INVASIVE MEASUREMENT:

THE NEW GOLD STANDARD FOR DIAGNOSIS OF HFpEF?

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Objectives

Discuss the current diagnostic algorithms for the diagnosis of HFpEF

Understand the rationale and methodology for invasive exercise stress testing for the diagnosis of HFpEF

Discuss the role of invasive exercise testing in the context of other stimuli or non-invasive testing

Current Diagnostic Algorithms for HFpEF

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Current Definitions for the Diagnosis of HFpEF

SIGNS + SYMPTOMS	
BNP	
ECHOCARDIOGRAPHY	

CCS (2017)	HFpEF ≥ 50% HFmEF 41-49% "recovered EF" > 40%
ESC (2016)	HFpEF > 50% HFmrEF 41-49%
AHA/ACC (2013)	HFpEF ≥ 50% HFpEF borderline 41-49% Improved > 40%

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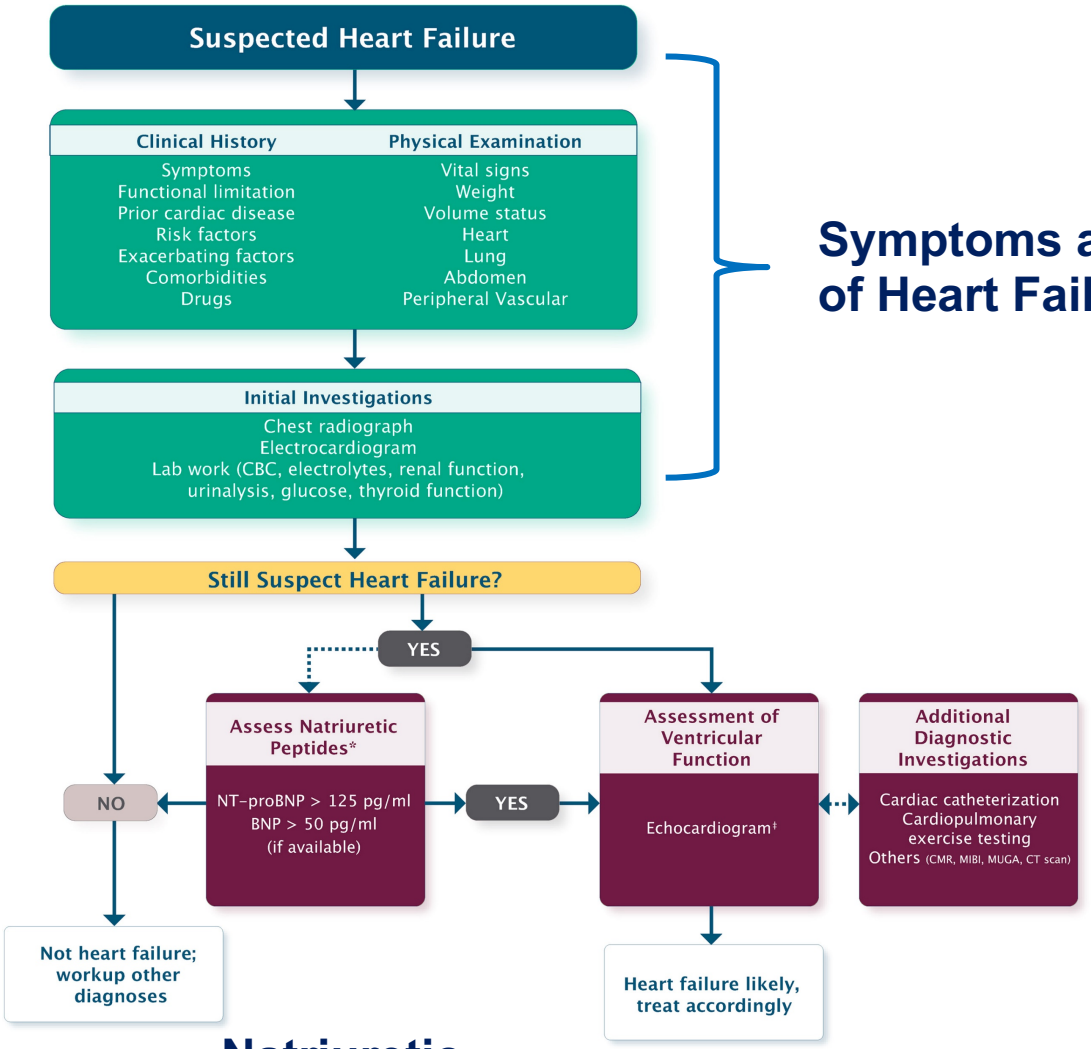
Canadian Journal of Cardiology, Volume 33, Issue 11, November 2017 Pager 1342-13

