Paris, 12 -13 Mars 2026

Réadaptation des HFpEF

Session “Réadaptation”

ULS LISBOA OCIDENTAL
Hospital de Santa Cruz

Hospital CUF Tejo - Lisboa
Unidade de Reabilitação Cardíaca

Miguel Mendes

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Conflits d’intérêts

- Pas de conflits d’intérêts

Presentation summary

- Diagnosis
- Epidemiology/prevalence
- Patophysiology
- Exercise training and cardiac rehabilitation trials
- Benefits/outcomes
- Take-home message

HFpEF | a disease or a construct?

JACC: HEART FAILURE
VOL. ■, NO. ■, 2026

PUBLISHED BY ELSEVIER

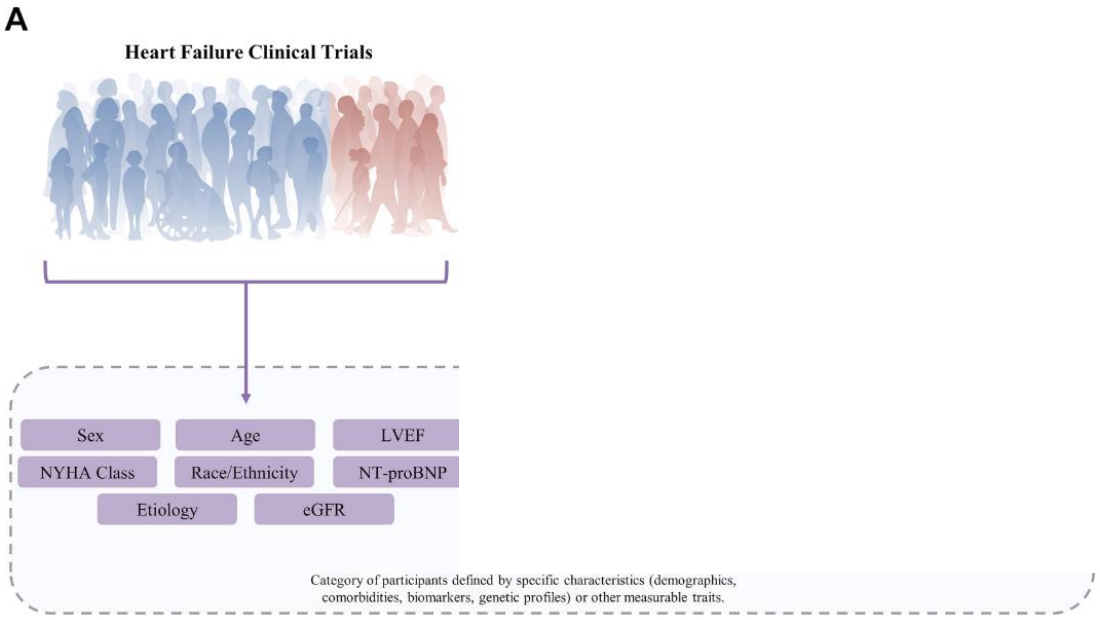
LEADING EDGE COMMENTARY

Subgroups and Special Populations in Heart Failure Clinical Trials

Insights From the HFC-ARC Expert Consensus Panel

Vanessa Blumer, MD,[a] Biykem Bozkurt, MD, PhD,[b] Marvin A. Konstam, MD,[c] Mona Fiuzat, PharmD,[d] William T. Abraham, MD,[e] Michael R. Bristow, MD, PhD,[f] Isabella Cavagna, BS,[a] Ari Cedars, MD,[g] Barry Greenberg, MD,[h] Christian Guilliod, MD,[i] Carolyn Ho, MD,[j] James L. Januzzi, MD,[k,l,m] Anuradha Lala, MD,[n,o,p] Mathew S. Maurer, MD,[q] John J.V. McMurray, MD,[r] Mitchell A. Psotka, MD,[a] Benjamin R. Saville, PhD,[s,t] Scott D. Solomon, MD,[j] Janet Wittes, PhD,[u] JoAnn Lindenfeld, MD,[v] Christopher O'Connor, MD[a]

