HFpEF
What's New?

Felix J. Rogers, DO, FACC, FACOI

May 12, 2019

Meet Bill, my H.S. classmate

- Nov 27, 2018
- “I get short of breath when I climb a flight of stairs”
  Feels exhausted at the end of a day in his tire repair shop
- BP 126/78 HR 72 No JVD. No murmur.

- Echo
- LV normal size and thickness
- LV EF 63%
- Mild mitral annular calcification
- Grade I LV diastolic dysfunction

Meet Mike, my H.S. classmate

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Is this heart failure with preserved ejection fraction?

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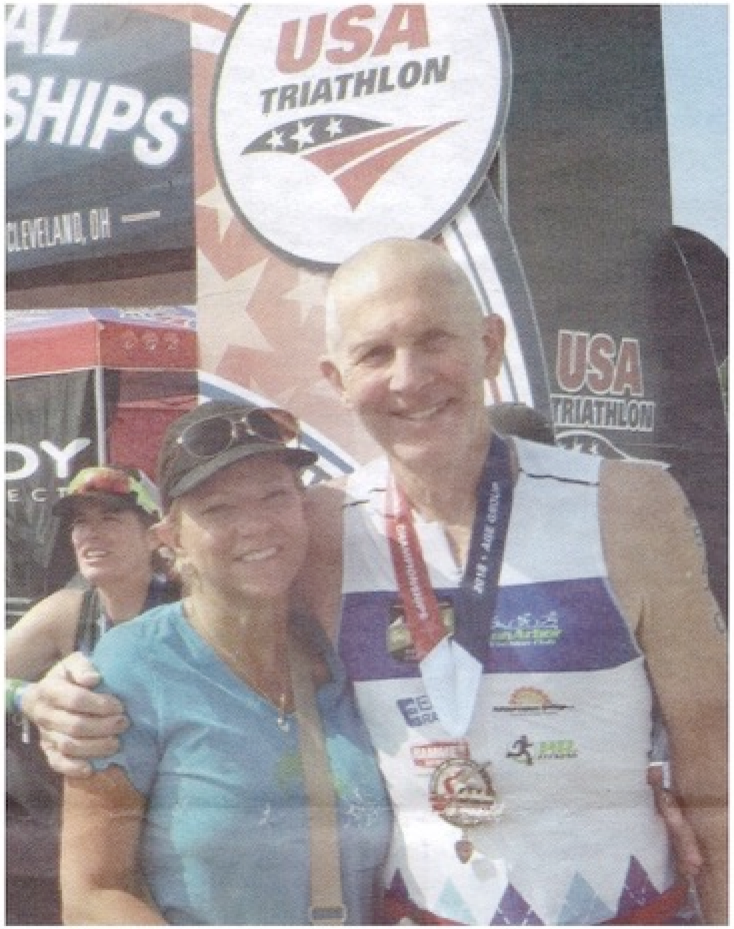
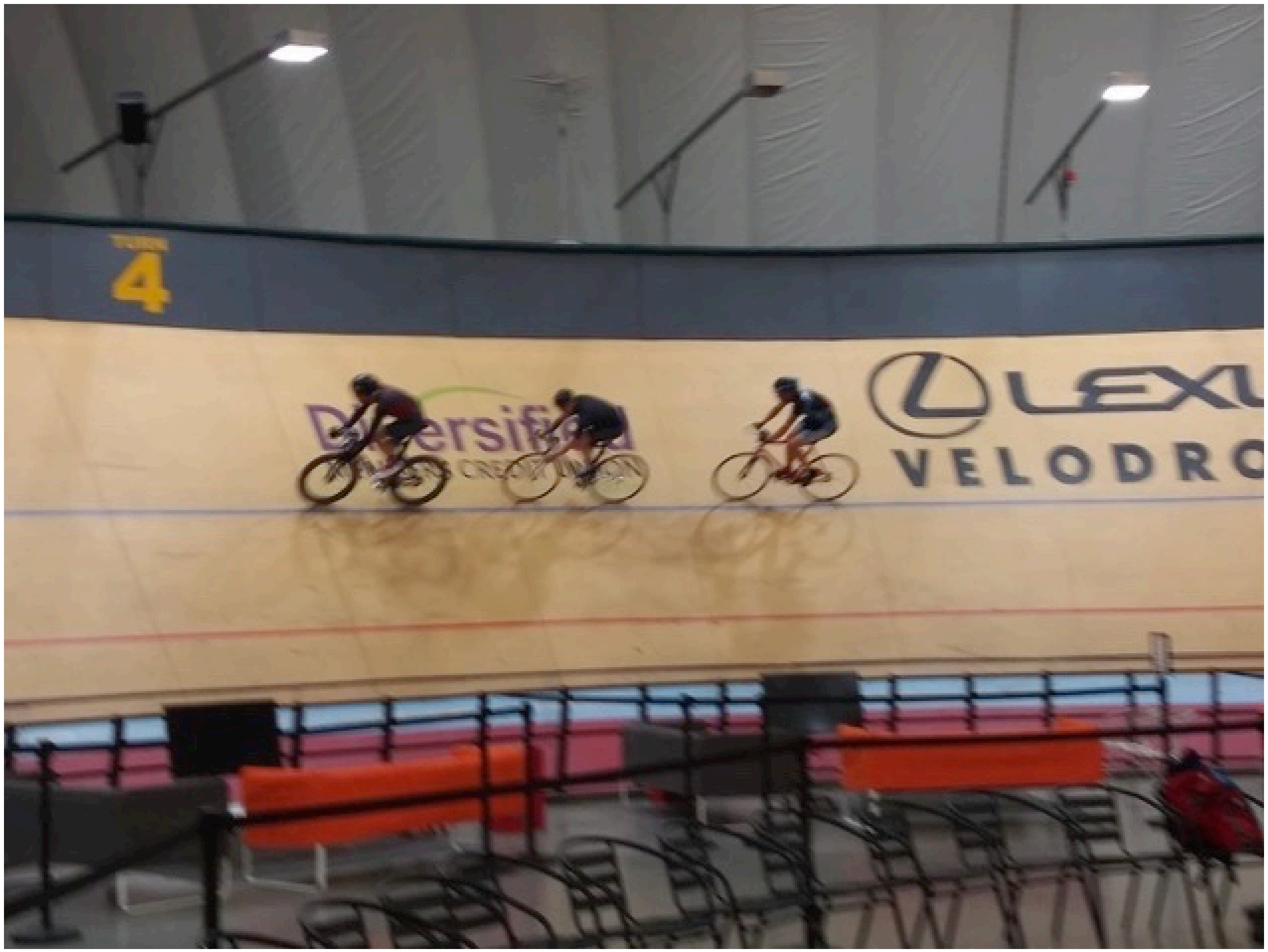
Exhausted at the end of the day

More information…



How Mike starts the day



Meet Mike, my H.S. classmate
More information

- Nov 27, 2018
- "I get short of breath when I climb a flight of stairs"
  Exhausted at the end of the day
- Additional history. He's a triathlete
  - Exercises regularly. Runs 5-8 miles at least once a week
    Works out for an hour at the Lexus Velodrome
  - Ranked No. 63 in the USA in his age group in 2018

___ Is this heart failure with preserved ejection fraction?

___ Is this normal aging?

Today's agenda

- Pathophysiology
  - Normal aging vs HFpEF
  - Echo findings
  - Fat… epicardial and visceral
  - Obesity
  - Acute decompensated HFpEF

- Treatment
  - Mechanical: reduction in LA pressure
    bariatric surgery

  - Medical: statins
    mineralocorticoid inhibitors
    SGLT-2i

  -- Exercise and lifestyle
  -- Traditional cardiac risk factors

Exercise and aging

Exercise and aging (*Aging Cell* 10.1111/2018)

- 100 cyclists aged 55-79
- All cycle more than 100 miles/week
- Quadriceps muscle biopsy
  - Muscle fiber type
  - Muscle fiber size
  - ATP activity
  - Capillary density
  - Mitochondrial proteins

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- All cycle more than 100 miles/week
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  - Muscle fiber type
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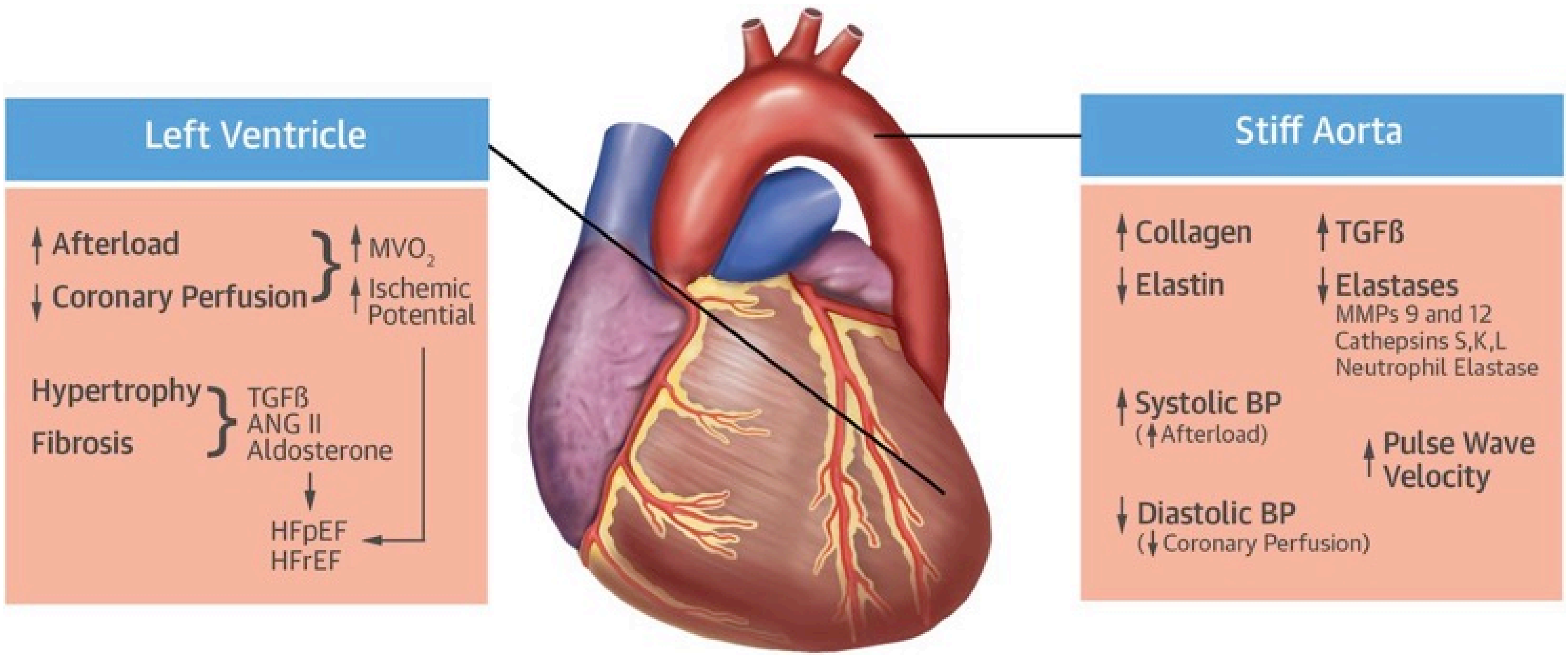
  - ATP activity
  - Capillary density
  - Mitochondrial proteins

- Only capillary density decreased with age

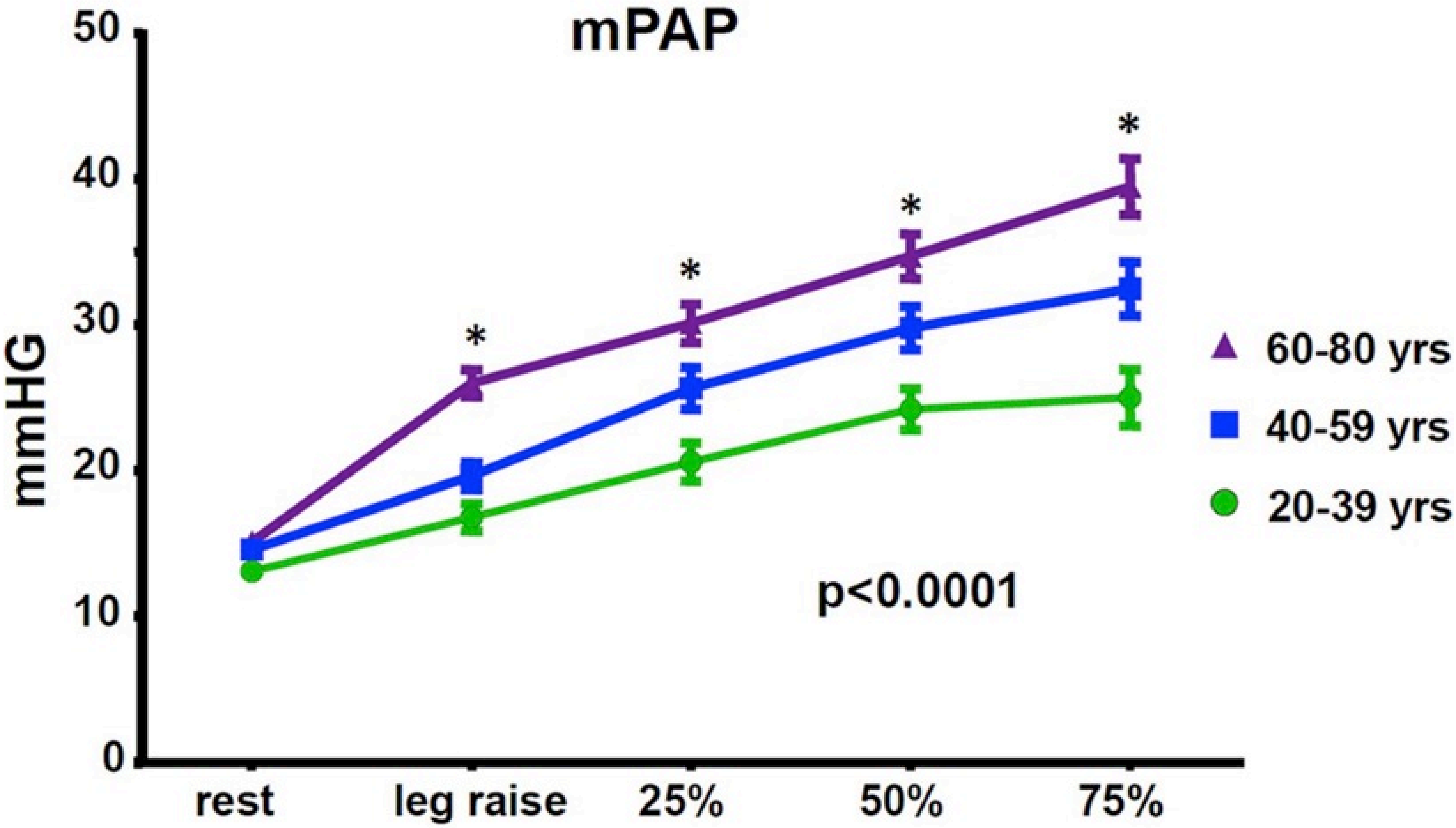
Pathophysiology of aortic-LV dynamics in the aging CV system