European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200, https://doi.org/10.1093/eurheartj/ehw128

Circulation, Volume 128, Issue 16, October 2013



Symptoms and Signs of Heart Failure

Natriuretic Peptides

Echocardiography

Additional Diagnostics Relevant to HFpEF

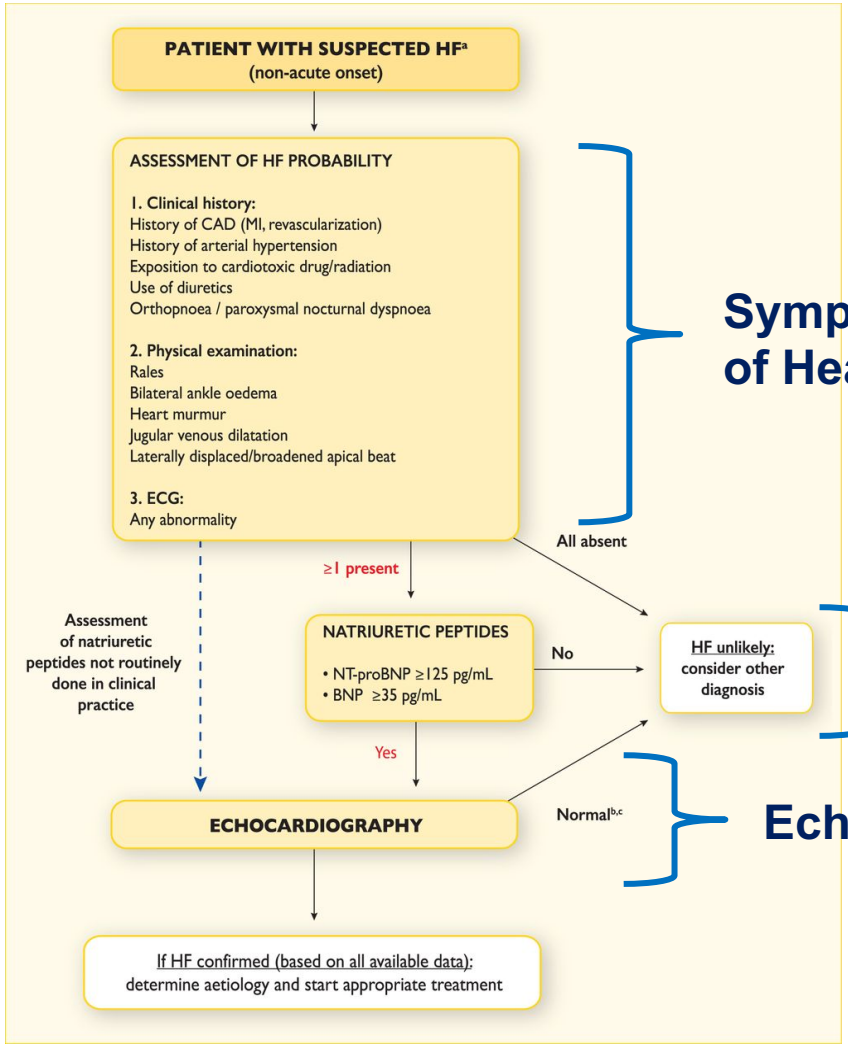
Evaluation of Ischemia
Stress testing, cath

Evaluation for infiltration
MRI, iron studies/light chains, biopsy

?CPET

Canadian Journal of Cardiology 2017 33, 1342-1433DOI: (10.1016/j.cjca.2017.08.022)

Figure 4.1 Diagnostic algorithm for a diagnosis of heart failure of non-acute onset



European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200, https://doi.org/10.1093/eurheartj/ehw128

Rationale for additional criteria to demonstrate HF pathophysiology in HFpEF

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms and Signs*	Symptoms and Signs*	Symptoms and Signs*
	2	**LVEF < 40%**	**LVEF 40-49%**	**LVEF ≥ 50%**
	3		1. Elevated levels of natriuretic peptides 2. **At least** 1 additional criterion a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction	1. Elevated levels of natriuretic peptides 2. **At least** 1 additional criterion a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction

*** Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics**

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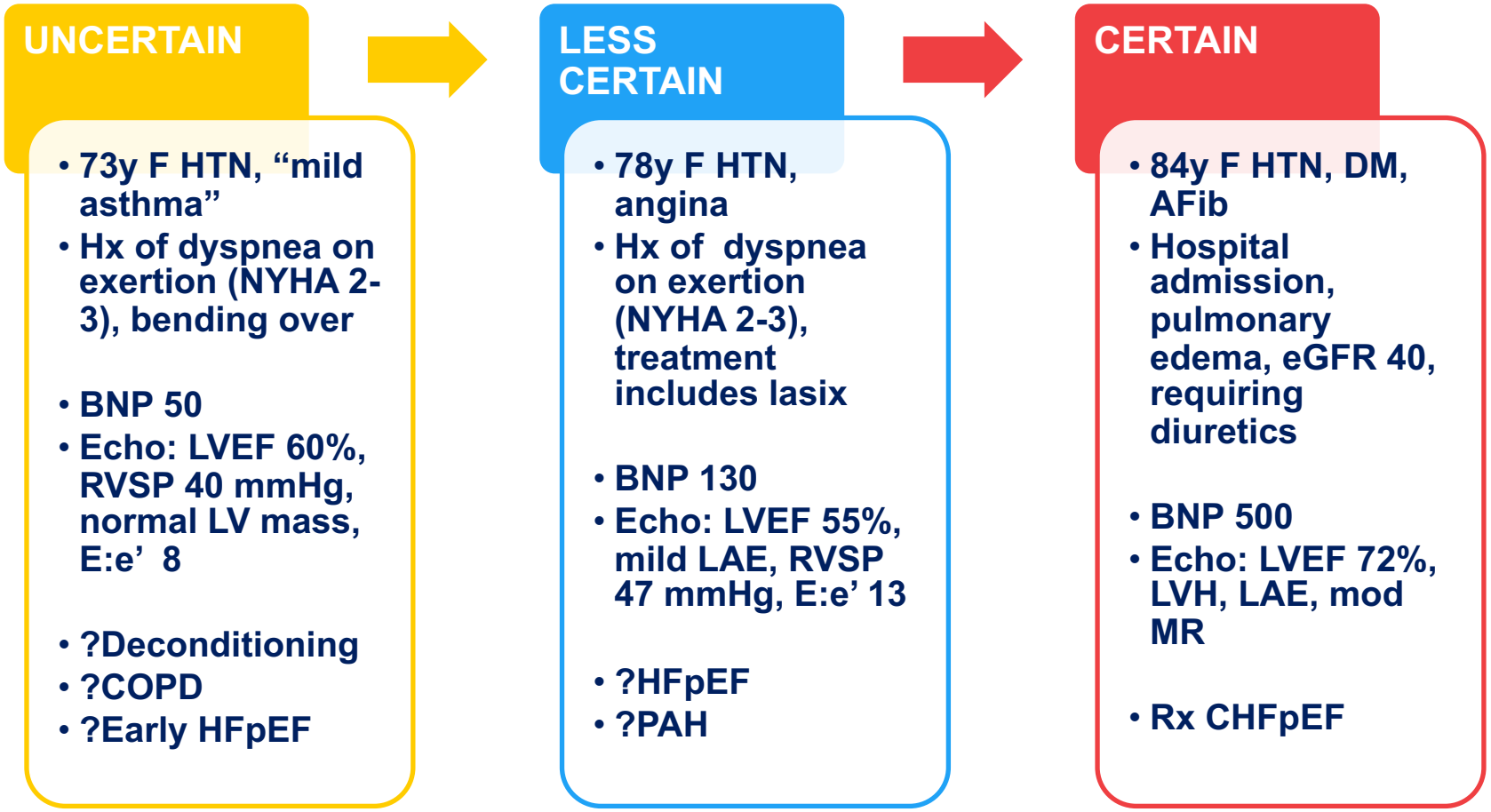
European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200, https://doi.org/10.1093/eurheartj/ehw128, Table 3.1

In the absence of a validated gold standard for HFpEF, there is a continuum of confidence for the diagnosis



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Supporting evidence of relevant structural heart disease or diastolic dysfunction: Echocardiography

- Left atrial volume index ≥ 34ml/m2
- Left ventricular mass index ≥ 115 g/m2, ≥ 95 g/m2
- E/e' ≥ 13, mean e' septal and lateral ≤ 9 cm/s
- TR jet velocity
  - Upwards of 80% HFpEF exhibit PH
  - Overlap: PAH versus PH-LHD

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European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200, https://doi.org/10.1093/eurheartj/ehw128, Table 3.1