FIGURE 1 Subgroups and Special Populations in Heart Failure Trials



HFpEF | epidemiology

Epidemiology of heart failure with preserved ejection fraction

Shannon M. Dunlay[1,2], Véronique L. Roger[1,2] and Margaret M. Redfield[1]

Abstract | Heart failure (HF) with preserved ejection fraction (HFpEF) is a clinical syndrome associated with poor quality of life, substantial health-care resource utilization, and premature mortality. We summarize the current knowledge regarding the epidemiology of HFpEF with a focus on community-based studies relevant to quantifying the population burden of HFpEF. Current data regarding the prevalence and incidence of HFpEF in the community as well as associated conditions and risk factors, risk of morbidity and mortality after diagnosis, and quality of life are presented. In the community, approximately 50% of patients with HF have HFpEF. Although the age-specific incidence of HF is decreasing, this trend is less dramatic for HFpEF than for HF with reduced ejection fraction (HFrEF). The risk of HFpEF increases sharply with age, but hypertension, obesity, and coronary artery disease are additional risk factors. After adjusting for age and other risk factors, the risk of HFpEF is fairly similar in men and women, whereas the risk of HFrEF is much lower in women. Multimorbidity is common in both types of HF, but slightly more severe in HFpEF. A majority of deaths in patients with HFpEF are cardiovascular, but the proportion of noncardiovascular deaths is higher in HFpEF than HFrEF.

NATURE REVIEWS | CARDIOLOGY

doi:10.1038/nrcardio.2017.65

Published online 11 May 2017

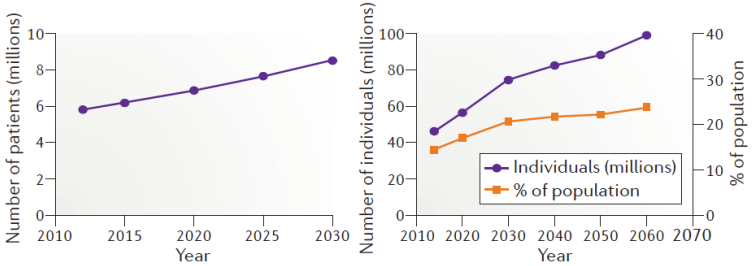
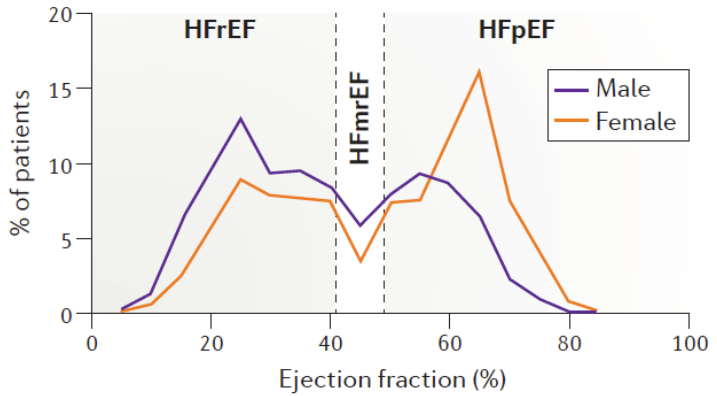


Figure 1 | **Projected population burden of heart failure in the USA. a** | Projected increases in the number of patients with heart failure in the USA from 2012 to 2030 assuming stable age-specific, sex-specific, and ethnicity-specific incidences[1]. **b** | Increases are caused largely by the projected changes in population demographics, with increases in the number and percentage of individuals aged >65 years[5].



HFpEF | prevalence in Portugal

ESC European Heart Journal (2026) 00, 1–17 https://doi.org/10.1093/eurheartj/ehag030

CLINICAL RESEARCH
Epidemiology, prevention, and health care policies

Heart failure in the Portuguese population aged ≥50 years: prevalence and phenotypes in the PORTHOS study