Francesco Paneni et al. JACC 2017;69:1952-1967

JACC

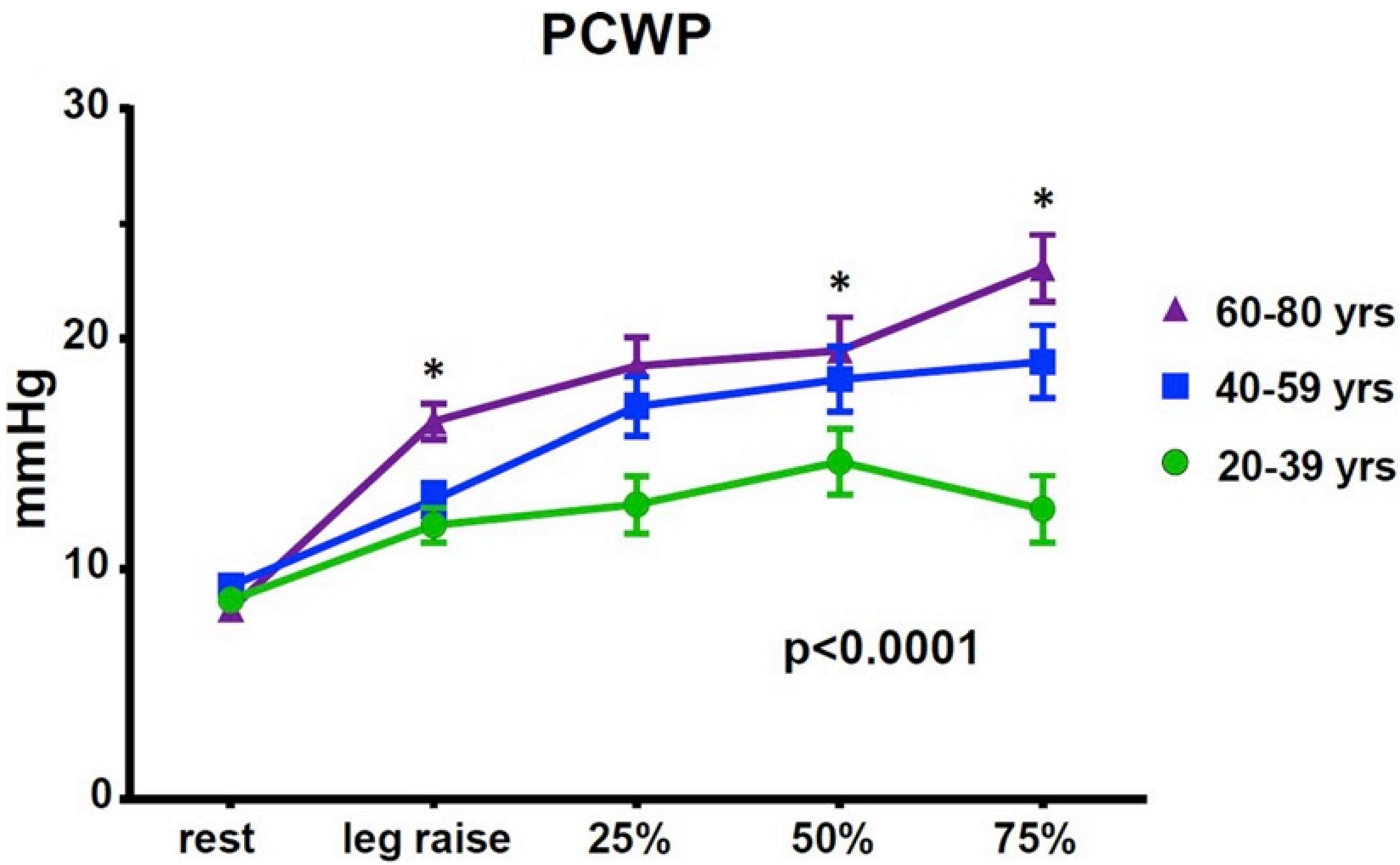
Effect of age on hemodynamic changes during progressive exercise



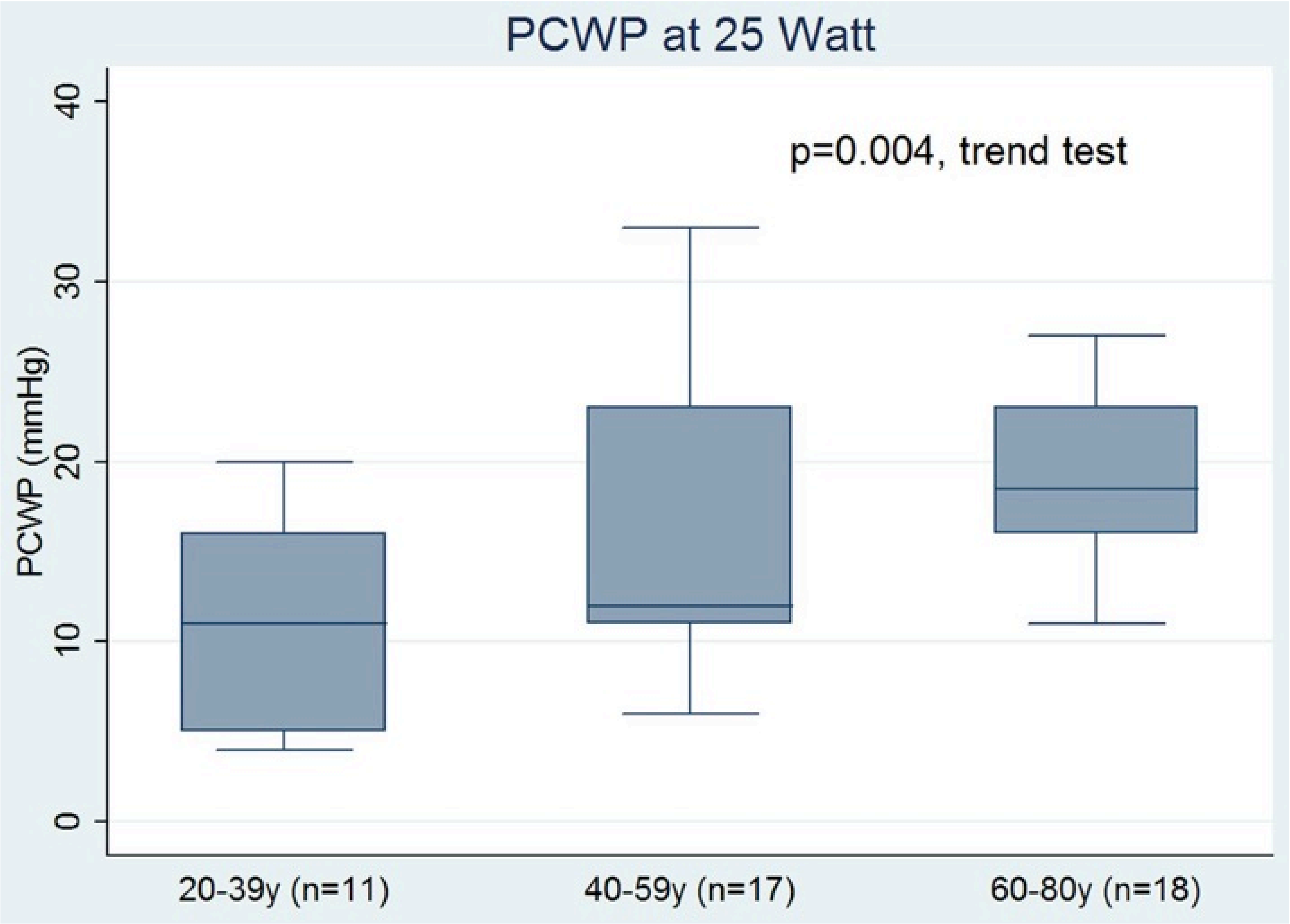
Emil Wolsk et al. JCHF 2017;5:337-346

JACC Heart Failure

Effect of age on hemodynamic changes during progressive exercise



Emil Wolsk et al. JCHF 2017;5:337-346



Emil Wolsk et al. JCHF 2017;5:337-346

Cardiopulmonary exercise testing

Postgrad Med J. 2007 Nov; 83(985): 675–682.

Peak exercise capacity

- “the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood”

CPE in dyspneic pt with Normal EF

YNV Reddy, BA Borlaug, et al. JACC HF 2018; 6:665-75

- 206 patients with dyspnea and normal LV EF
  - Noncardiac dyspnea (NCD) = 72
  - HFpEF = 134
- Diagnostic evaluation
  - Transthoracic echocardiogram (TTE)
  - Upright bicycle cardiopulmonary exercise
  - Supine bicycle cardiopulmonary exercise in the cardiac cath lab with hemodynamic monitoring !

Results – CPE testing

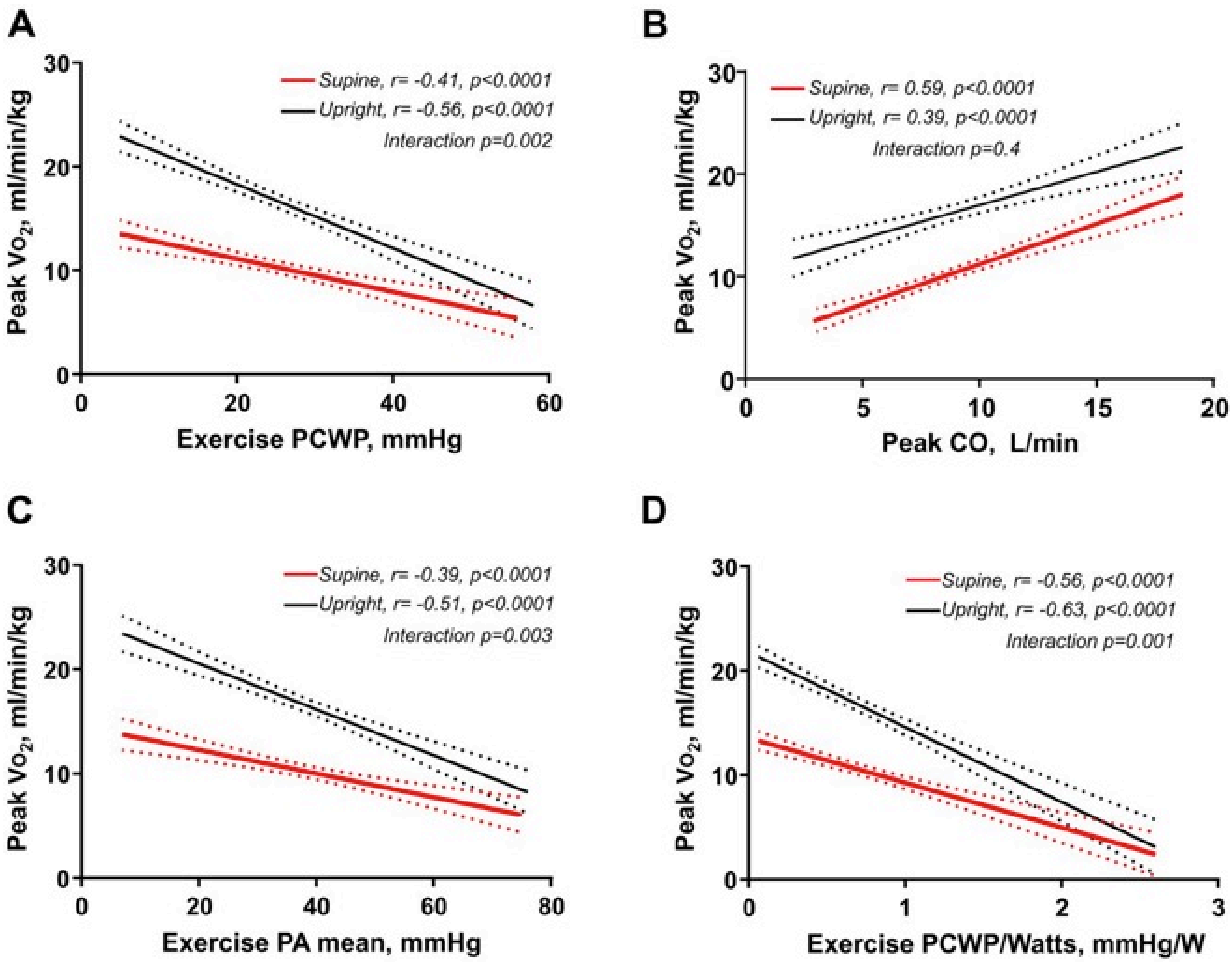
- HFpEF
  - – Lower peak VO_2 both supine and upright
  - – Very low peak $VO_2 < 14$ ml/kg/min clearly discriminated HFpEF from NCD
    - Specificity 91% Sensitivity 50%
  - – Preserved $VO_2 > 20$ ml/kg/min reliably excluded HFpEF with excellent specificity.

Results – CPE testing

- HFpEF
- Intermediate outcomes: Peak VO_2
  greater than 14, but < 20 ml/kg/min

Non-invasive testing not adequate to discriminate HFpEF from non cardiac dyspnea.

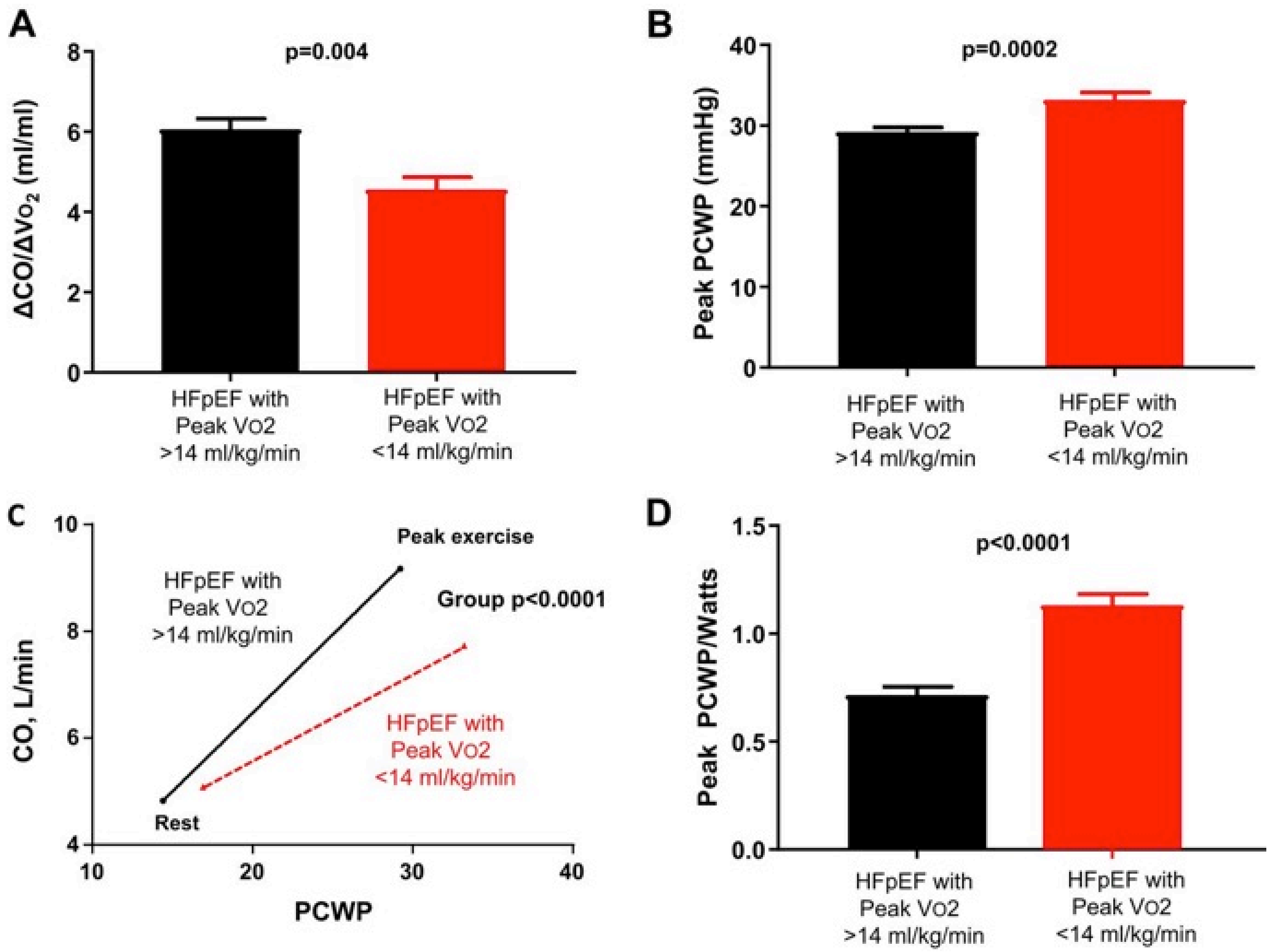
Relationship between hemodynamics and exercise capacity



