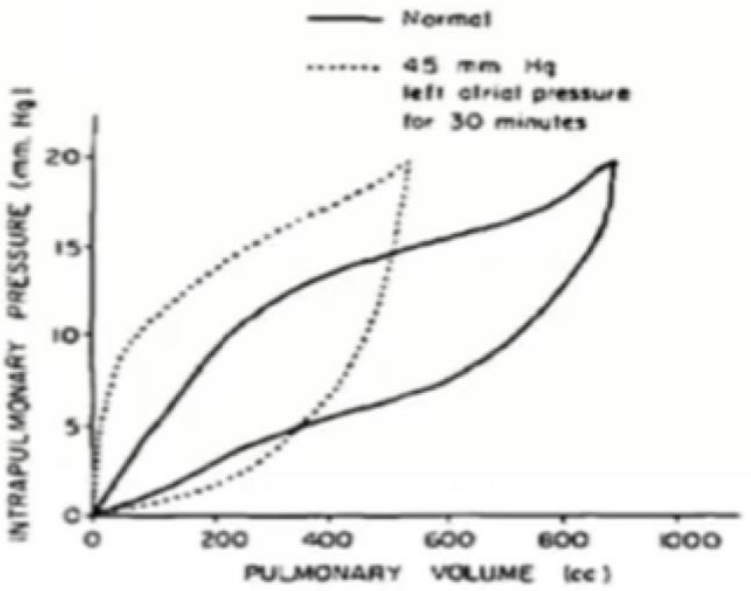
- Half (n=27, 53%) of patients developed EVLW during 20W exercise