Rui Baptista[1,2,3,4,5], Ana Maria Rodrigues[6], Filipa Bernardo[7], Lígia Lopes Mendes[8], Fátima Franco[9], Joana Pimenta[10,11], Sara Gonçalves[12], Ana Rita Henriques[4], Jorge M. Mendes[4], Ana Teresa Timóteo[6,13], Aurora Andrade[14], Brenda Moura[15], Cândida Fonseca[16,17], Carlos Aguiar[18], Dulce Brito[19,20], Jorge Ferreira[18], Marisa Peres[21], Paulo Santos[22,23], Pedro Moraes Sarmento[24], Rui Cernadas[25], Mário Santos[26,27,28], Ricardo Fontes-Carvalho[29,30], Marisa Pardal[7], Adalberto Campos Fernandes[31], Hugo Martinho[7], José R. González-Juanatey[32,33,34], Luís Filipe Pereira[35], Cláudia Raquel Marques[36], Luís Filipe Azevedo[22,23], Helena Canhão[17], José Silva-Cardoso[11,37], Victor Machado Gil[38], Gianluigi Savarese[39], and Cristina Gavina[39,40,41,*]

[1]Cardiology Department, Unidade Local de Saúde de Entre o Douro e Vouga, Santa Maria da Feira, Portugal; [2]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [3]Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, Coimbra, Portugal; [4]Clinical Academic Center of Coimbra (CACC),

Key Question
What is the prevalence of heart failure (HF) and its phenotypes in the population aged 50 years and older?

Key Finding
In the PORTHOS cross-sectional, population-based two-staged observational study combining NT-proBNP, symptoms and echocardiographic evaluation estimated an HF prevalence of 16.54%. HF with preserved ejection fraction, representing 93.4% of HF cases, was independently associated with older age, female sex, type 2 diabetes, atrial fibrillation, and dyslipidaemia.

Take Home Message
NT-proBNP-based screening combined with echocardiography improves early HF detection, revealing that 90% of cases were previously undiagnosed.

Prevalence > 50 years old:
HF (p + r) EF = 16.54%
HFrEF = 1.1%

HFpEF only = 15,44% (93.39%)
- Male = 9.15 %
- Women = 19.68 %

Aim

PORTHOS aimed to assess the contemporary prevalence of HF in Portuguese individuals aged ≥50 years

Methods

18 969 Individuals of ≥50 years old were contacted

Stage 1

6189 Screening through NT-proBNP assessment

- 297 — 4.8% with no prior HF diagnosis and NT-proBNP <125 pg/mL — Screening validation sample
- 2249 — Prior HF diagnosis and/or NT-proBNP ≥125 pg/mL

Stage 2

2498 Confirmatory through echocardiography and ECG

LVEF <50% / LVEF ≥50%

NYHA class ≥II, self-reported oedema, dyspnoea or orthopnoea

- LVEF ≤40% — HFrEF
- LVEF 41–49% — HFmrEF
- HFA-PEFF ≥5 — HFpEF
- HFA-PEFF ≤4 — No HF

Results

HF prevalence was **16.54%** (95% CI: 13.71–19.82%)
- Higher in **women** vs men (21.00% vs 10.47%)
- **Increases with age**, from 4.01% (50–59 years) to 30.68% (≥70 years)

Most (**93.39%**) had HFpEF
- More men had **HFrEF** (**0.45%** vs 0.28%)
- More women had **HFpEF** (**19.68%** vs 9.15%) and **HFmrEF** (**1.04%** vs 0.86%)

90% were unaware of their condition

Individuals with HF

Characteristics
- Older
- Higer % of women
- Lower educational level
- Lower household income
- Lower alcohol consumption
- Lower % of smokers

Comorbidities
- History of myocardial infarction
- High blood pressure
- Dyslipidaemia
- Type 2 diabetes mellitus
- Valvular heart disease
- Atrial fibrillation
- Chronic kidney disease

Conclusions

PORTHOS estimated a HF prevalence of 16.54% in individuals aged ≥50 years, with a clear predominance of HFpEF

By aligning with the most recent HF definition and incorporating the latest diagnostic guidelines (NT-proBNP, symptoms, and echocardiographic techniques) → Highlights the high burden of HF in Portugal and supports the importance of early detection

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HFpEF | prevalence and outcomes

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 81, NO. 18, 2023

THE PRESENT AND FUTURE

JACC SCIENTIFIC STATEMENT

Heart Failure With Preserved Ejection Fraction

JACC Scientific Statement

Barry A. Borlaug, MD,[a] Kavita Sharma, MD,[b] Sanjiv J. Shah, MD,[c] Jennifer E. Ho, MD[d]