Yogesh N.V. Reddy et al. JCHF 2018;6:665-675

JACC Heart Failure

Characteristics of HFpEF with severely depressed aerobic capacity



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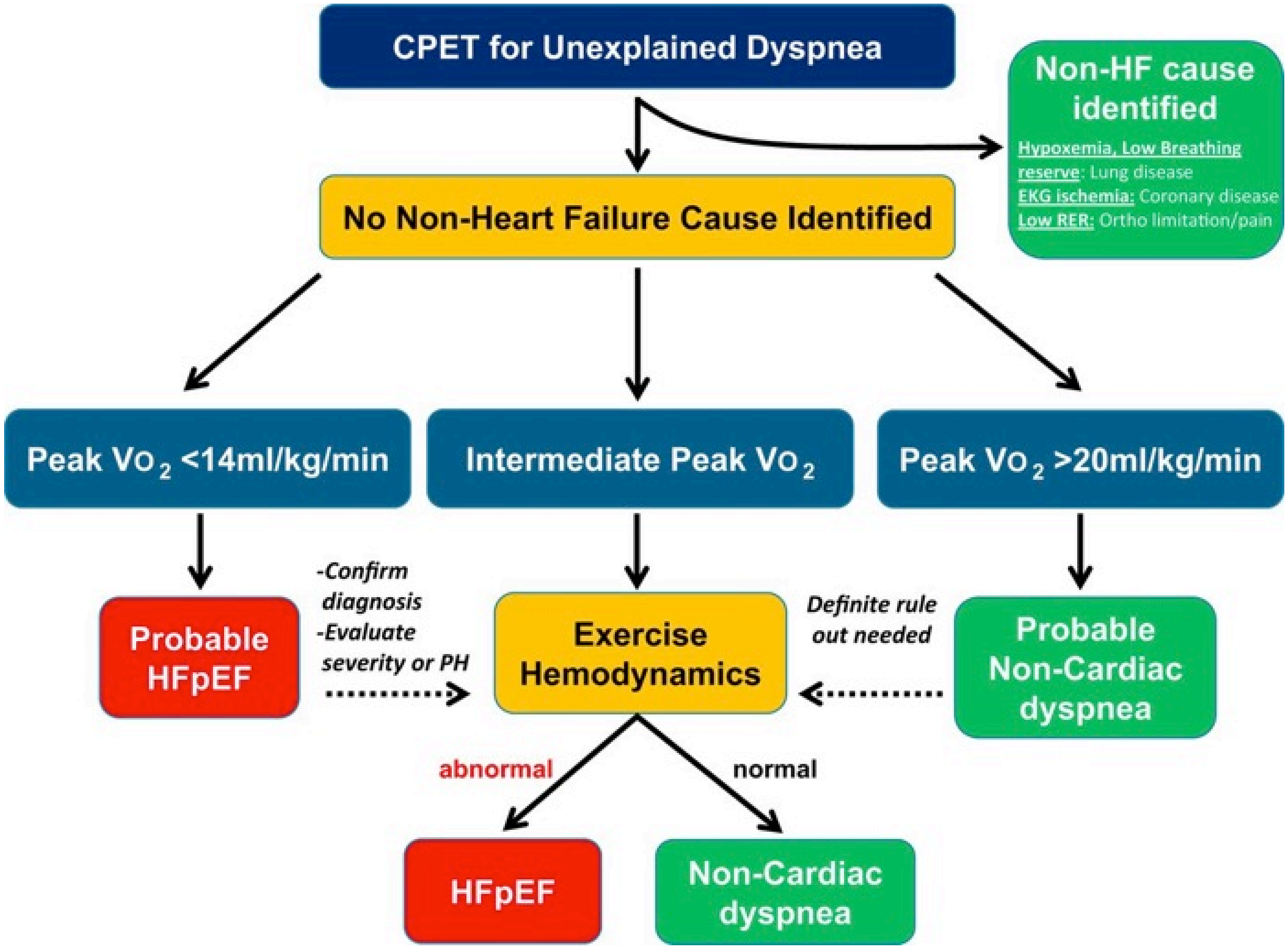
JACC Heart Failure



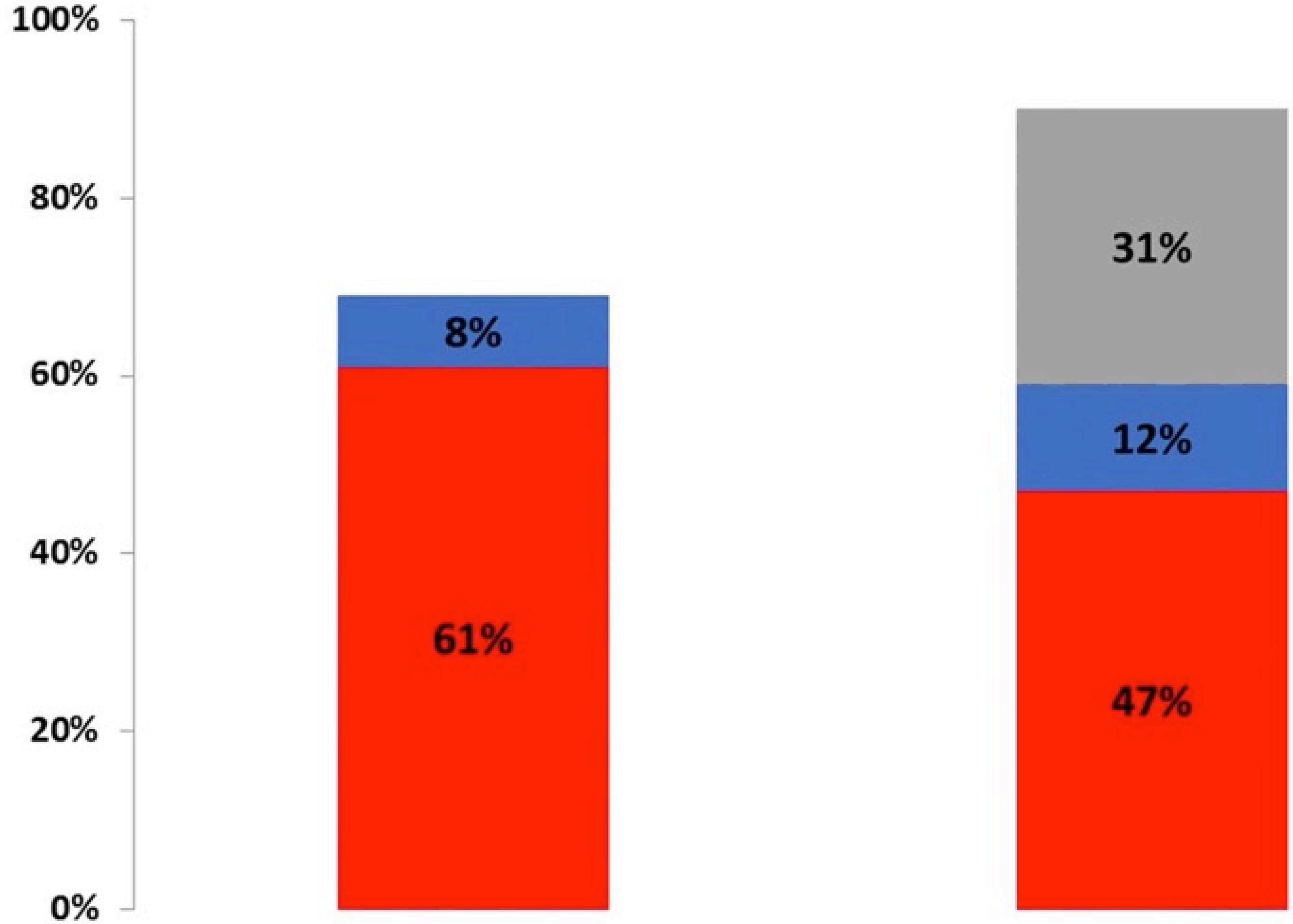
Yogesh N.V. Reddy et al. JCHF 2018;6:665-675

JACC Heart Failure

Second Study

- Compare exercise hemodynamics of patients with HFpEF to normal controls.
- HFpEF Patients were enrolled from two trials,
  - REDUCE-LAP HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure)
  - HemReX (Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans)

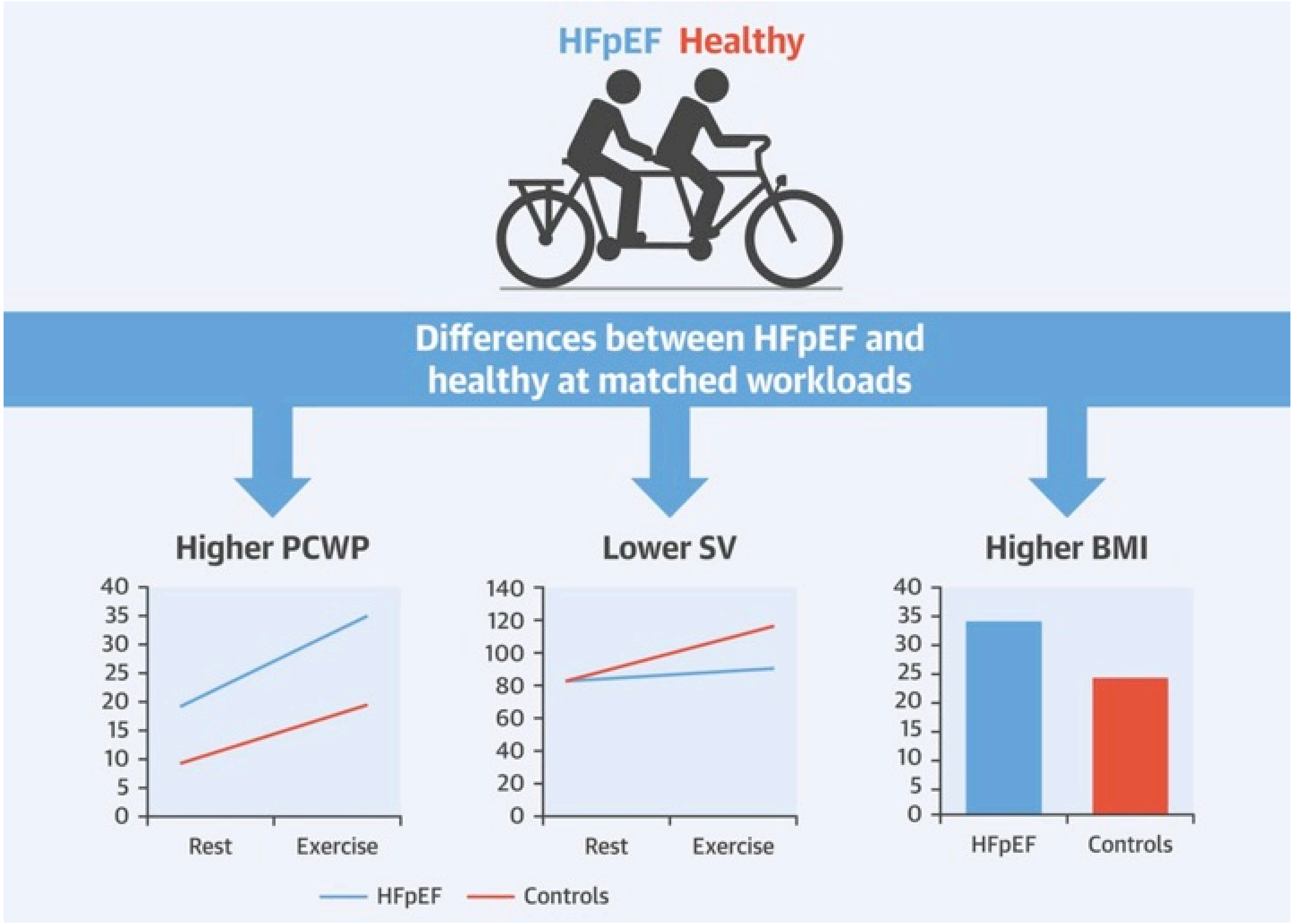
Contribution of independent variables associated with HFpEF during exercise
Red = PCWP, Blue = Stroke volume, Gray = BMI



Emil Wolsk et al. JCHF 2019;j.jchf.2019.01.006

- **Workload-Corrected Hemodynamic Variables Associated With HFpEF During Peak Exercise**

- When the model was adjusted for BMI and age, workload-corrected PCWP was still the largest contributor to the HFpEF phenotype: PCWP/workload (64%), BMI (21%), age (10%).

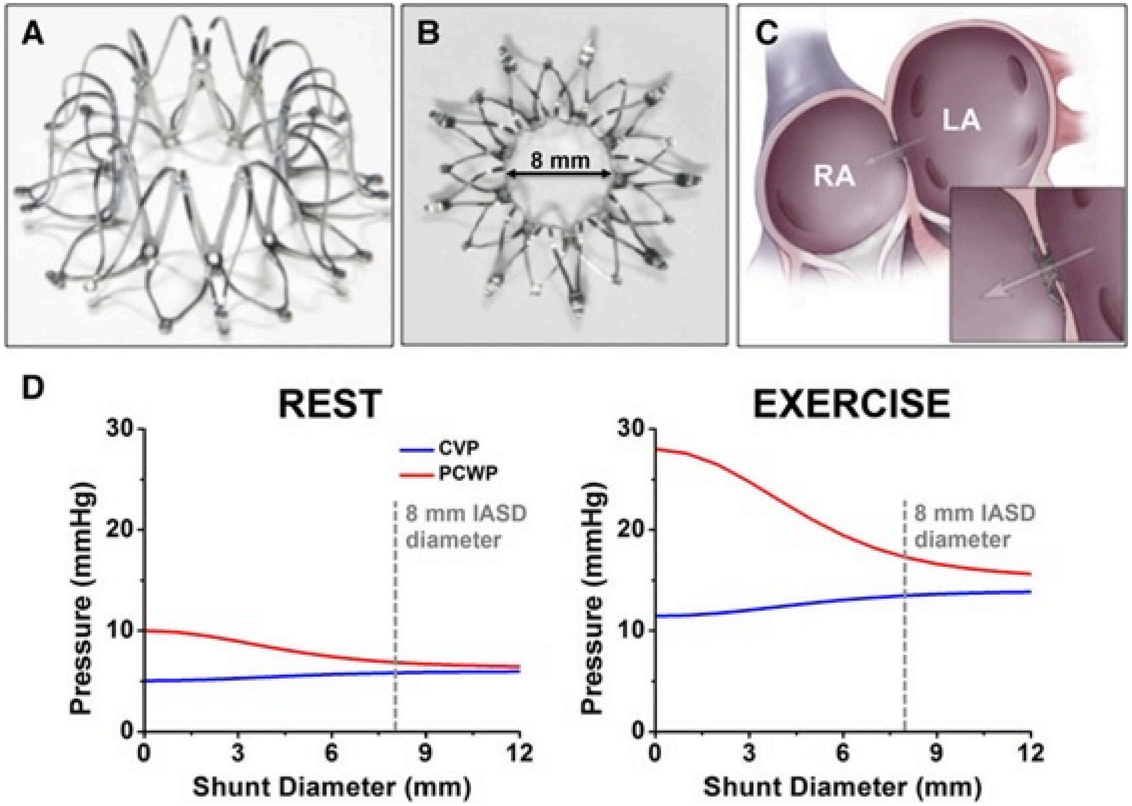


Emil Wolsk et al. JCHF 2019;j.jchf.2019.01.006

New treatment based on increased LA pressure during exercise

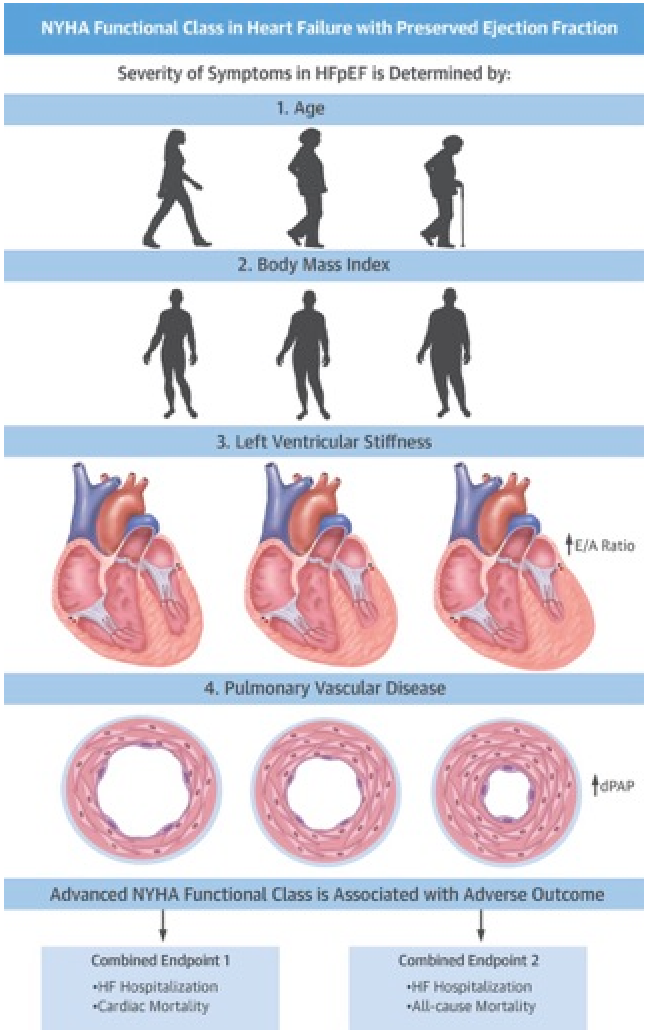
- Novel therapy for patients with heart failure (HF) with preserved ejection fraction (EF >50%) or midrange EF (40% to 50%) utilizing an implanted device to create an atrial shunt (inter- atrial shunt device [IASD]).
- The objective of the IASD is to dynamically (at rest and during exercise) decompress left atrial pressure overload associated with HF with preserved EF and HF with midrange EF.
- At 1 month after randomization, the IASD treatment group had a significantly greater reduction in pulmonary capillary wedge pressure during exercise compared with the control group.
- Circulation. 2018;137:364–375.