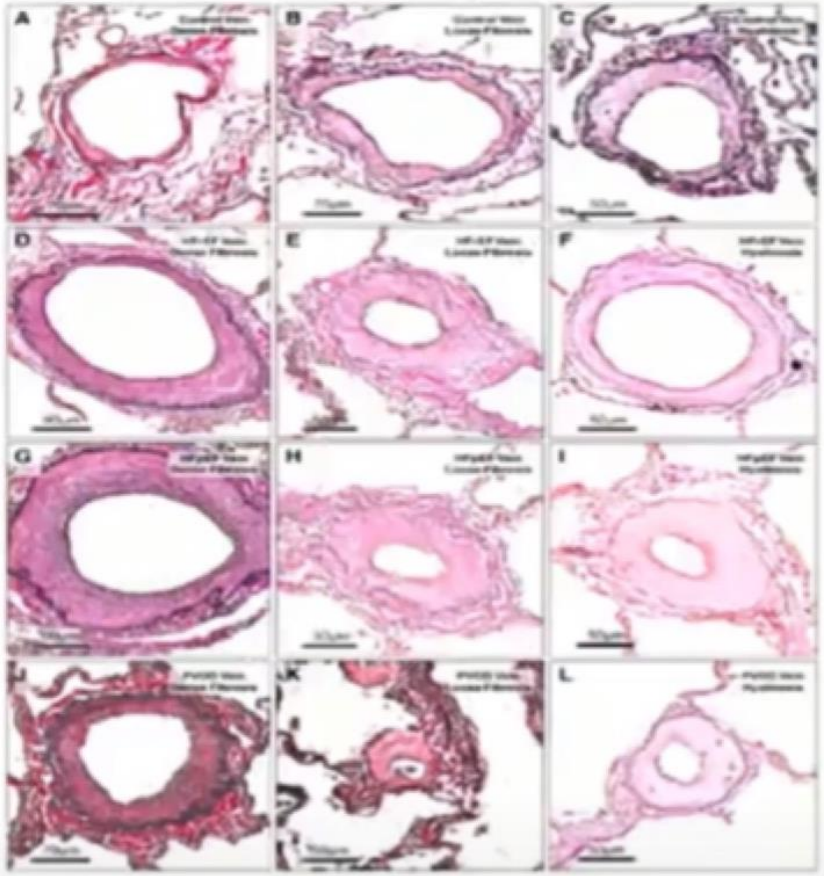


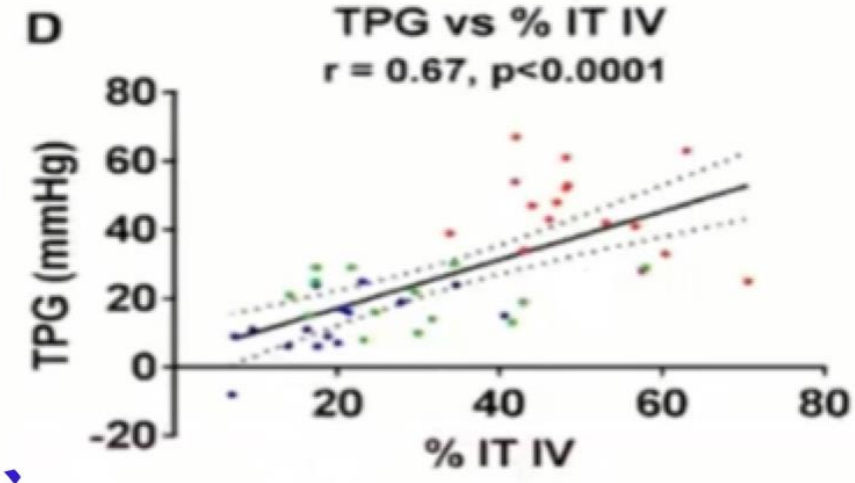
Acute Effects of LA Hypertension



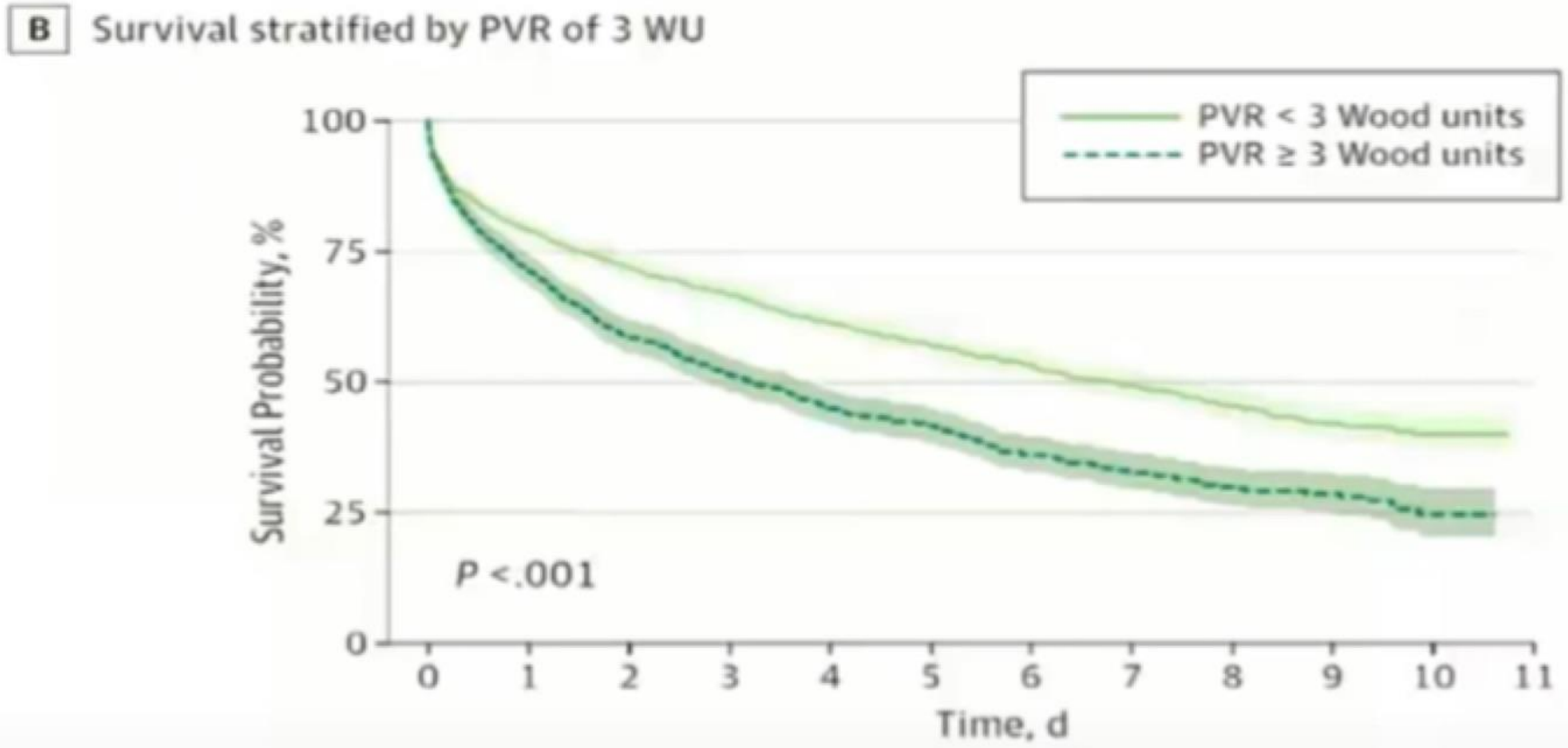


PV remodeling with chronic ↑PCWP





The presence of Pulmonary Vascular Disease Identifies ↑Risk in HFpEf



What is Unique about PVD-HFpEF?

- 3 types of HFpEF with↑PCWP at rest
  - No PH (rest mPA<25, n=21)
  - Isolated post capillary PH
    - IpcPH (rest mPA≥25 + PVR<3 & DPG<7, n=95)
  - PVD HFpEF
    - CpcPH (rest mPA≥25 + PVR≥3 &/or DPG≥7, n=45)
- Rest-Exercise Hemodynamics + Gas Exchange

Is Pulmonary Vascular Reserve Treatable?