FIGURE 1 Epidemiology of HFpEF

	HFpEF Incidence	HFpEF Prevalence	HFpEF Clinical Outcomes
	• 27 cases per 10,000 person-years • Lifetime risk: 1 in 10 at age 45 years	• 1.0%-1.5% of population • Highly age dependent	• 5-year mortality: 75.3% (GWTG registry) • 30-day all-cause readmission rate: 21%
Secular trends	↑ incidence over time	↑ prevalence over time	?
Sex differences	↔	>	<
HFpEF vs HFrEF	HFpEF incidence rising relative to HFrEF	HFpEF prevalence rising relative to HFrEF	Similarly poor survival ↓ CV death in HFpEF vs HFrEF

Summary of current understanding of HF incidence, prevalence, and outcomes and influence of sex drawn from references 10-17 and 24-27.
CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; GWTG = AHA Get With The Guidelines.

HFpEF | pathophysiology of exercise intolerance

JACC: HEART FAILURE VOL. 8, NO. 8, 2020

FOCUS ISSUE: RV DYSFUNCTION AND HFpEF

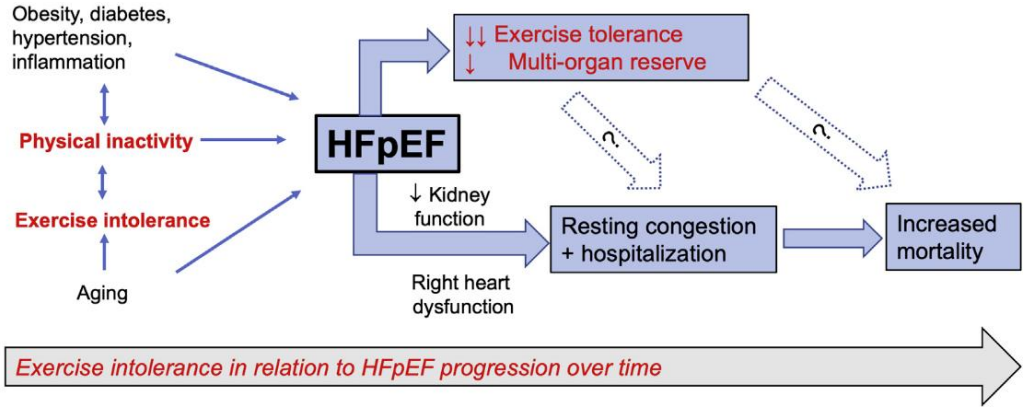
STATE-OF-THE-ART REVIEW

Impaired Exercise Tolerance in Heart Failure With Preserved Ejection Fraction

Quantification of Multiorgan System Reserve Capacity

Matthew Nayor, MD, MPH,[a] Nicholas E. Houstis, MD, PhD,[a] Mayooran Namasivayam, MBBS, PhD,[a] Jennifer Rouvina, NP,[b] Charles Hardin, MD,[b] Ravi V. Shah, MD,[a] Jennifer E. Ho, MD,[a,c] Rajeev Malhotra, MD,[a,c] Gregory D. Lewis, MD[a,b,c]

FIGURE 1 The Role of Exercise Intolerance in HFpEF



Exercise intolerance is a cardinal manifestation of HFpEF. Whether ambulatory patients with exercise intolerance progress to the phenotype of rest congestion with frequent need for hospitalization requires further investigation, but exercise intolerance itself is a highly morbid condition in HFpEF.

HFpEF | exercise intolerance

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VOL. 80, NO. 12, 2022

JACC FOCUS SEMINAR: EXERCISE, CARDIOVASCULAR DISEASE, AND THE ATHLETE'S HEART

Heart Failure With Preserved Ejection Fraction as an Exercise Deficiency Syndrome