Device to reduce LAP pressure. Circulation. 2018;137:364–375.
Reduce LAP-HF I Trial. Feldman, et al.



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]), Volume: 137, Issue: 4, Pages: 364-375, DOI: (10.1161/CIRCULATIONAHA.117.032094)

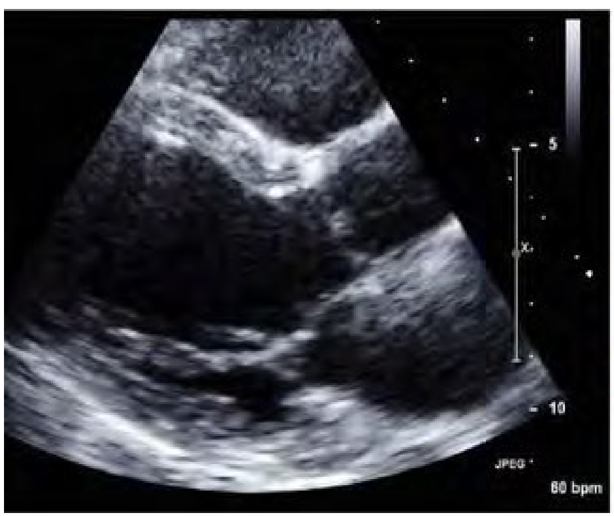
NYHA Functional Class in HFpEF

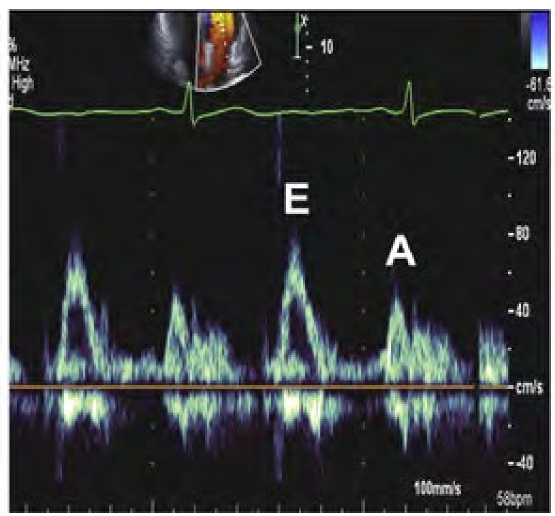


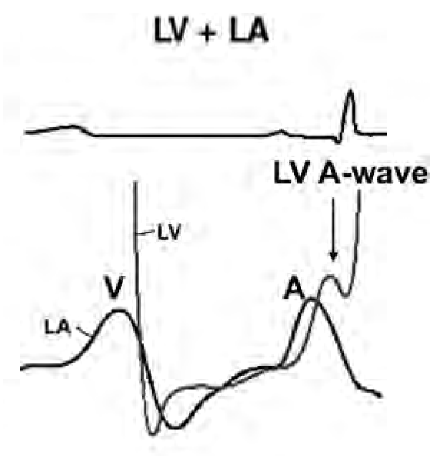
Daniel Dalos et al. JACC 2016;68:189-199

Let’s brush up on the evaluation of diastolic function

Normal LV filling velocity and pressure

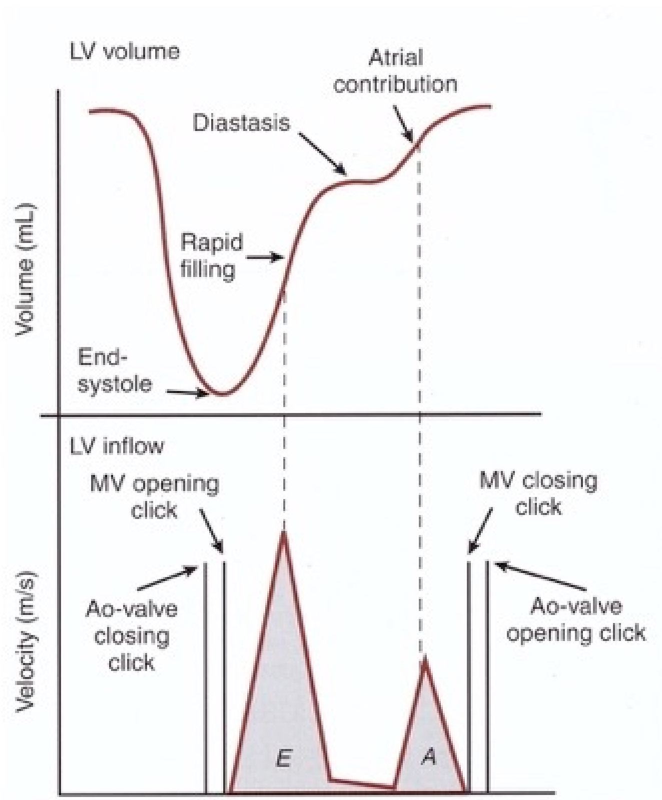




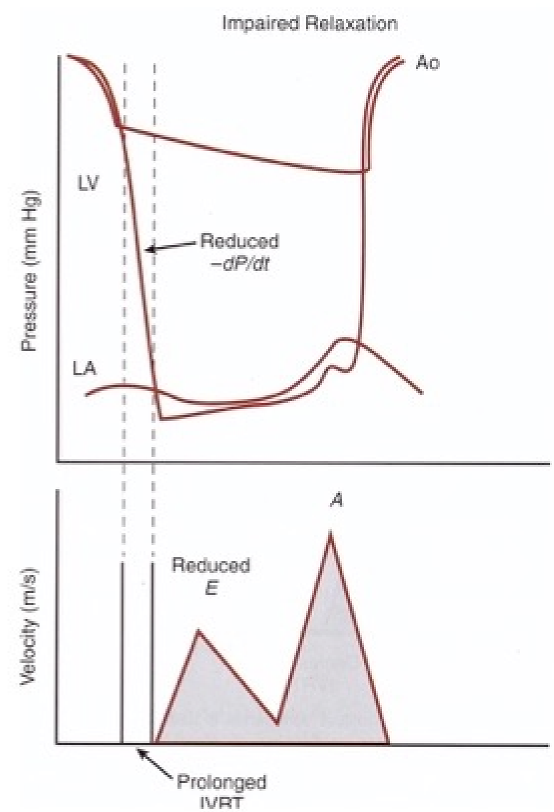


Mitral inflow patterns in diastole

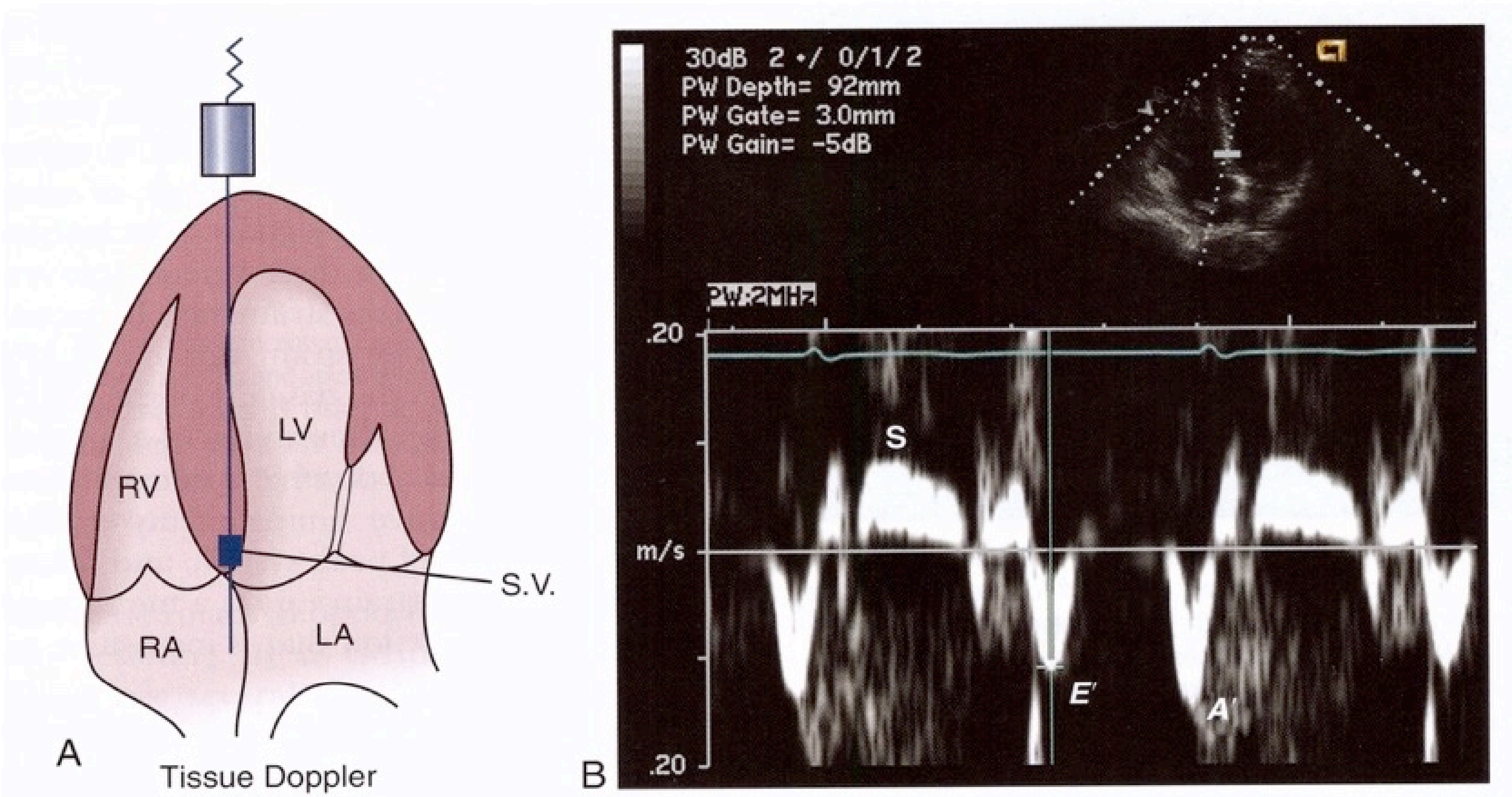
Normal



Grade I Dysfunction



LV relaxation: tissue Doppler

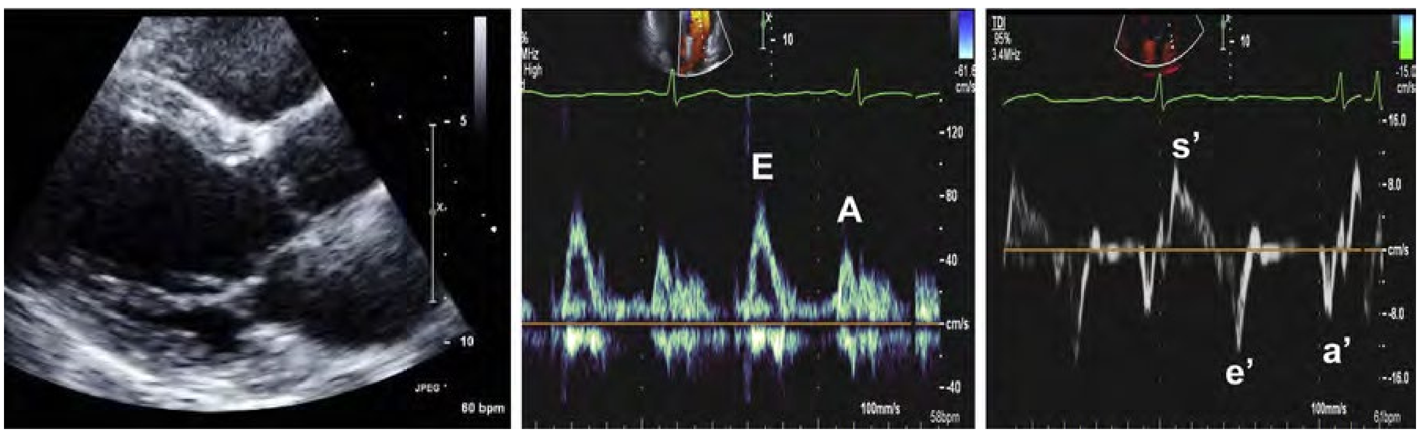


Diastolic parameters

- Tissue Doppler records the actual movement of the LV in early diastole, and reflects *LV relaxation*

- The mitral flow characteristics reflect not only the flow velocity, but the *left ventricular filling pressure* when that flow occurs.

Normal LV filling



ASE Guidelines, April, 2016. (J Am Soc Echocardiogr 2016;29:277-314.)

Diastolic parameters

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- The best estimate of the *diastolic function* takes into account the mitral flow velocity (E wave) and the LV relaxation (tissue Doppler), the *tissue Doppler index (E/e')*

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Grades of Diastolic Dysfunction

- Grade 1 Delayed early relaxation with normal filling pressure
- Grade 2 Delayed relaxation and increased LV end diastolic pressure
- Grade 3 Progressive reduction in LV compliance and elevation of LV filling pressures

Diagnosis of HFpEF

- In some studies, up to 80% of patients enrolled as symptomatic HFpEF had normal or grade I LV Diastolic dysfunction.
- The diagnosis of HFpEF must include parameters that account for the hemodynamic and clinical abnormalities described earlier, including
  - Increased LA pressure
  - Increased PA pressure

HFpEF : Diagnosis

- European Society of Cardiology, 2013

- 3 basic aspects

  – Signs or symptoms of heart failure
  – Normal or nearly normal LV EF (~50%)
  – Evidence of diastolic dysfunction

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- European Society of Cardiology