Clinical Track

The β-Adrenergic Agonist Albuterol Improves Pulmonary Vascular Reserve in Heart Failure With Preserved Ejection Fraction

A Randomized Controlled Trial

Yogesh N.V. Reddy, Masaru Obokata, Katlyn E. Koepp, Alexander C. Egbe, Brandon Wiley, Barry A. Borlaug

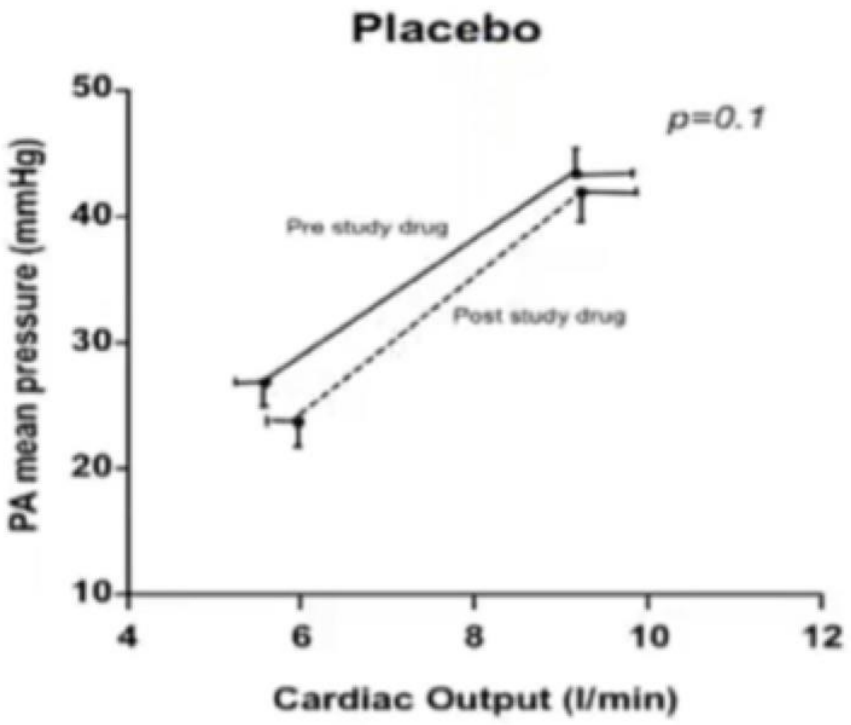
Rationale: Pulmonary vascular resistance fails to decrease appropriately during exercise in patients with heart failure with preserved ejection fraction (HFpEF). Interventions that enhance pulmonary vasodilation might be beneficial in this cohort but could also worsen left atrial hypertension, exacerbating lung congestion. Intravenous β-agonists reduce pulmonary vascular resistance but are not suitable for chronic use.

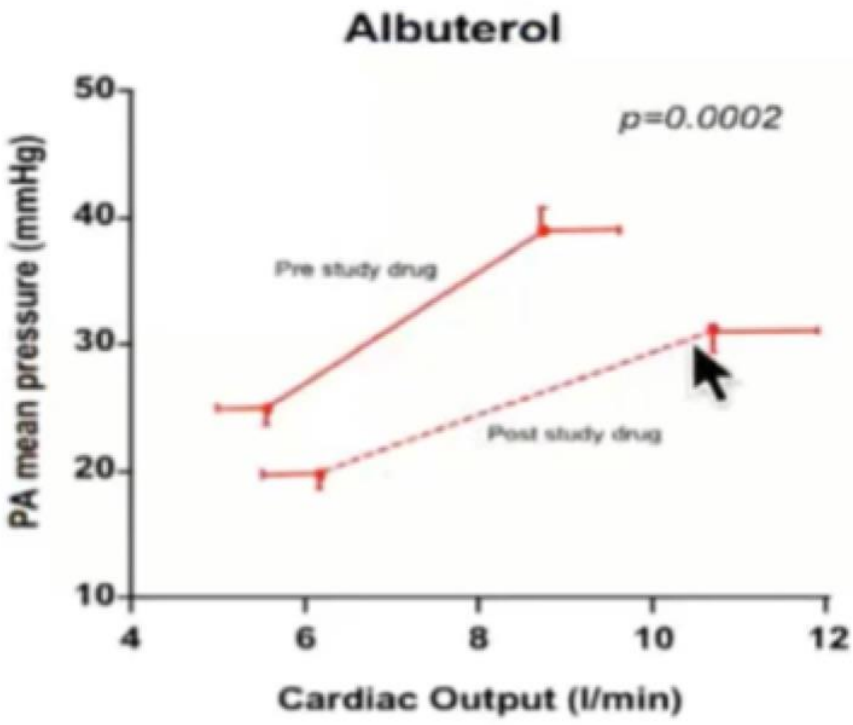
Objective: We hypothesized that the inhaled β-adrenergic agonist albuterol would improve pulmonary vasodilation during exercise in patients with HFpEF, without increasing left heart filling pressures.

Methods and Results: We performed a randomized, double-blind, placebo-controlled trial testing the effects of inhaled albuterol on resting and exercise hemodynamics in subjects with HFpEF using high-fidelity micromanometer catheters and expired gas analysis. The primary end point was pulmonary vascular resistance during exercise. Subjects with HFpEF (n=30) underwent resting and exercise hemodynamic assessment and were then randomized 1:1 to inhaled, nebulized albuterol or placebo. Rest and exercise hemodynamic testing was then repeated. Albuterol improved the primary end point of exercise pulmonary vascular resistance as compared with placebo (−0.6±0.5 versus +0.1±0.7 WU; P=0.003). Albuterol enhanced cardiac output reserve and right ventricular pulmonary artery coupling, reduced right atrial and pulmonary artery pressures, improved pulmonary artery compliance, and enhanced left ventricular transmural distending pressure (all P <0.01), with no increase in pulmonary capillary hydrostatic pressures.