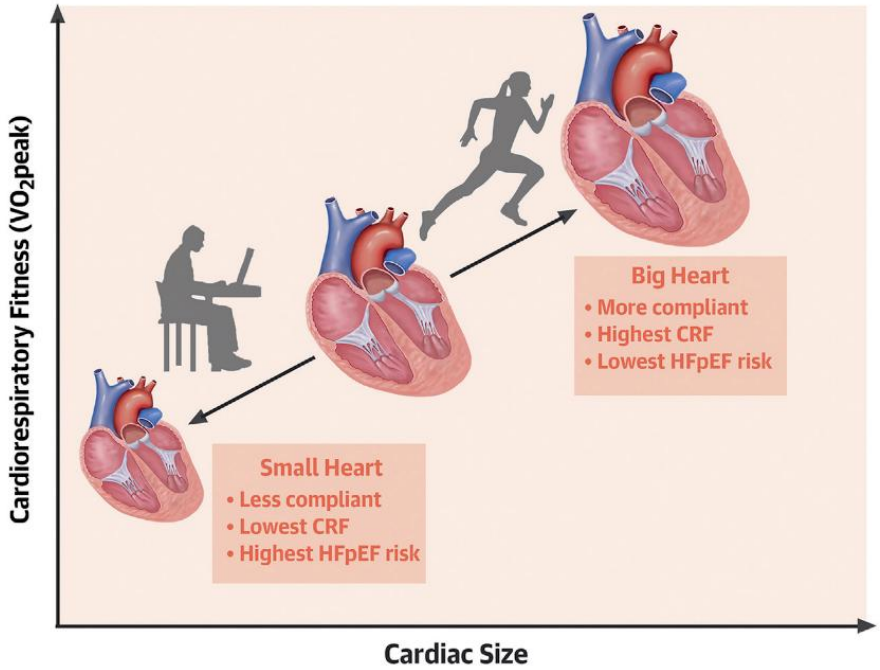
JACC Focus Seminar 2/4

Andre La Gerche, MBBS, PhD,[a,b,c] Erin J. Howden, PhD,[a] Mark J. Haykowsky, PhD,[d,e] Gregory D. Lewis, MD,[e] Benjamin D. Levine, MD,[f,g] Jason C. Kovacic, MBBS, PhD[h,i,j]

HIGHLIGHTS

- Physical activity is associated with increases in cardiac mass, stroke volume, cardiac output, and peak oxygen consumption, and reduction of clinical events. As a corollary, inactivity results in cardiac atrophy, reduced cardiac output and chamber size, and impaired augmentation of cardiac performance during exercise.
- A chronic lack of exercise is a risk factor for HFpEF in certain individuals.
- Lifelong physical activity improves cardiorespiratory fitness in middle-life and can allow for normal age-related declines in cardiac function without disability.

CENTRAL ILLUSTRATION The Spectrum of Physical Activity, Cardiorespiratory Fitness, and Cardiac Remodeling



La Gerche A, et al. J Am Coll Cardiol. 2022;80(12):1177-1191.

HFpEF | diagnosis

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PUBLISHED BY ELSEVIER

VOL. 81, NO. 18, 2023

THE PRESENT AND FUTURE

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TABLE 3 Mechanisms of Abnormal Hemodynamics in HFpEF

Mechanism	Specific Causes	Relevant Phenogroups
Intrinsic myocardial dysfunction[a]	Pressure-overload hypertrophy/remodeling Vascular rarefaction Interstitial fibrosis Ischemia Cardiomyocyte energy deprivation Oxidative/nitrosative stress Insulin resistance	Stiff vasculature/hypertensive Ischemic (epicardial or microvascular) Obese LA myopathy
Hypervolemia	Obesity Renin-angiotensin-aldosterone activation Chronic kidney disease	Obese Chronic kidney disease
↑Stressed blood volume	Obesity Excessive sympathoexcitation	Obese Autonomic dysfunction
↑Ventricular interaction & pericardial restraint	Obesity Right-sided heart remodeling & dysfunction Tricuspid regurgitation	Pulmonary vascular disease Obesity Atrial tricuspid regurgitation
Afterload-mediated myocardial dysfunction	Systolic hypertension Aortic stiffening	Stiff vasculature/hypertensive Chronic kidney disease