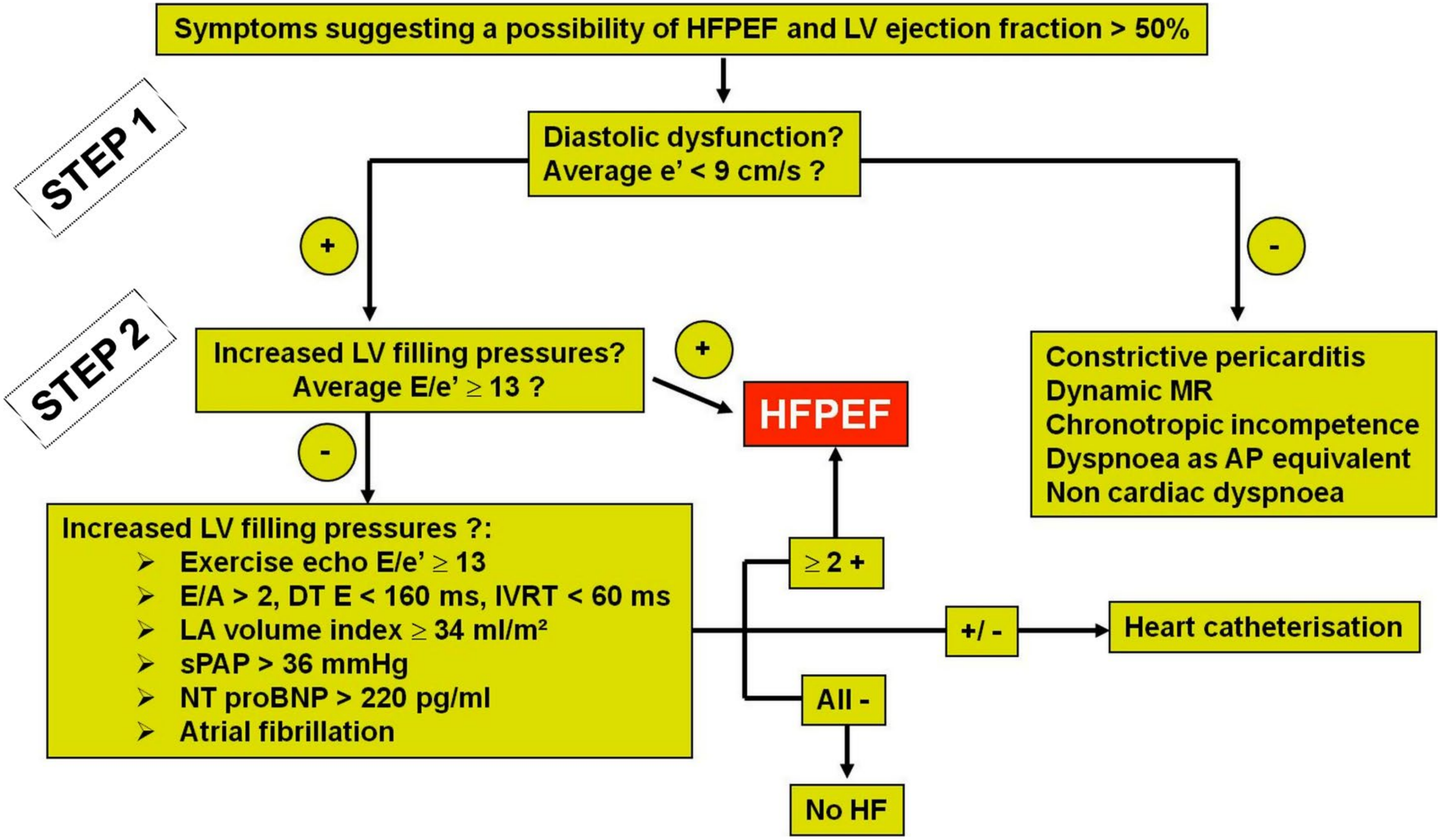
- 3 basic aspects

1. Signs or symptoms of heart failure
2. Normal or nearly normal LV EF (~50%)
3. Evidence of diastolic dysfunction

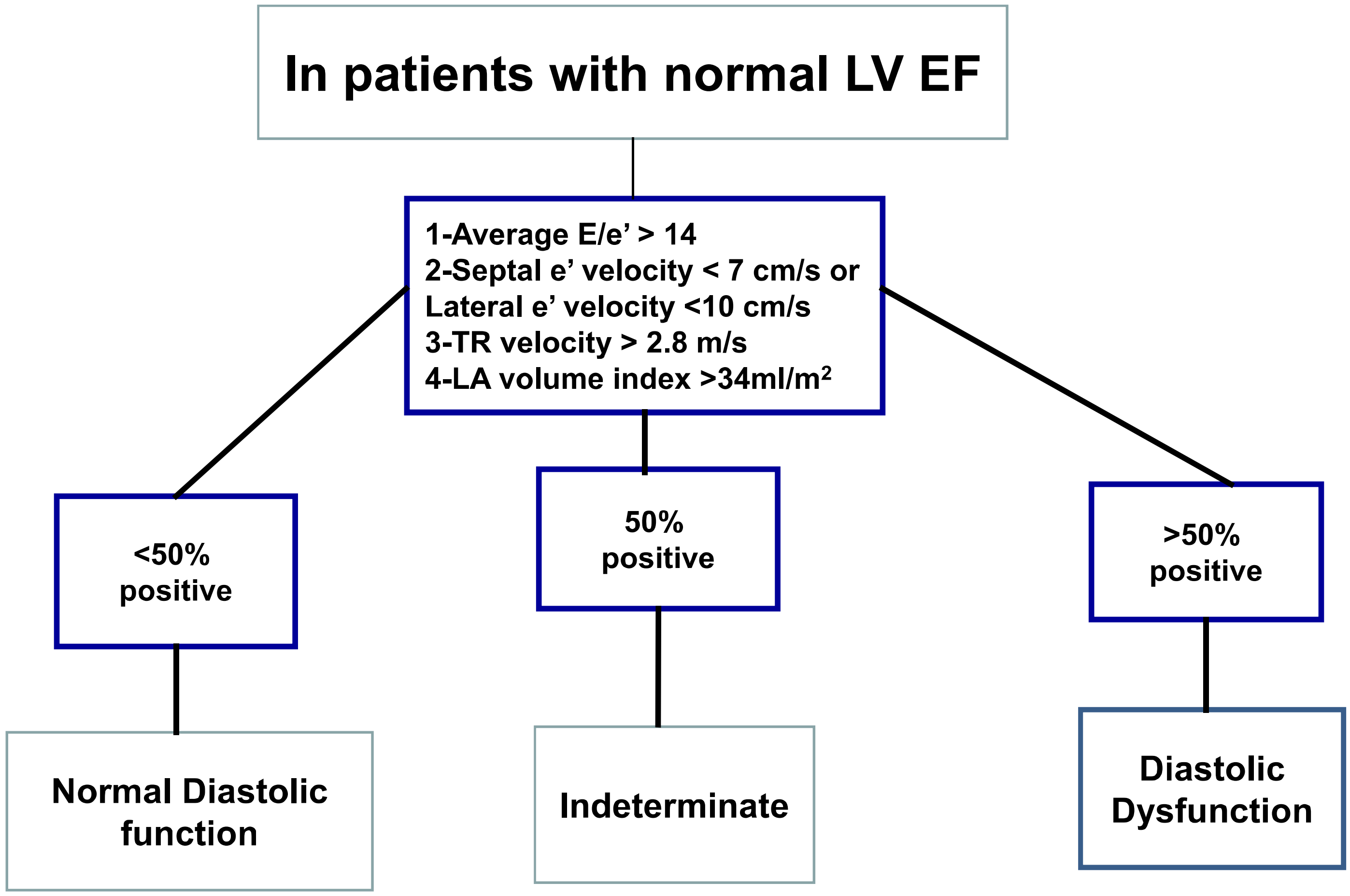
   Evidence of abnormal LV relaxation, abnormal filling, diastolic stiffness

    - Cardiac cath – elevated LVEDP > 16 mm Hg, mean PCWP > 12 mm Hg
    - NT- pro BNP > 220
    - Tissue Doppler Index E/e’ > 15

Stepwise approach to the diagnosis of heart failure with preserved EF in elderly ambulatory patients with equivocal symptoms. Penicka M, *Heart* 2014;100: 68-76



HF preserved EF, *Am Soc Echo*, 2016



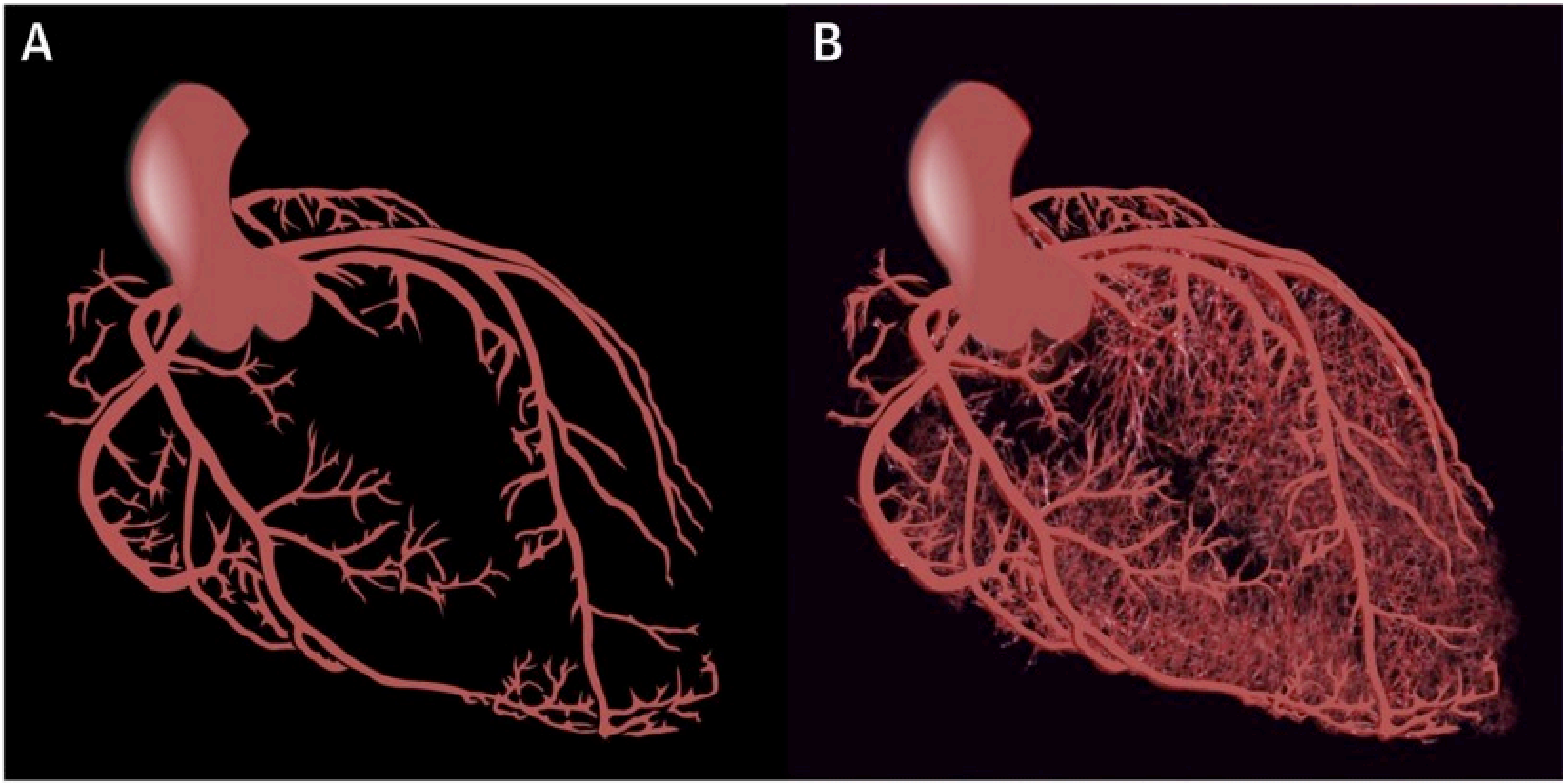
Pathophysiology of HFpEF

- A new paradigm – Paulus & Tschope – comorbidities such as obesity, diabetes and COPD lead to a systemic pro-inflammatory state that induces coronary microvascular endothelial inflammation.
- This inflammation and resultant oxidative stress cause stiff myocytes and interstitial fibrosis.
- Although hypertension is commonly felt to cause HFpEF by afterload excess, this model changes the emphasis to inflammation

Aging: microvascular circulation

- Coronary microvascular disease (CMD)
  - refers to disorders affecting the structure and function of the coronary microcirculation
  - Is prevalent in patients across a broad spectrum of CV risk factors
  - Is associated with increased risk of adverse events.
- Most patients with CMD have macrovessel atherosclerosis

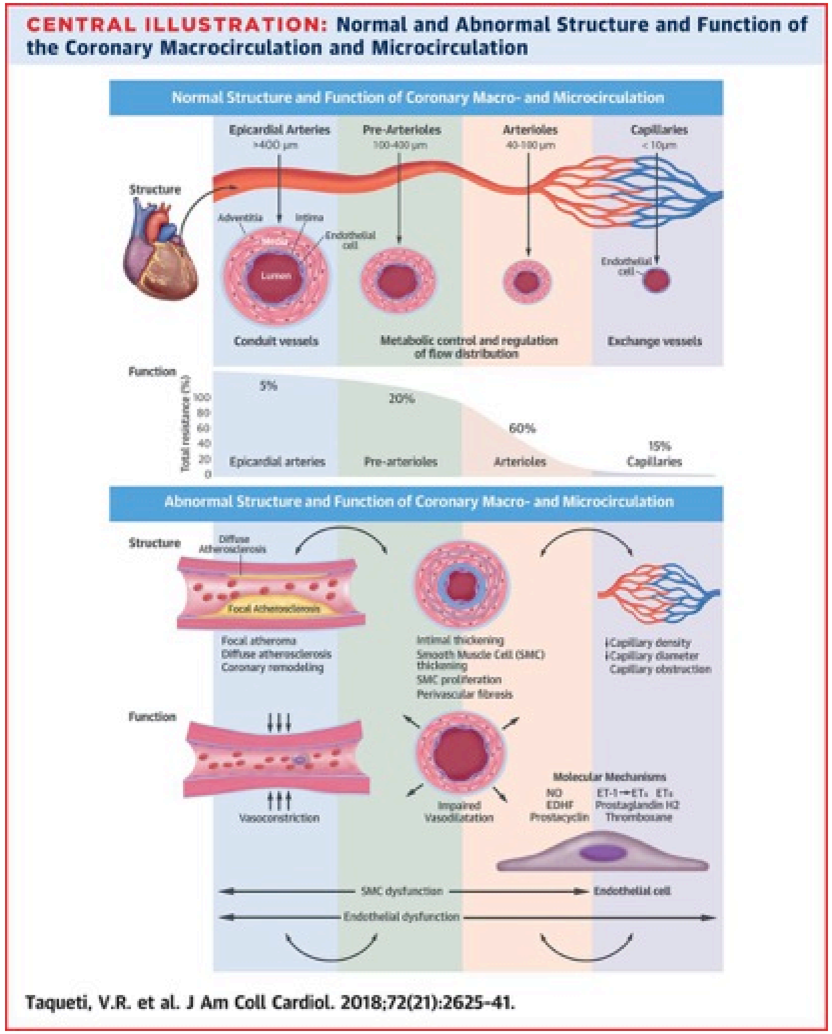
Schematic of the Epicardial Coronary Arteries and the Full Coronary Circulation



Viviany R. Taqueti, and Marcelo F. Di Carli JACC 2018;72:2625-2641

JACC

Normal & Abnormal Structure and function of the coronary macro- and microcirculation



Viviany R. Taqueti, and Marcelo F. Di Carli JACC 2018;72:2625-2641

JACC Journals

From: A Novel Paradigm for Heart Failure With Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation

J Am Coll Cardiol. 2013;62(4):263-271. doi:10.1016/j.jacc.2013.02.092

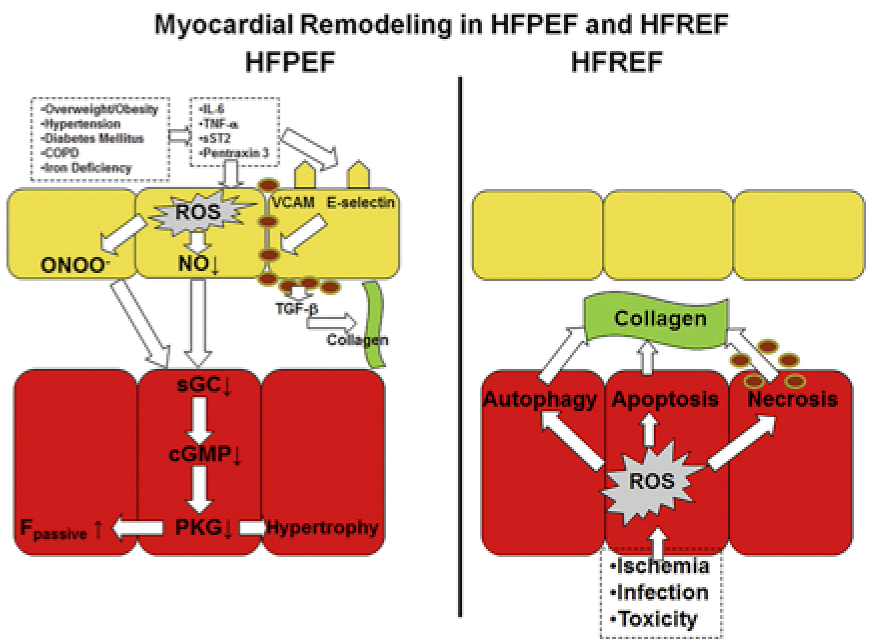


Figure Legend:

Myocardial Dysfunction and Remodeling in HFPEF and HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial inflammation and oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes because of ischemia, infection, or toxic agents. ROS trigger cardiomyocyte autophagy, apoptosis, or necrosis. The latter attracts leukocytes. Dead cardiomyocytes are replaced by fibrous tissue. cGMP = cyclic guanosine monophosphate; HFREF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.

Pathophysiology of HFpEF

- **Vascular abnormalities**
  - Arterial stiffness increases with aging and is amplified by hypertension, diabetes and renal disease

- This leads to impaired LV reserve function, labile systemic hypertension, diminished coronary flow reserve and increased diastolic filling pressures, leading to breathlessness.