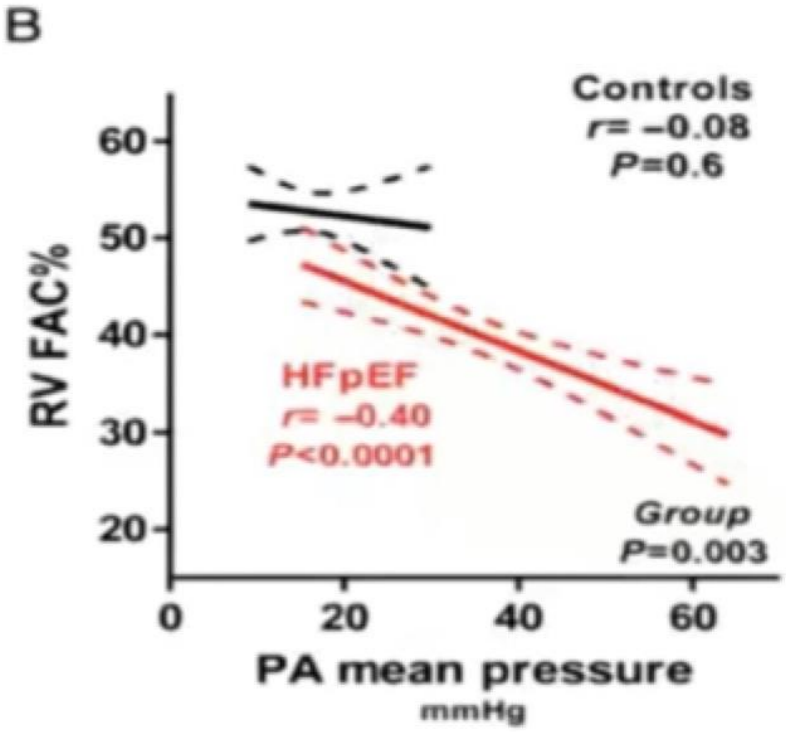
Conclusions: Albuterol improves pulmonary vascular reserve in patients with HFpEF without worsening left heart congestion. Further study is warranted to evaluate the chronic efficacy of β-agonists in HFpEF and other forms of pulmonary hypertension.

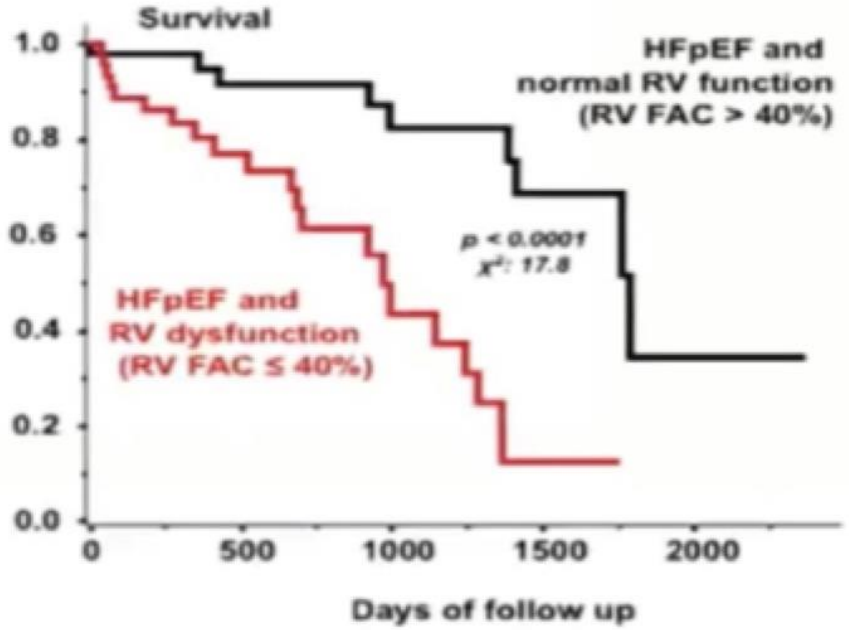
Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02884636. (*Circ Res.* 2019;124:306-314. DOI: 10.1161/CIRCRESAHA.118.313832.)


Placebo
p=0.1
Pre study drug
Post study drug
PA mean pressure (mmHg)
50
40
30
20
10
4
6
8
10
12
Cardiac Output (l/min)


Albuterol
p=0.0002
Pre study drug
Post study drug
PA mean pressure (mmHg)
50
40
30
20
10
4
6
8
10
12
Cardiac Output (l/min)

Who is the Final Victim of PH in HFpEF?





What is RV Natural History in HFpEF?

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 689–698
doi:10.1093/eurheartj/ehy809

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction

Masaru Obokata[1], Yogesh N.V. Reddy[1], Vojtech Melenovsky[1,2], Sorin Pislaru[1], and Barry A. Borlaug[1]*

[1]The Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55906, USA; and [2]Institute for Clinical and Experimental Medicine—IKEM, Prague, Czech Republic