Supporting evidence of abnormal cardiac chamber physiology: Role of Cardiac Catheterization

- **“In cases of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis”**
  - ***ESC HF Guidelines***

- **“Right heart catheterization (RHC) is required to make the diagnosis of PAH” (and differentiate from PH-LHD)**
  - ***ESC PH Guidelines***

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Updated Hemodynamic Definitions for PH-LHD

Hemodynamic classification	Definition	Updates	Clinical Group(s)
PH	mPAP ≥ 25 mmHg	mPAP > 20 mmHg	All
Pre-capillary PH	mPAP ≥ 25 mmHg PAWP < 15 mmHg	mPAP > 20 mmHg PAWP < 15	Group 1,3-5
Post capillary PH	**mPAP ≥ 25 mmHg PAWP ≥ 15 mmHg LVEDP > 15 mmHg**	**mPAP > 20mmHg PAWP ≥ 15 mmHg LVEDP > 15mmHg**	**Group 2 PH-LHD**
Isolated post-capillary PH	**DPG < 7 mmHg and/or PVR ≤ 3WU**	**PVR ≤ 3WU**	
Combined post-capillary and pre-capillary PH	**DPG ≥ 7 mmHg and/or PVR > 3 WU**	**PVR > 3 WU**	

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Galie et al, Guidelines for diagnosis and treatment of pulmonary hypertension, Eur Heart J 2016 January 1;37(1):67-119, Eur Resp J 2019

Methodology and Interpretation of Invasive Hemodynamic Assessment

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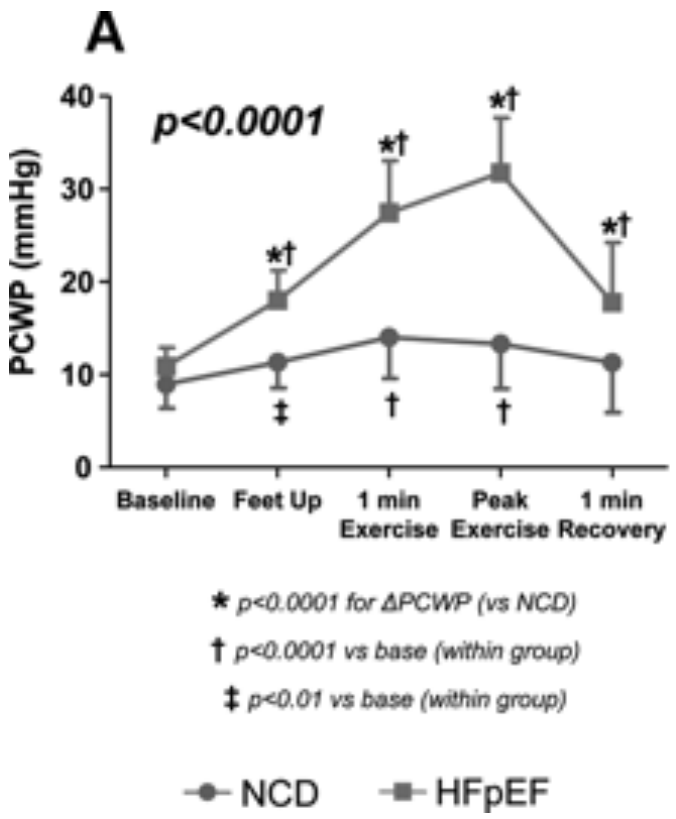
“Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction”



- Dyspnea of unknown origin
- Normal BNP and echo
- Subgroup with “exaggerated” PAWP response to even slight exercise
- Hypothesized to reflect diastolic impairment as a cause of dyspnea