HFpEF | diagnosis

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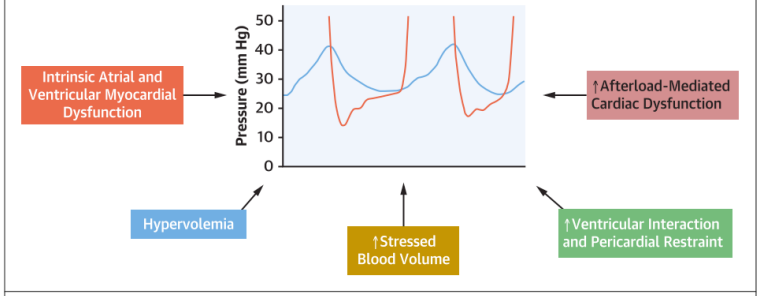
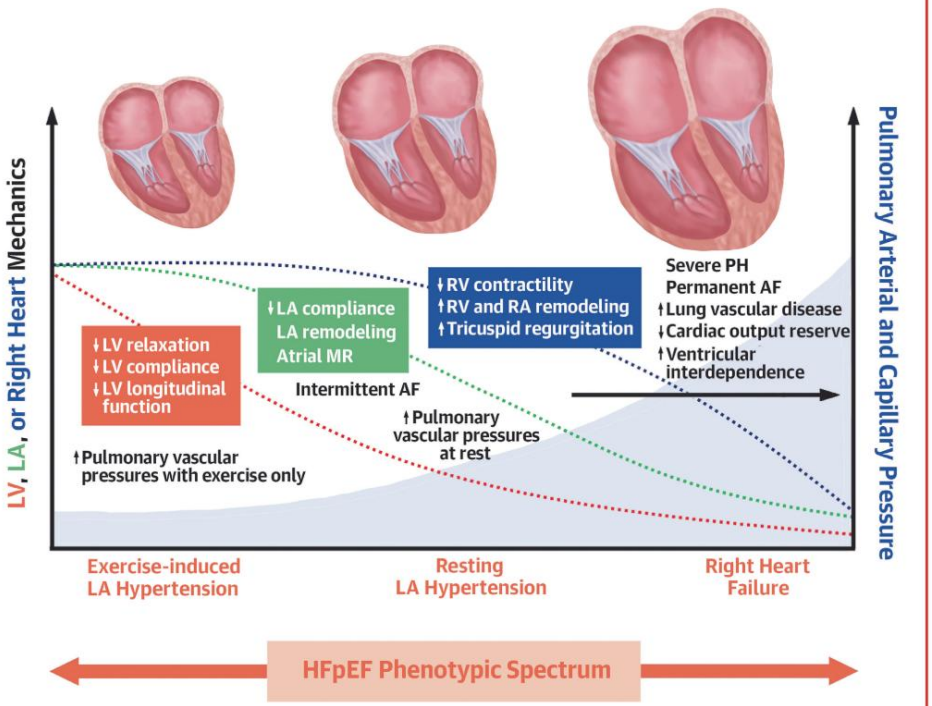
FIGURE 4 Mechanisms of Hemodynamic Congestion in HFpEF



Increases in pulmonary capillary wedge pressure **(blue)** and left ventricular end diastolic pressure **(red)** develop through a variety of pathophysiological perturbations in HFpEF, many of which coexist within the same patient, but some that do not, and may require different treatments. Abbreviation as in Figure 1.

CENTRAL ILLUSTRATION Temporal Disease Progression in Heart Failure With Preserved Ejection Fraction



Borlaug BA, et al. J Am Coll Cardiol. 2023;81(18):1810-1834.