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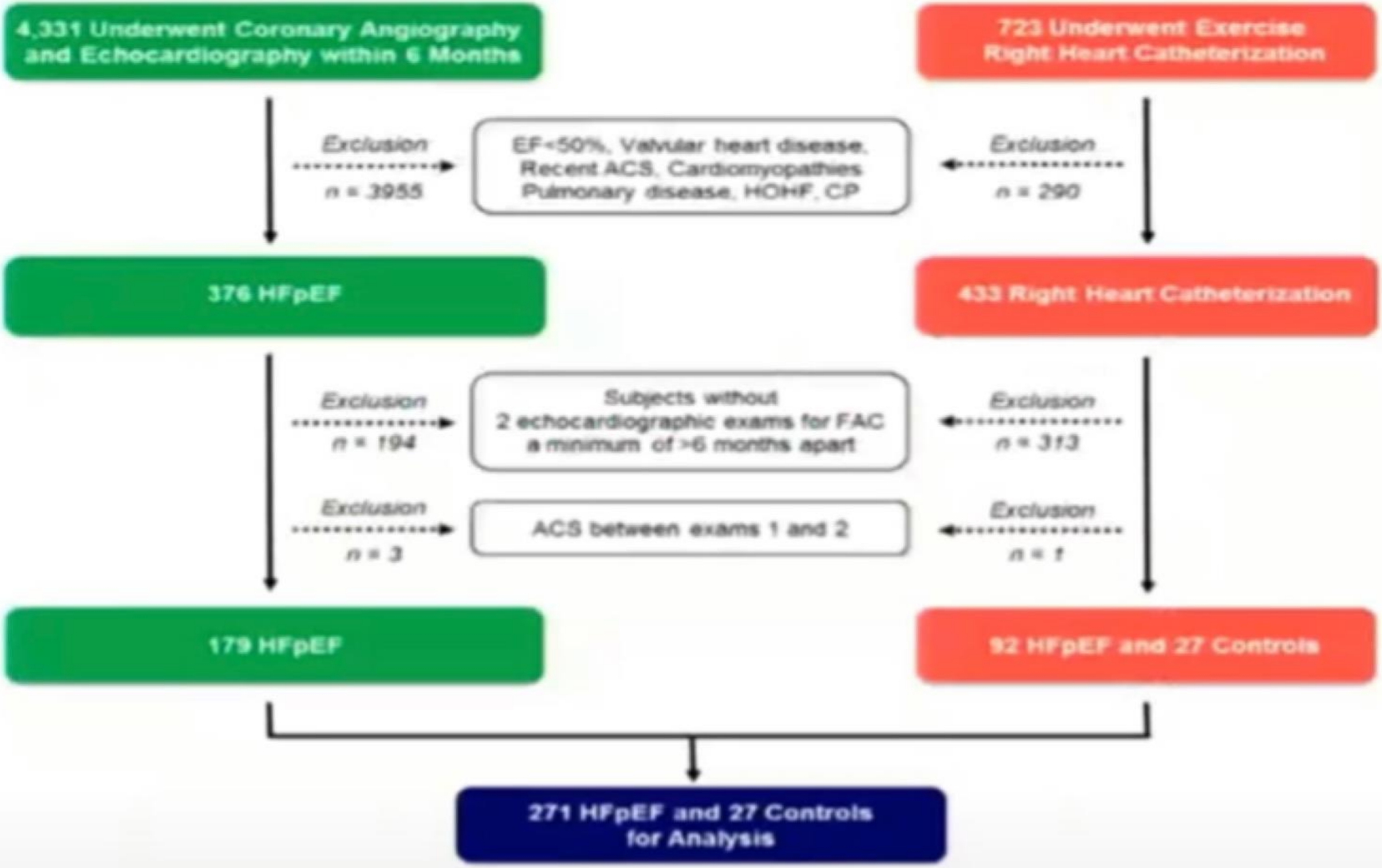
See page 699 for the editorial comment on this article (doi: 10.1093/eurheartj/ehy900)