Pathophysiology of HFpEF

- The end systolic stiffness of the LV and the arteries increases with aging, especially in women, who are disproportionately represented in HFpEF
- Women also develop more concentric LVH in the setting of pressure overload compared to men.
- With exercise, the patient with HFpEF has a limited vasodilator response to activity.
- These patients often have marked systemic hypertension with exercise stress.

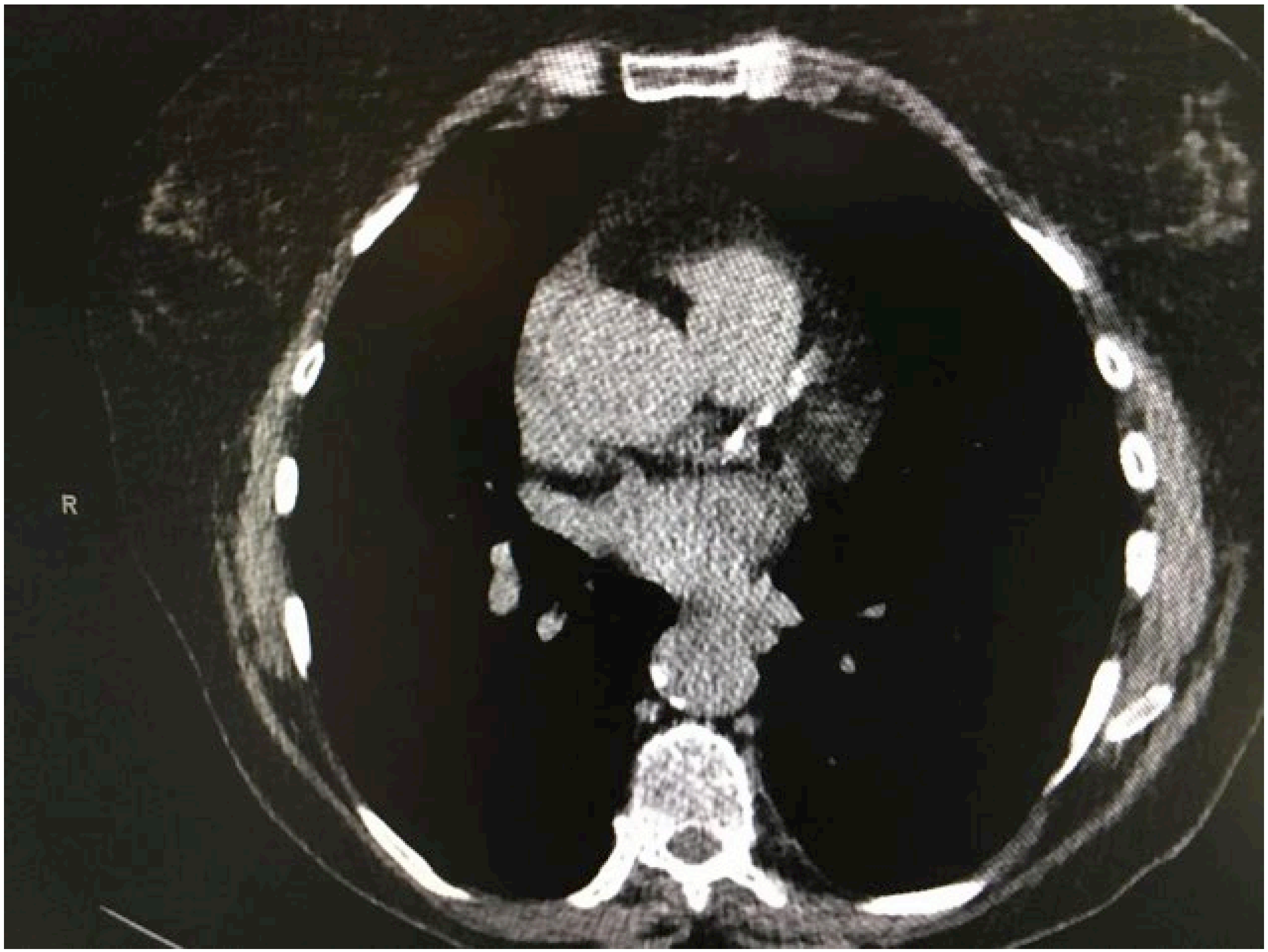
Case Presentation: CVM

- 69 year old female seen for shortness of breath and coronary calcium seen on CT images performed as part of low-dose protocol for cancer screening.
- Quit cigarets 6 years ago. No CAC 5 years ago
- PE: 5’4, 167 lbs BMI 28.7

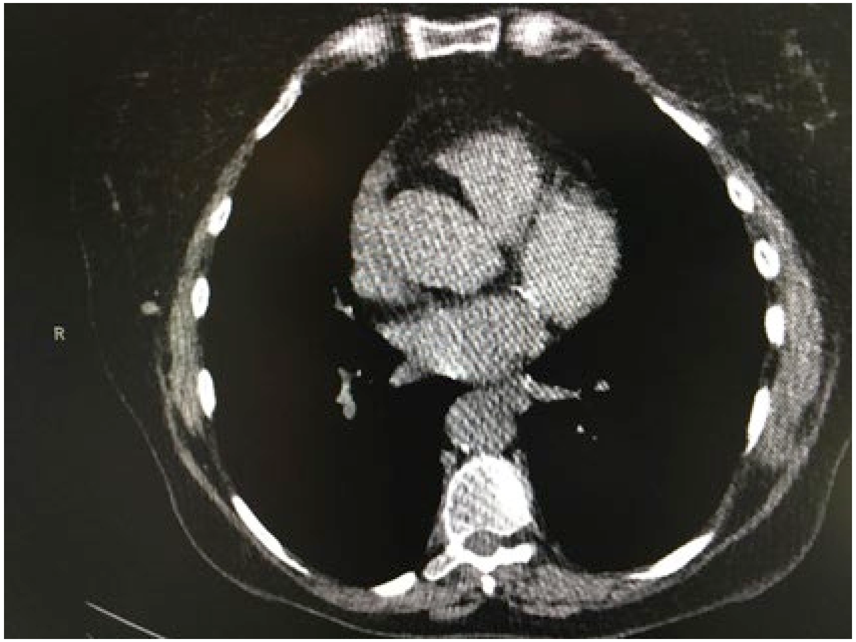
  BP 120/82

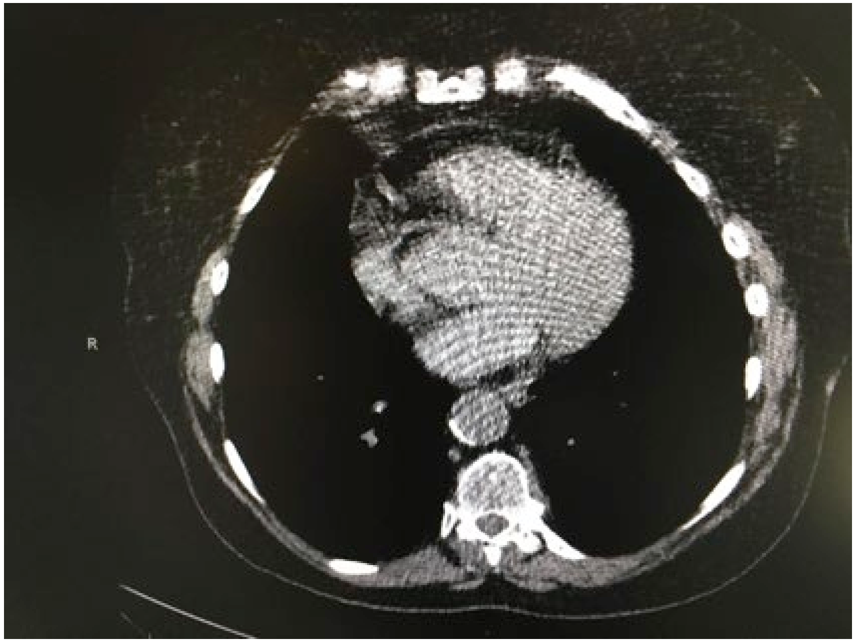
10 year pooled cohort risk: 8%

CVM CT for Cancer Detection
LAD embedded in epicardial fat



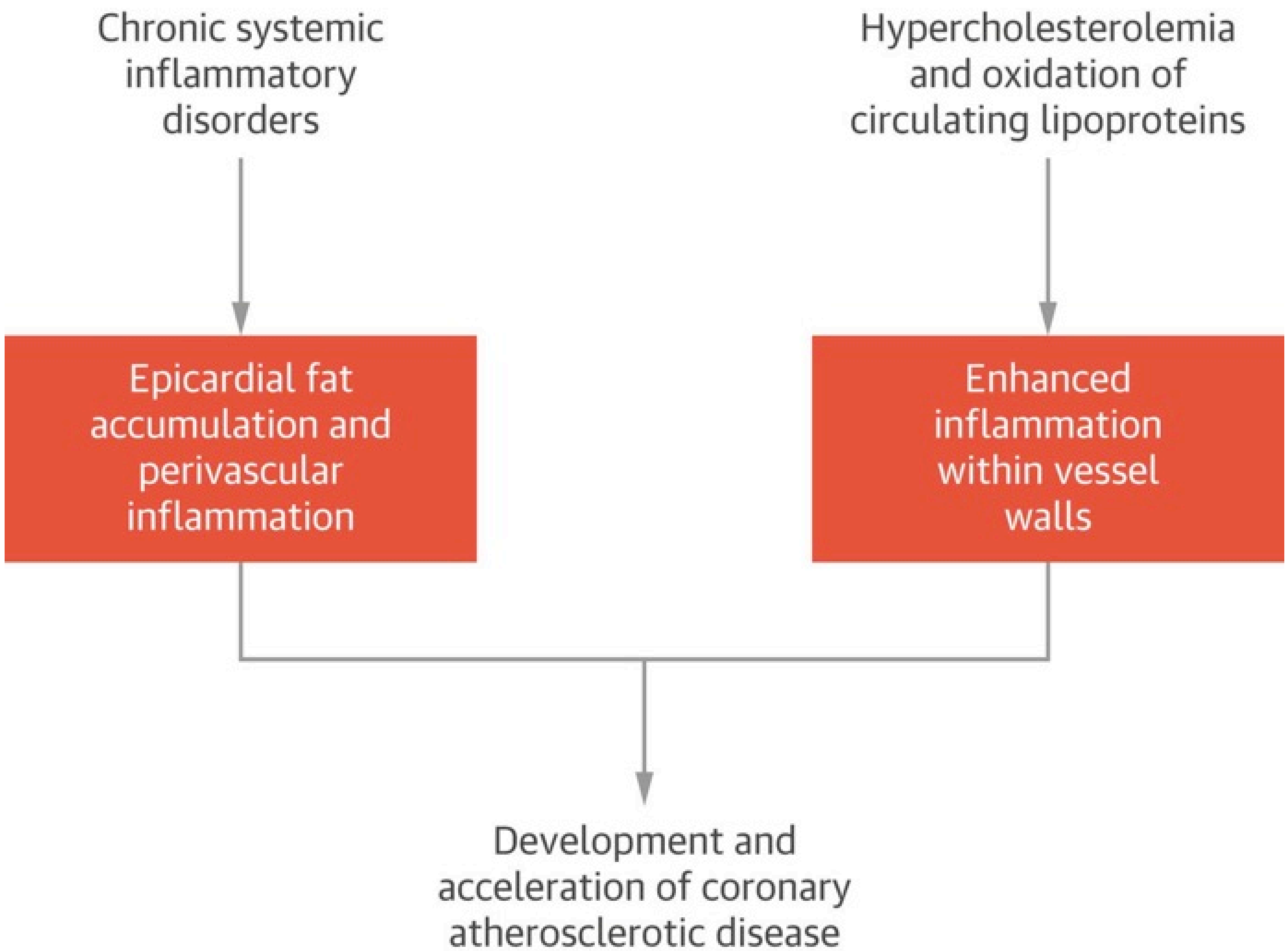
Circumflex (L) and RCA (R) embedded in epicardial fat.