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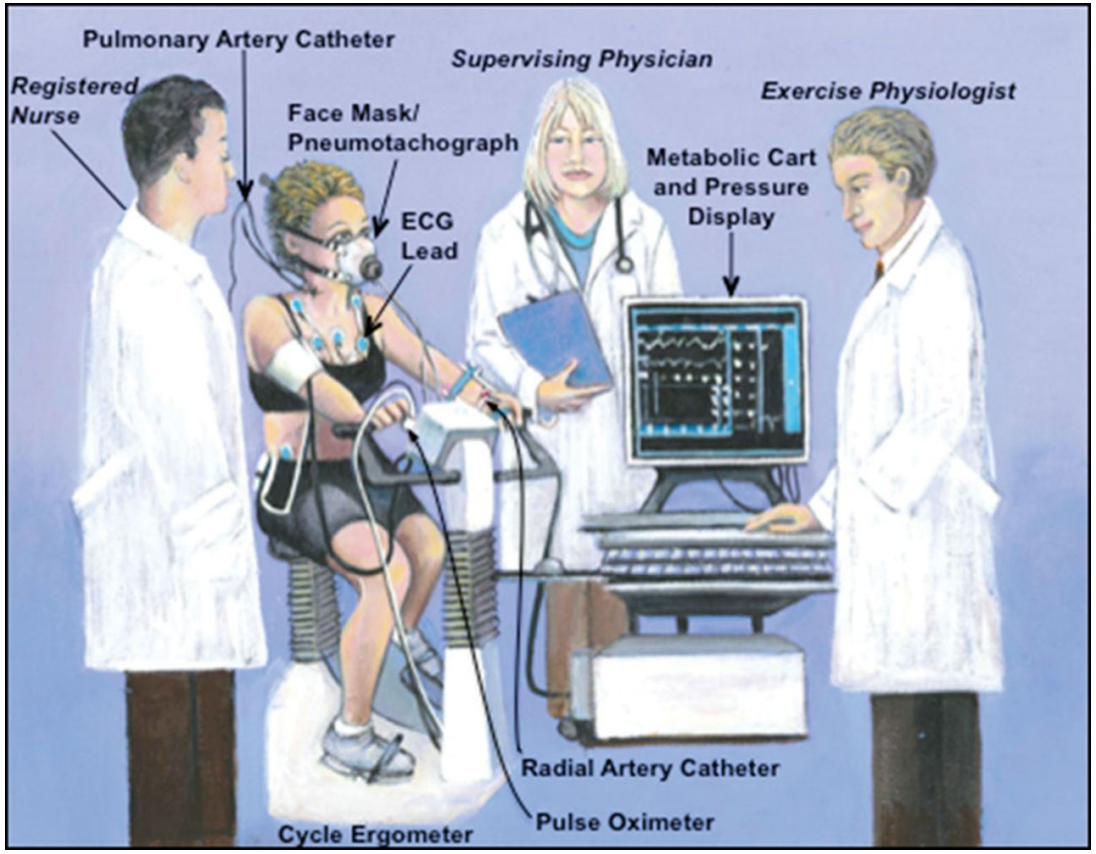
Borlaug, Circulation HF2010:3:588

5th World PH Symposium 2013:
Significant Knowledge Gaps Preclude Recommendation of Exercise Hemodynamics

- **Exercise hemodynamics likely to be useful, however exercise criteria cannot be reintroduced at the present time**
- **Prognostic and therapeutic implications of exercise-induced hemodynamic responses unclear**
- **Refinement of exercise stress protocol (position, type, intensity) required**
- **Age adjusted "normal" values or reference ranges in health are unknown**

Improving Standardization of Exercise Hemodynamic Testing

Wright et al, Heart 2016; 102:438-443



Maron BA et al, Circulation. 2013;127:1157-1164

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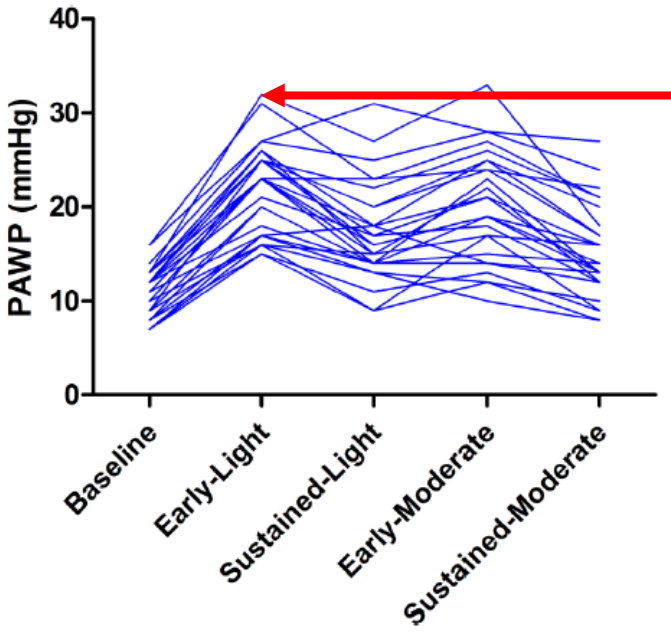
Design of the Exercise Challenge: Necessary Elements