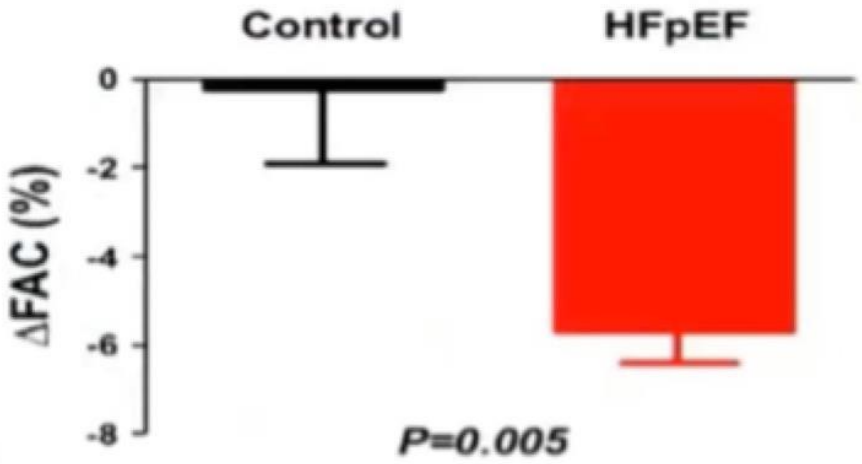
Longitudinal Observational Study

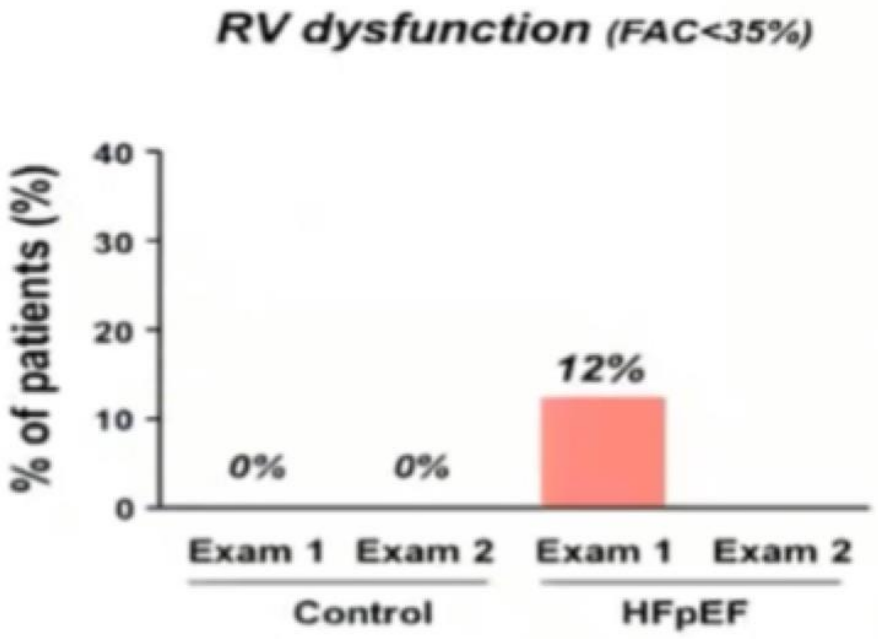


Baseline Characteristics: Typical HFpEF

	Control (n=27)	HFpEF (n=271)	P value
Age (years)	64±11	71±9	0.003
Female, n (%)	16 (59%)	151 (56%)	0.7
Body mass index (kg/m^2)	30±5	32±7	0.006
Diabetes mellitus, n (%)	7 (26%)	90 (33%)	0.4
Hypertension, n (%)	22 (81%)	227 (84%)	0.8
Atrial fibrillation, n (%)	2 (7%)	114 (42%)	0.0004
Coronary artery disease, n (%)	9 (33%)	155 (57%)	0.02
LV EF (%)	**64±4**	**62±7**	**0.01**
E/e' ratio	**11±5**	**16±8**	**<0.0001**
RV FAC (%)	**52±6**	**48±10**	**0.003**
RVSP (mmHg)	**33±7**	**44±15**	**<0.0001**

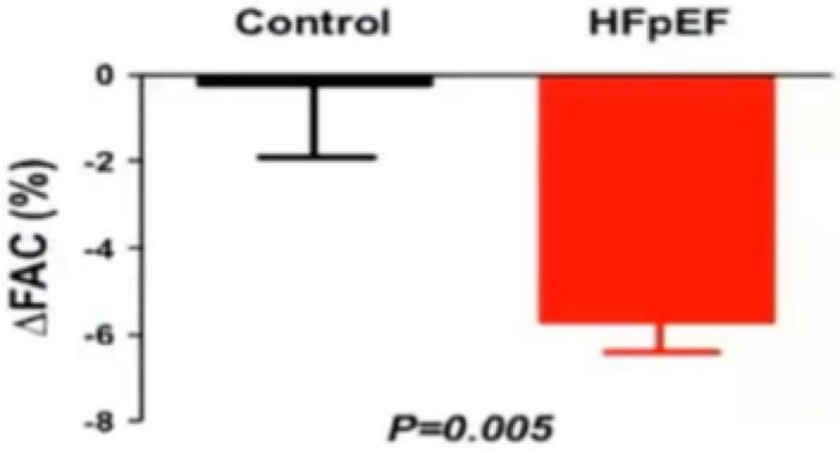
Long-Term Changes in RV Function

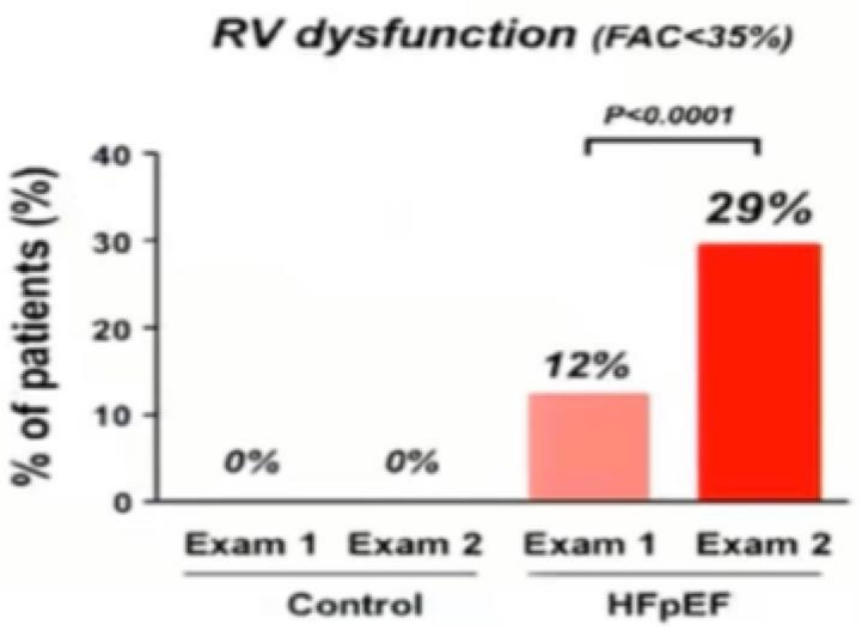




The median time between exams 1 and 2: **4.0 years** (IQR 2.1, 6.1)