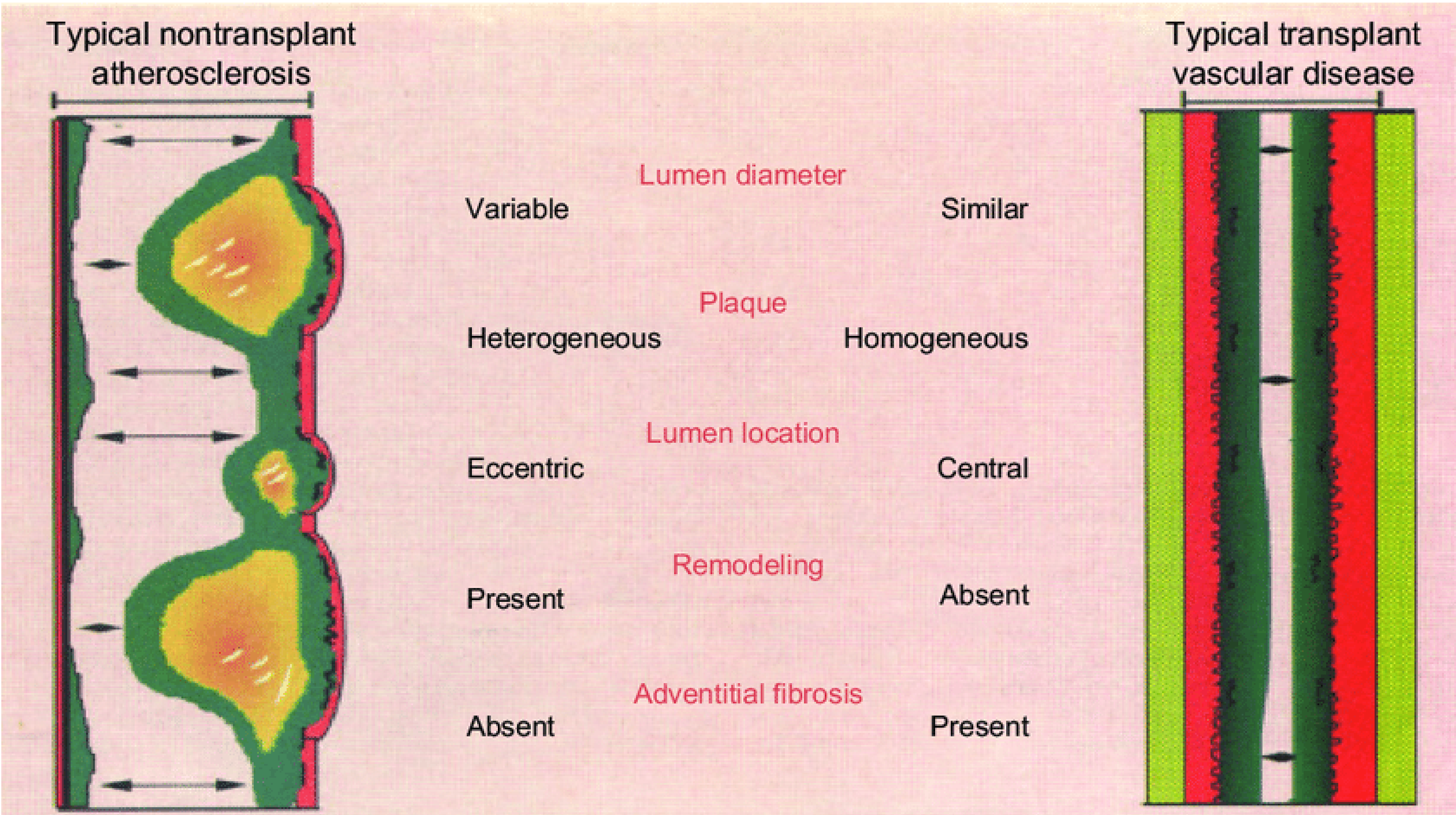
Epicardial fat

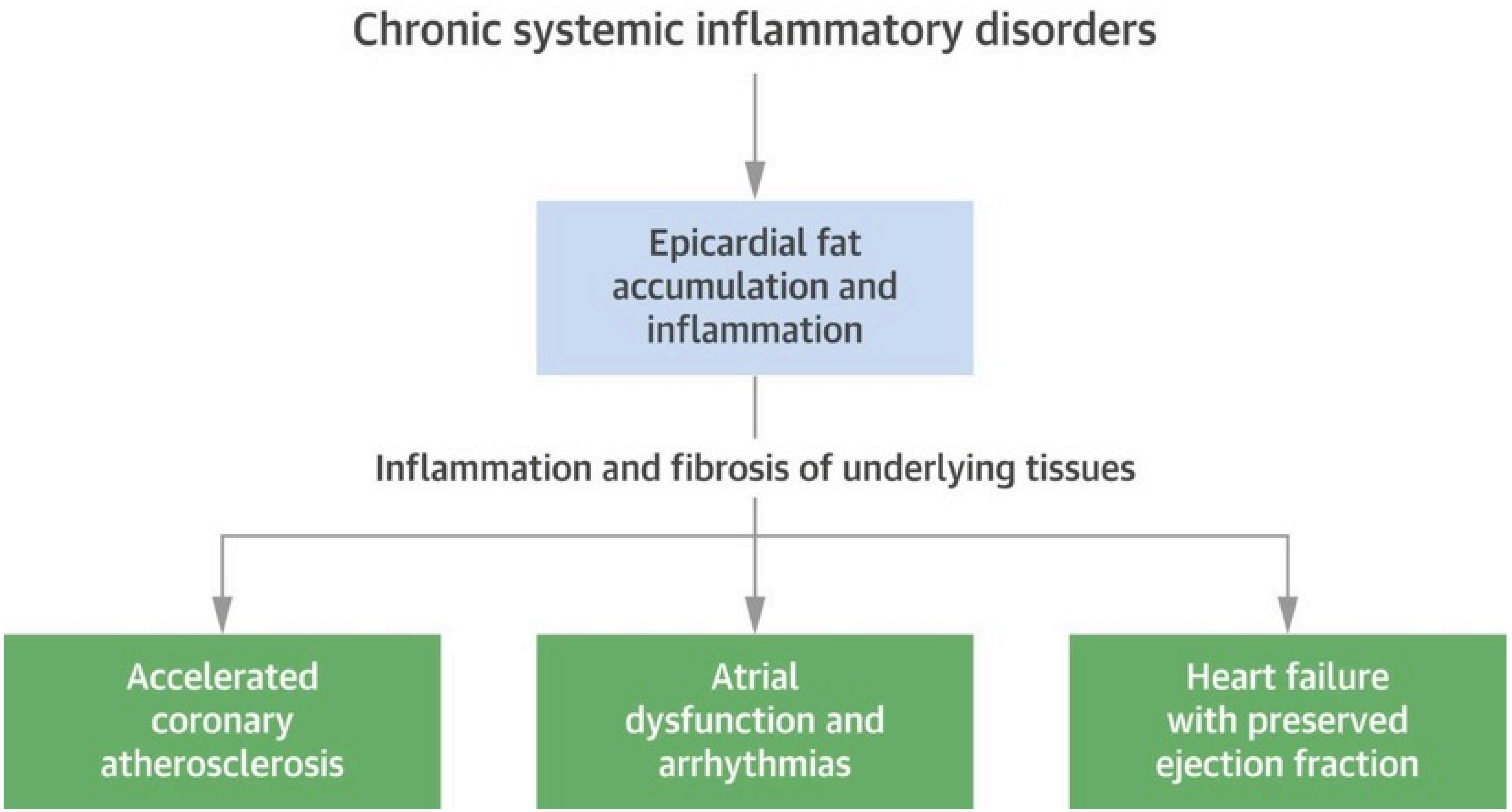
- Milton Packer, MD
- “Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium”
- J Am Coll Cardiol 2018; 71: 2360-72



Milton Packer JACC 2018;71:2360-2372

Comparison of typical CAD with allograft angiopathy (TCAD)





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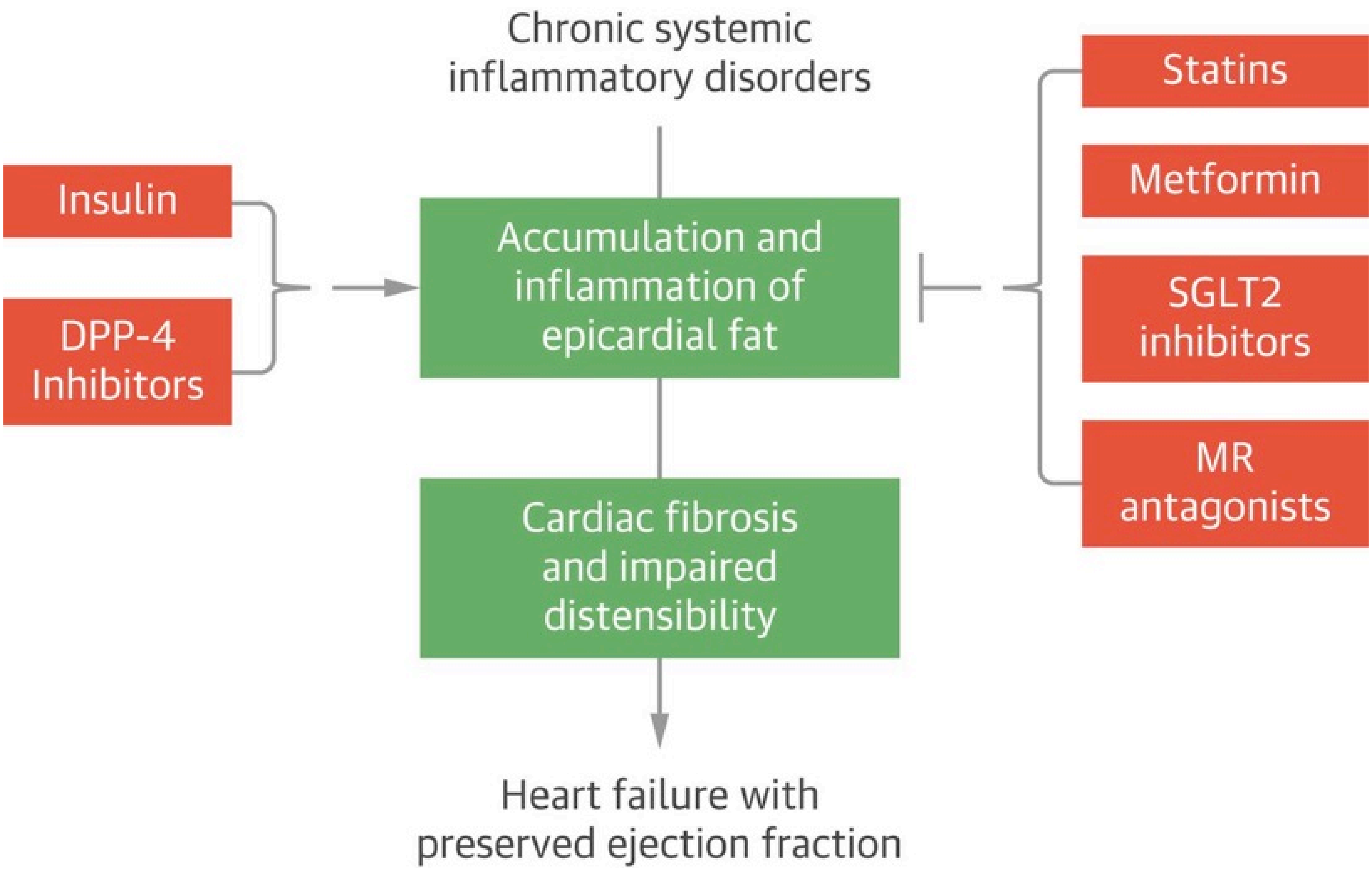
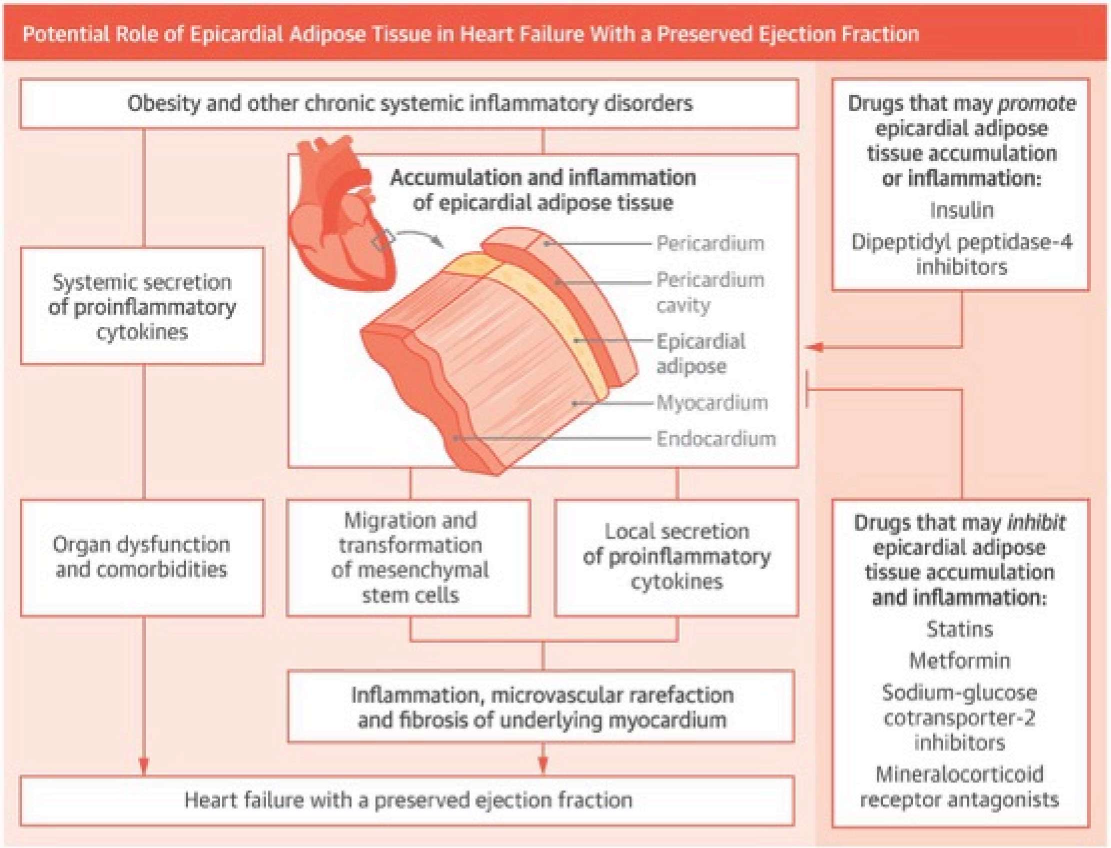


Milton Packer JACC 2018;71:2360-2372

CENTRAL ILLUSTRATION: Potential Role of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction



Packer, M. J Am Coll Cardiol. 2018;71(20):2360-72.

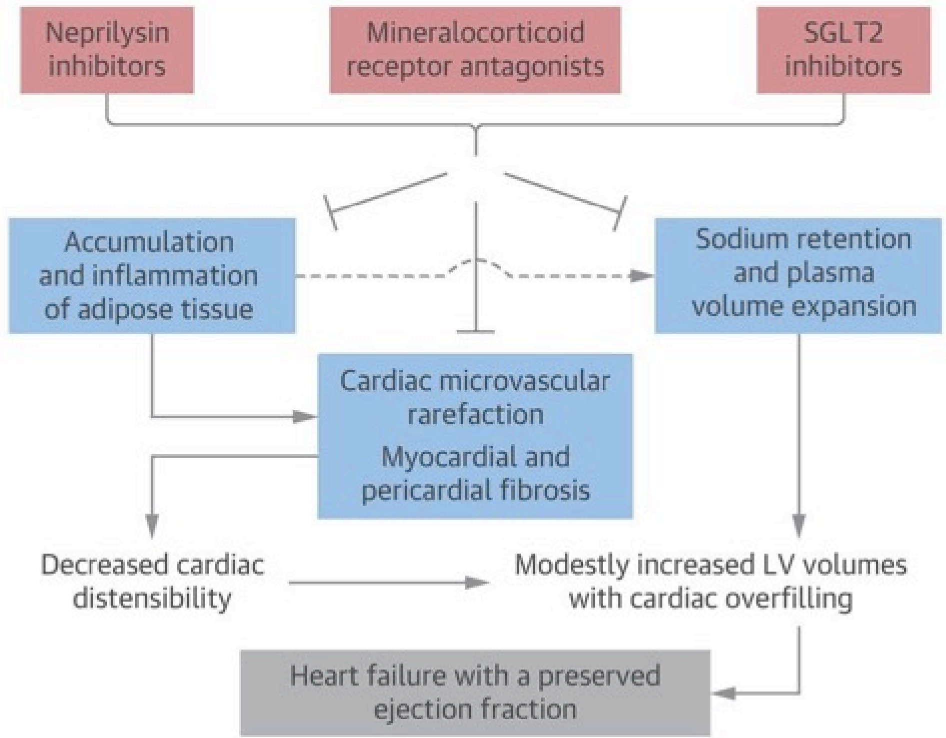
Milton Packer JACC 2018;71:2360-2372

Let’s look more closely at obesity

Mechanisms of obesity-related HFpEF

- Especially important in patients with T2D and HLD, who have marked increase in plasma volume and limited ventricular distensibilty, most likely due to:
  - Cardiac microvascular disease acting in concert with:
  - Myocardial and pericardial fibrosis
- May be related to overproduction of aldosterone and neprilysin

CENTRAL ILLUSTRATION: Potential Therapeutic Approaches to Inhibiting the Pathophysiological Mechanisms That Contribute to Obesity-Related Heart Failure With a Preserved Ejection Fraction



Packer, M. et al. J Am Coll Cardiol HF. 2018;6(8):633-9.

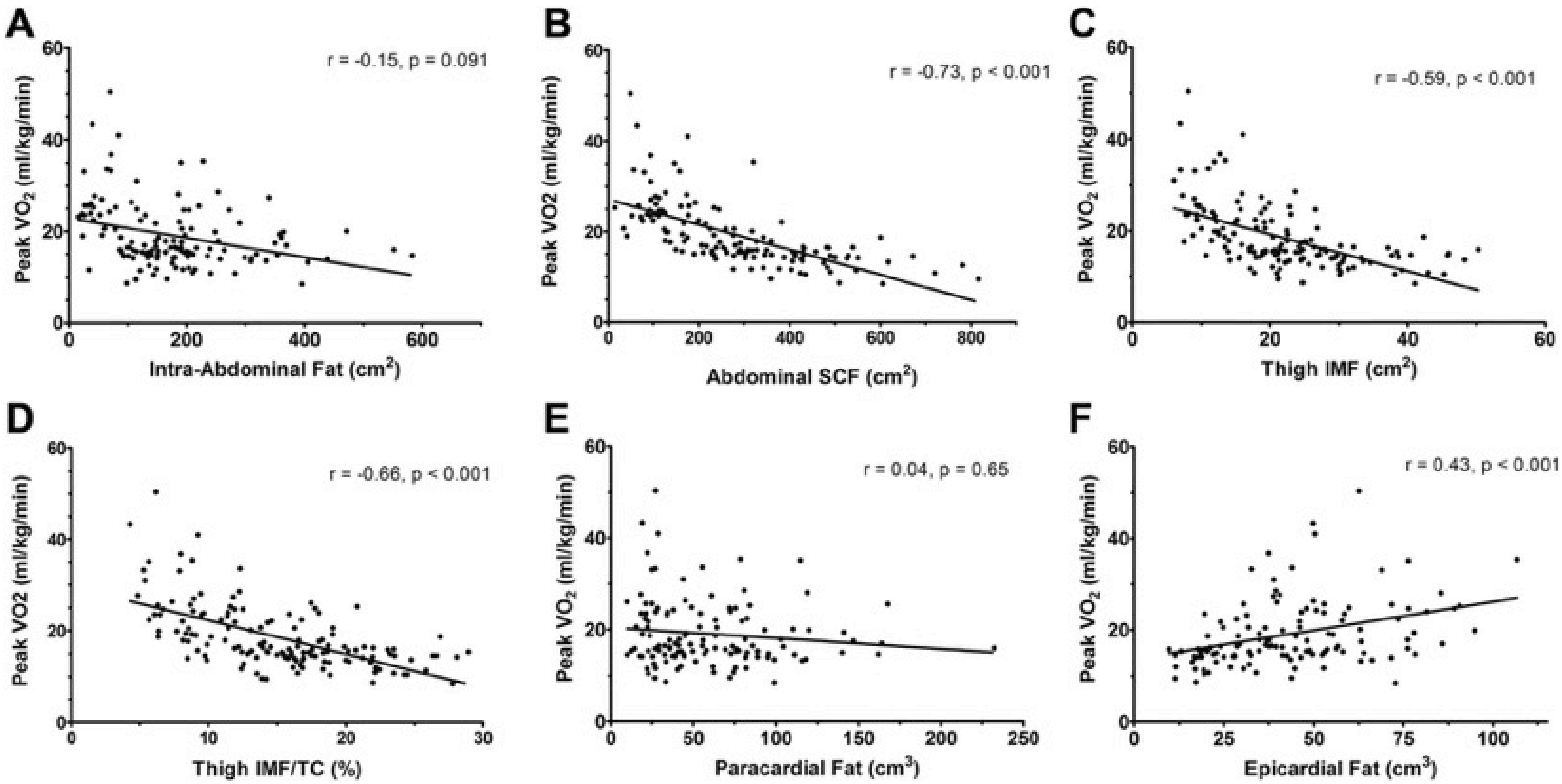
Milton Packer, and Dalane W. Kitzman JCHF 2018;6:633-639