Wright et al, Heart 2016; 102:438-443

- Cycle Ergometry Preferred
  - Upright positioning
  - Supported body weight
  - Measurable workloads
  - Maximal or submaximal protocols
  - Disadvantages – submaximal efficiency
  - +/- metabolic testing
- Ensure 2-3 minute warmup to avoid sampling early after initiation or escalation of workrate

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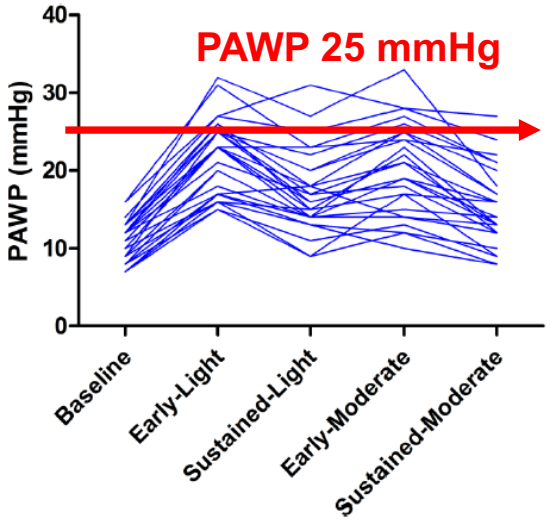
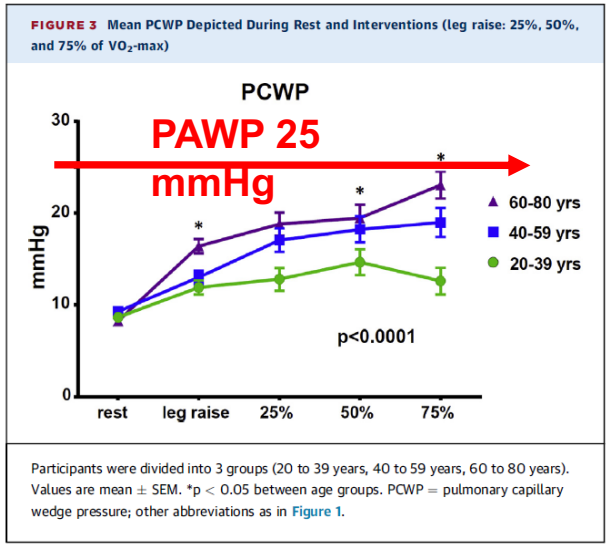
Hemodynamic Interpretation in Exercising Older Adults

PAWP > 25 mmHg considered as ULN in adults > 40years



Wright et al, Heart 2016



Wolsk et al, JACC HF 2017

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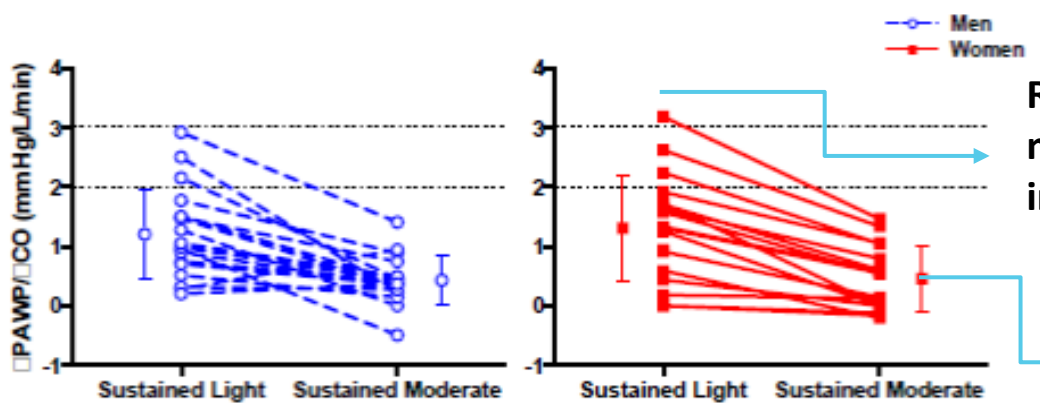
Additional Criteria: Increase in PAWP adjusted for the Increase in CO < 2mmHg/L/min



Reflects early ↑in PAWP vs moderate ↑ in CO within initial exercise stage

As exercise duration and intensity ↑, PAWP ↔ or ↓ with further↑ in CO

FIGURE 1. From Esfandiari et al, 2017 Med Sci Sport Ex. We studied healthy untrained older men and women using our submaximal exercise hemodynamic protocol. The PAWP responses at Light and Moderate exercise are depicted here: the PAWP (upper left panel), the PAWP adjusted for Workrate and body size, and the change in PAWP relative to the change in cardiac output (bottom left and right). All 3 metrics demonstrate "time variance". By sustained moderate exercise, the mean values and range of the PAWP adjusted for either workrate or cardiac output are lowest and as such may be more reliable as a reference range. If exercise duration is short, there may be significant overlap in the PAWP responses between healthy normal subjects and patients with disease.