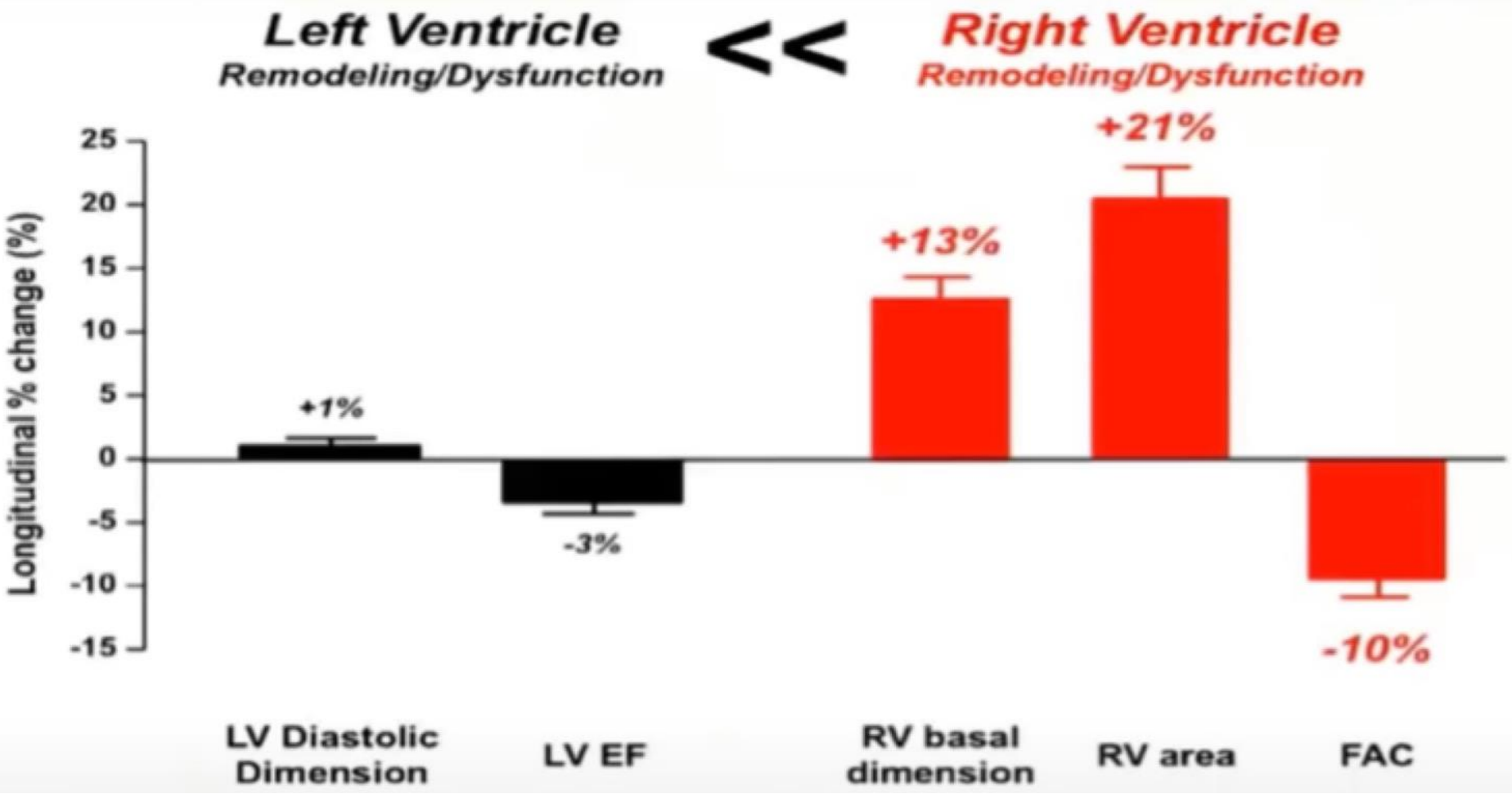
Long-Term Changes in RV Function



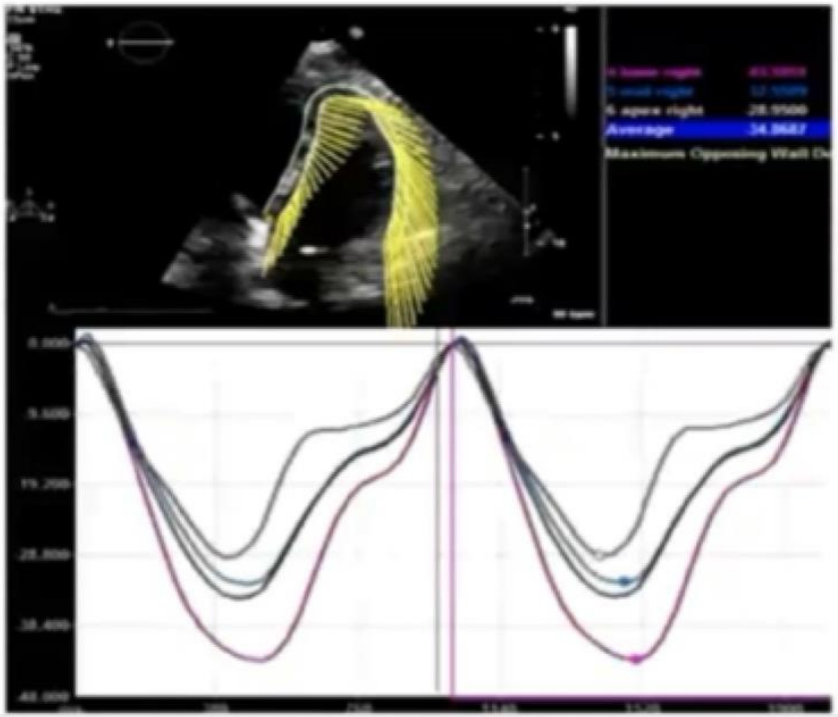


The median time between exams 1 and 2: **4.0 years** (IQR 2.1, 6.1)

Long-Term Changes in the RV and LV in HFpEF



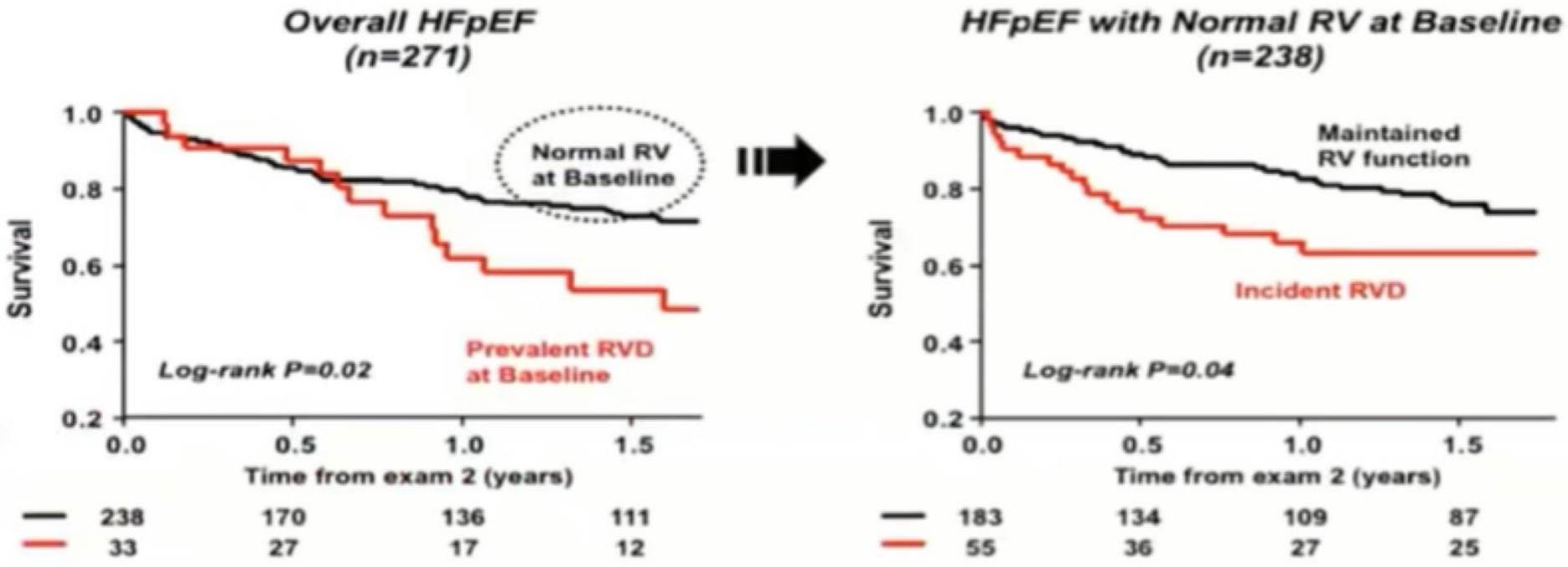
Similar Findings Using RV free wall strain



	HFpEF (n=271)		p value
	Exam 1	Exam 2	
RV free wall strain (%)	20.4 ± 6.2	**18.6 ± 6.9**	0.003
RV GLS (%)	17.7 ± 5.2	**16.0 ± 5.7**	0.0006

Impact of Incident RV Dysfunction on Mortality in HFpEF

Over a median follow-up of 15 months (IQR 5.1-21) after exam 2, there were **71 deaths (26%)**



Development of RVD: adjusted HR 1.89; 95%CI, 1.01-3.44, p=0.04

Predictors of Incident RV dysfunction

	Development of RV Dysfunction		
	No (n=183)	Yes (n=55)	P value
Body weight (kg)	89±21	98±25	0.01
Prevalent AF at baseline	31%	56%	0.0009
Incident persistent AF	21%	43%	0.007
PCWP	16±5	20±5	0.004

Conclusion: LVDD Causes…

- Elevated LVFP with exercise in HFpEF
  - ↑symptoms; ↓exercise capacity & survival
  - Lead to lung congestion (together with RVD)
  - Cause lung remodeling
    - Capillaries, arteries & veins
  - Impairs gas exchange
  - Causes pulmonary hypertension & PVD
  - RV dysfunction, atrial remodeling, & TR