JACC Heart Failure

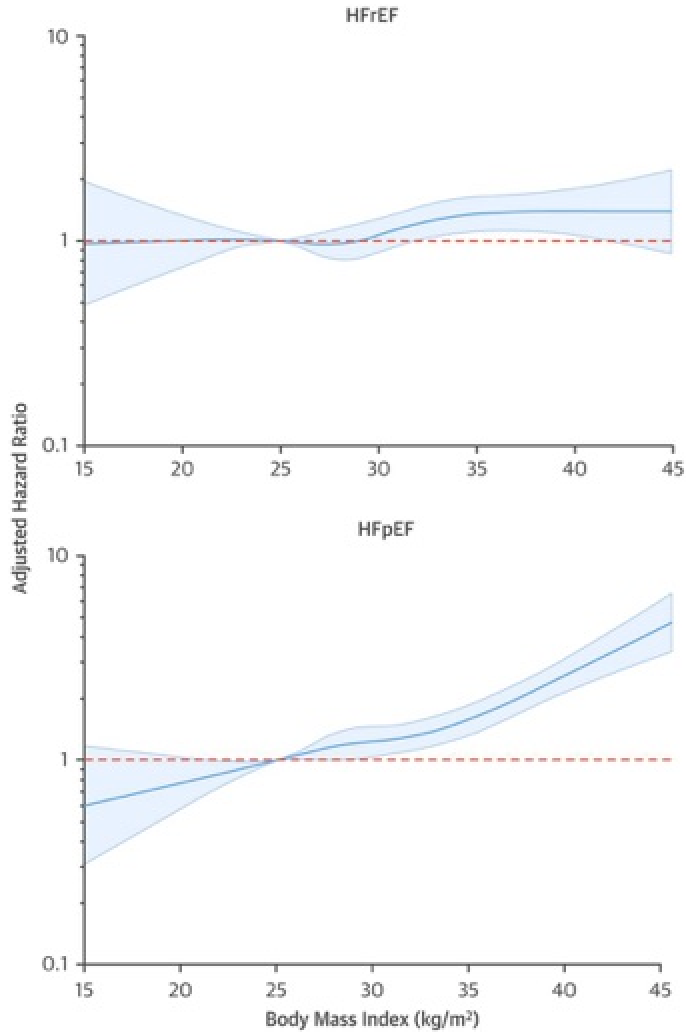
Regional adipose distribution and exercise intolerance

- Regional adipose deposition may have important adverse consequences beyond total body adiposity
- Intra-abdominal fat was strongest independent predictor of impairment in VO_2 and 6 minute walk test
- Epicardial fat was lower in patients with HFpEF than healthy controls
- Haykowsky et al, JACC HF 2018; 6: 640-9

Regional adipose distribution and exercise intolerance

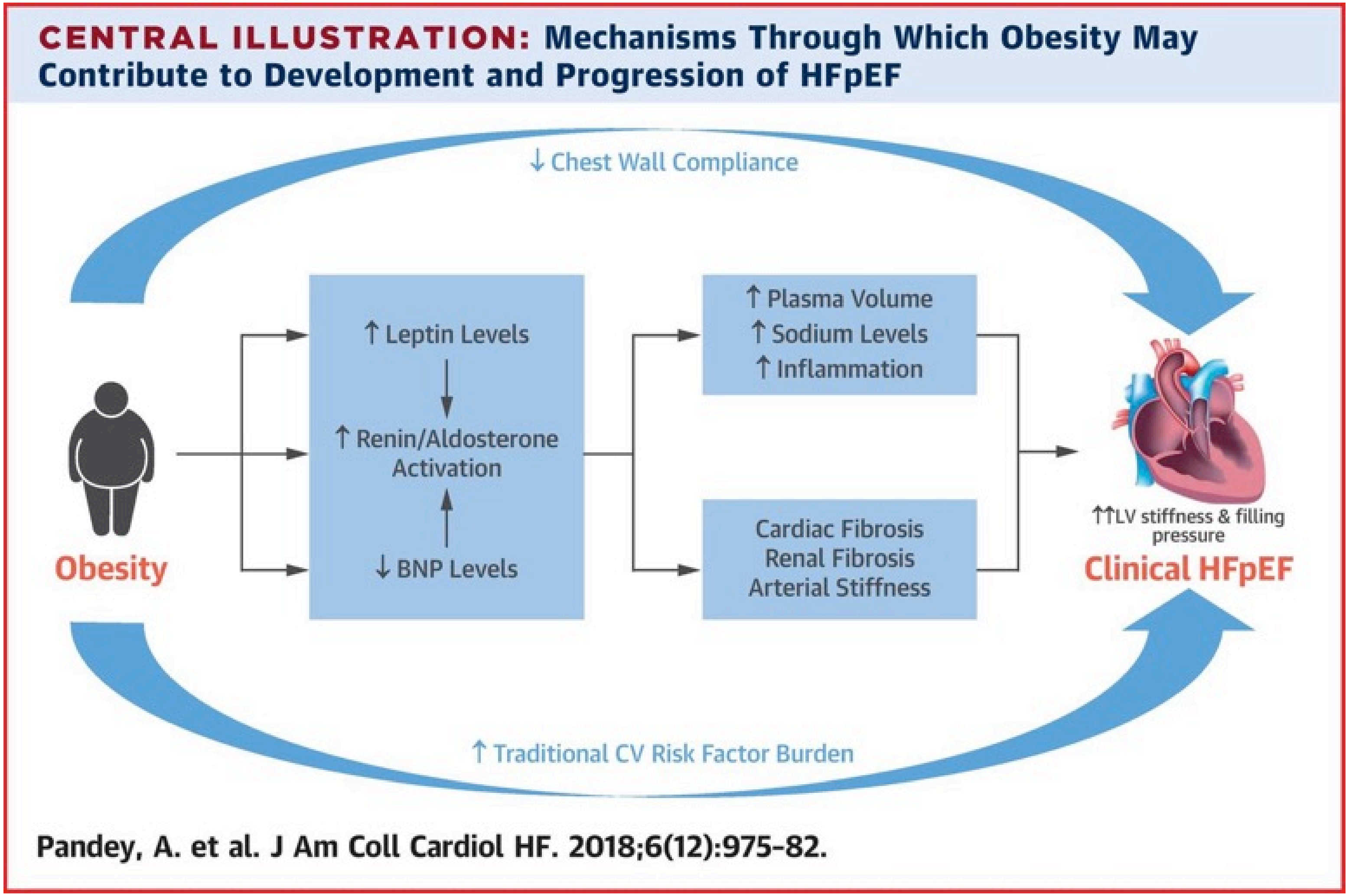


Mark J. Haykowsky et al. JCHF 2018;6:640-649



Ambarish Pandey et al. JCHF 2018;6:975-982

JACC Heart Failure



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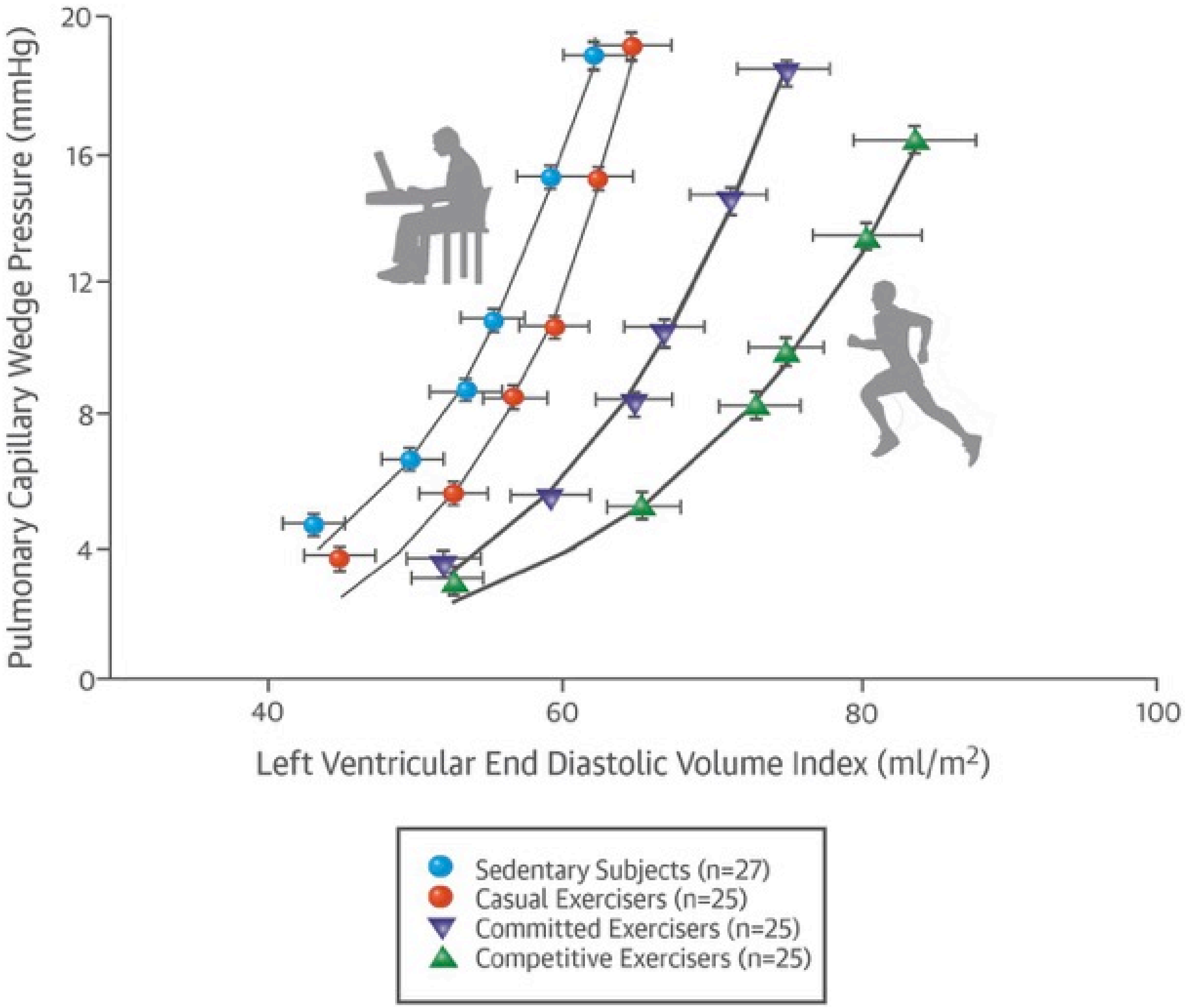

Ambarish Pandey et al. JCHF 2018;6:975-982

JACC Heart Failure

Exercise in HFpEF (From Rogers, Serajian. *JAOA*, 2015)

Trial	Number of subjects (n)	Intensity	Length of training program (wks)	Major Conclusions
Smart[29], 2012	ET = 12 Cnt = 13	60-70% peak VO2	16	↑ Peak exercise capacity ↔ QOL
Alves[24], 2012	ET = 20 Cnt = 22	70-75% HRmax for 3-5 min (5-7 intervals)	24	↑ peak METS ↑ rest LVEF ↓ L atrial pressure ↓ LV stiffness
Haykowski[27], 2012	ET = 22 Cnt = 18	40-70% HHR	16	↑ Peak exercise capacity ↑ peak HR
Edelmann[25], 2011 (EX-DHF)	ET = 44 Cnt = 20	50-70% HRmax, 60-65% PeakVO2, 1Repetition max	12	↑ Peak exercise capacity ↑ 6MWD ↑ self-reported physical function
Kitzman[28], 2010	ET = 24 Cnt = 22	40-70% HRR	16	↑ Peak exercise capacity ↑ 6MWD ↑ physical QOL
Gary[26], 2006	ET = 15 Cnt = 13	40-60% HRmax	12	↑ 6MWD ↑ physical QOL

HFpEF Conclusions

- The signs and symptoms of HFpEF are dramatically more pronounced with exertion than they are with rest.

HFpEF Conclusions

*HFpEF is a clinical syndrome of dyspnea and fatigue where there is normal LV EF, a stiff ventricle and stiff arteries and veins.

*The stiff LV and vasculature is worsened by inflammation, and the clinical syndrome of acute decompensated heart failure may be triggered by inflammation, especially lung disease, obesity, hypertension

HFpEF conclusions

- HFpEF differs from normal aging and from non-cardiac dyspnea by marked increases in LA pressure and volume, especially with exertion
- Therefore, key echocardiographic markers are
  - Left atrial enlargement (LAVi > 34 ml/m^2)
  - Pulmonary hypertension (PAP_{sys} > 34 mm Hg)
- Key clinical markers are
  - Atrial fibrillation, elevated BNP

HFpEF has two forms of inflammation

1. Chronic inflammation, due to
   - Obesity
   - Hypertension
   - Diabetes
   - Chronic kidney disease
   - Lung disease

- This inflammation creates microvascular coronary artery disease, myocardial fibrosis and abnormalities of skeletal muscle function

HFpEF has two forms of inflammation

2. Acute inflammation, due to
   - Acute respiratory infection
   - Exacerbation of COPD
   - Sepsis

JACC Journals

From: A Novel Paradigm for Heart Failure With Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation

J Am Coll Cardiol. 2013;62(4):263-271. doi:10.1016/j.jacc.2013.02.092

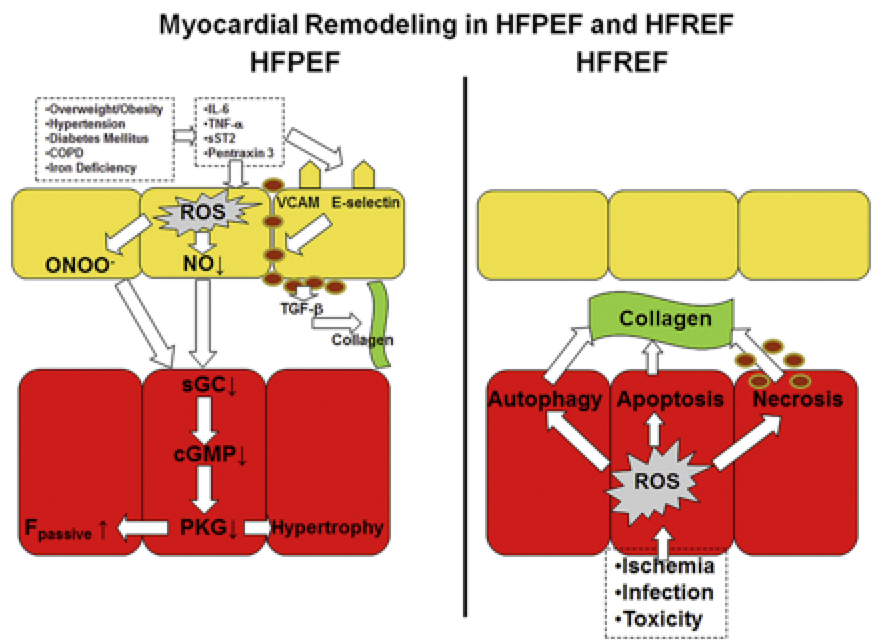

Figure Legend:

Myocardial Dysfunction and Remodeling in HFPEF and HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial inflammation and oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes because of ischemia, infection, or toxic agents. ROS trigger cardiomyocyte autophagy, apoptosis, or necrosis. The latter attracts leukocytes. Dead cardiomyocytes are replaced by fibrous tissue. cGMP = cyclic guanosine monophosphate; HFREF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.

Treatment

Mechanical: reduction in LA pressure

bariatric surgery

Medical: statins

mineralocorticoid inhibitors

SGLT2-I

Exercise and lifestyle changes

Control traditional cardiac risk factors