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Esfandiari et al, Med Sci Sports Ex 2017

Towards Increasing Acceptance

“In patients presenting exercise intolerance, in which noninvasive and resting invasive measurements are inconclusive, provocative testing in the cardiac catheterization laboratory should be considered to determine the presence of a cardiac etiology. Cycle ergometry exercise is the most physiologically relevant and sensitive stressor and is preferred over other maneuvers such as saline loading or arm exercise”

The Society of Cardiovascular Angiography and Interventions
Heart Failure Society of America

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Sorajja, P., Borlaug, B. A., Dimas, V. V., Fang, J. C., Forfia, P. R., Givertz, M. M., Kapur, N. K., Kern, M. J. and Naidu, S. S. (2017), SCAI/HFSA clinical expert consensus document on the use of invasive hemodynamics for the diagnosis and management of cardiovascular disease. Cathet. Cardiovasc. Intervent., 89: E233–E247

Clinical Utility in HFpEF and Alternatives

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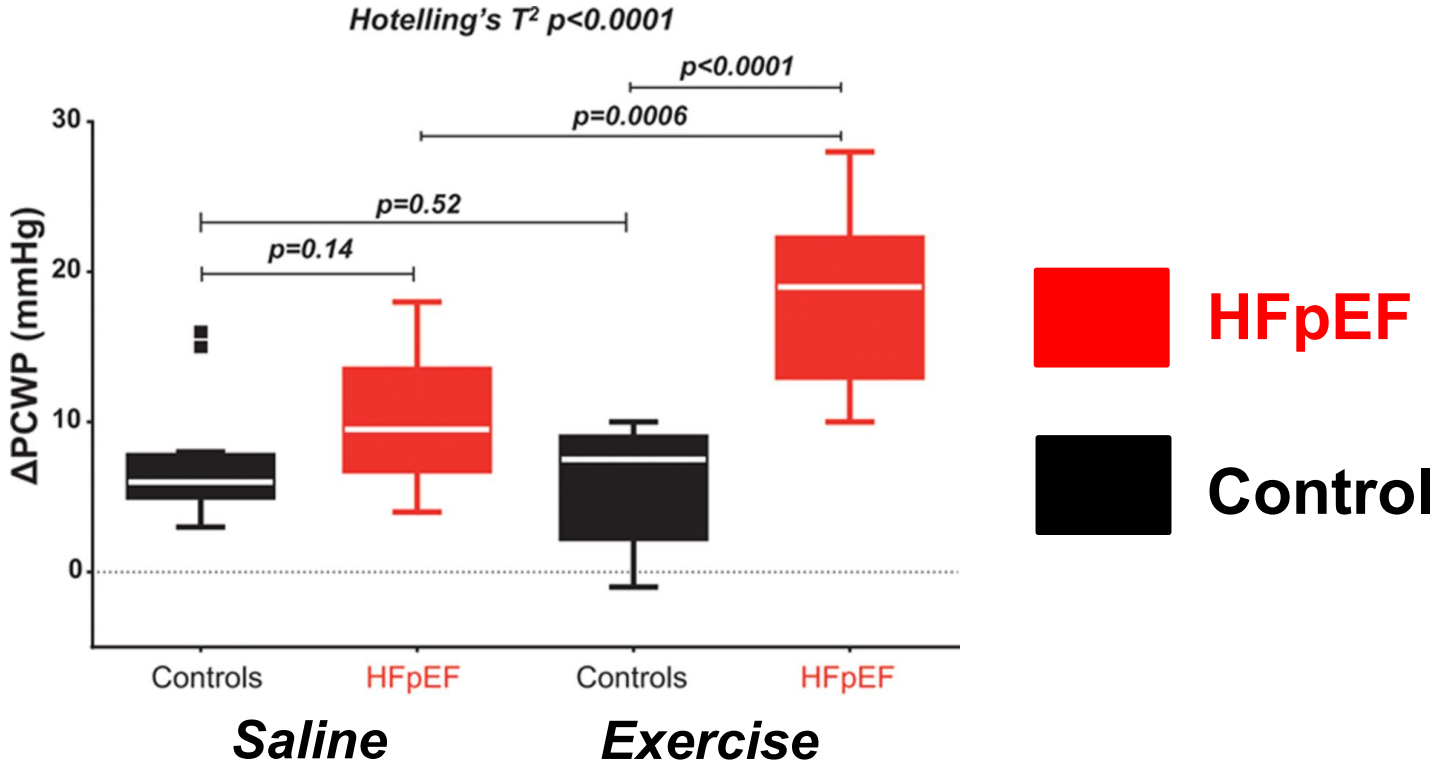
Exercise versus Saline Challenge

- Exercise is a classic physiologic stressor that reproduces symptoms and the patient experience
- More potent hemodynamic stress compared with saline



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Andersen et al, Circ Heart Fail 2015;8:41-48

Non-Invasive Diagnostic Modalities In Situations of Uncertain HFpEF

- **Diastolic Stress Echocardiography**
  - Limitations of measuring E:e' during exercise
  - Limitations of assessment of TR jet velocity
  - Studies directly comparing invasive and non-invasive diastolic stress testing limited
- **Cardiopulmonary Exercise Testing (CPET)**
  - Useful screen for exercise intolerance related to cardiac and pulmonary vascular limitation
  - + RHC, invasive CPET

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Invasive Hemodynamic Exercise Testing: A New Therapeutic Target for HFpEF

ORIGINAL RESEARCH ARTICLE

Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure])

A Phase 2, Randomized, Sham-Controlled Trial

Inclusion Criteria

- **Exercise PAWP > 25mmHg**
- **PAWP:RA difference > 5mmHg**

Primary endpoint

- **Exercise PAWP**

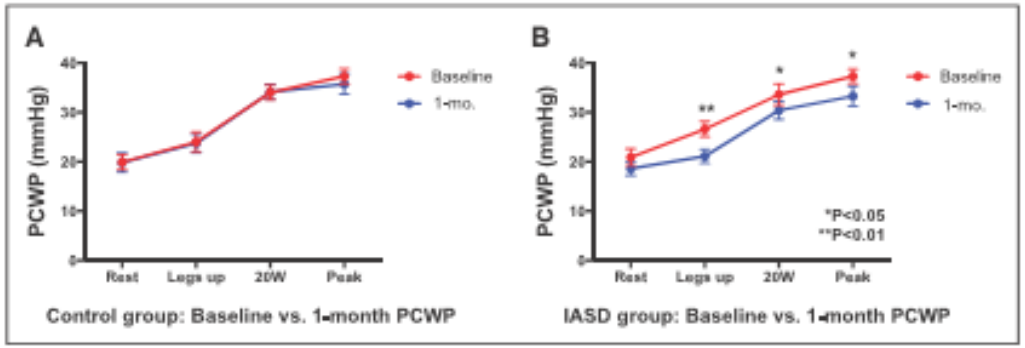

Figure 3. Pulmonary capillary wedge pressure during exercise hemodynamic testing: baseline versus 1-month postrandomization, stratified by treatment group.

A, Control group. **B,** IASD treatment group. IASD indicates interatrial shunt device; and PCWP, pulmonary capillary wedge pressure. *P* values were calculated using paired *t* tests (within-group comparisons of baseline versus 1-month values). Between-group comparison of peak exercise PCWP was not statistically significant (*P*=0.144), as shown in Table 3. **P*<0.05; ***P*<0.01.

Feldman et al, Circulation 2018;137:364-375

Clinical Trials for HFpEF Rx using Exercise Hemodynamic Entry Criteria are Currently Enrolling Patients

Agent	Study Design	Sponsor
AZD4831	Phase 2 RCT	Astra Zeneca
Metformin	Phase 2 Crossover	NIH
Myeloperoxidase inhibitor	Phase 1 RCT	Mayo Clinic
Saccubitril-Valasartan	Open label follow up	Mayo Clinic, NIH
Dapagliflozin	RCT	St. Luke's Health System
Oral Nitrate	Parallel design	NIH
Potassium Nitrate	RCT	University of Pennsylvania/Northwestern

Clinicaltrials.gov search terms HFpEF, intervention, actively recruiting, accessed March 14, 2019

Reddy et al, A simple, evidence-based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation 2018;138:861-870

	Clinical Variables	Values	Points
H_2	Heavy	Body mass index > 30 kg/m2	2
	Hypertensive	2 or more antihypertensive medications	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)

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