HFpEF | hemodynamic's

European Heart Journal (2011) 32, 670–679
doi:10.1093/eurheartj/ehq426

REVIEW

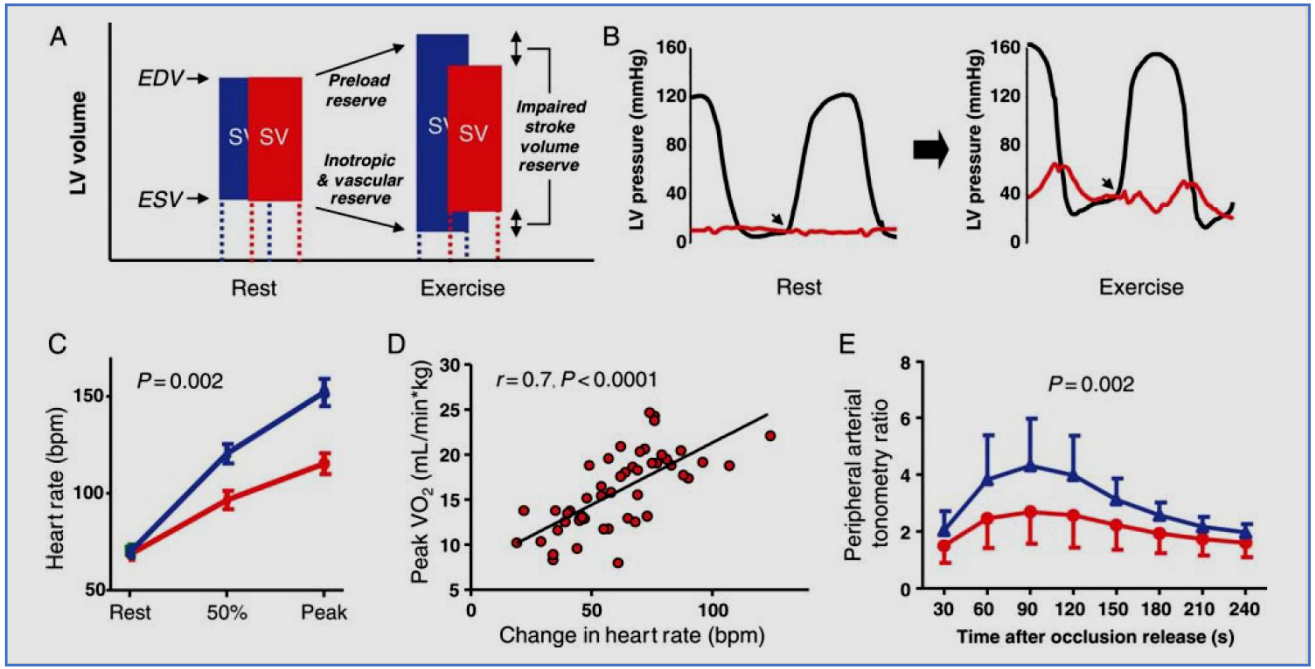
Frontiers in cardiovascular medicine

Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment

Barry A. Borlaug[1]* and Walter J. Paulus[2]

[1]The Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic Rochester, MN 55906, USA; and [2]The VU University Medical Center, Amsterdam, The Netherlands

Received 9 July 2010; revised 8 September 2010; accepted 14 October 2010; online publish-ahead-of-print 7 December 2010



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HFpEF | exercise intolerance

ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 1327–1345
doi:10.1002/ejhf.2601
POSITION PAPER

Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy – A clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology

Marco Guazzi[1]*, Matthias Wilhelm[2], Martin Halle[3,4], Emeline Van Craenenbroeck[5,6], Hareld Kemps[7,8], Rudolph A. de Boer[9], Andrew J.S. Coats[10], Lars Lund[11], Donna Mancini[12,13], Barry Borlaug[14], Gerasimos Filippatos[15], and Burkert Pieske[16,17,18]

The O2 cascade		HFPEF	
Critical steps	**Organ**	**Limitations in O2 cascade**	**Pathophysiology**
Alveolar ventilation (VA)		alveolar O2 exchange ↓	Pulmonary Reserve ↓ — Ventilatory reserve↓ (O2 alveolar diffusion ↓, respiratory muscle work ↑ Abnormal ventilatory regulation (ergoreflex ↑ , EOV)
Lung diffusion (DL)			
Hb		O2 delivery ↓	Anemia — Iron deficiency
Cardiac output (CO)		O2 delivery ↓	Cardiac reserve ↓ — Cardiac output reserve ↓ (Stroke volume ↓, chronotropic incompetence) Atrial arrythmia's, inducibel myocardial ischemia, dynamic mitral regurgitation Impaired LV filling (myocardial relaxation↓, LA dyfunction) Pulmonary hypertension and RV dysfunction
Vasodilatation		O2 delivery ↓	Vascular reserve ↓ — Arterial vasodilation↓, arterial stifness ↑, abnormal ventriculovascular coupling
Muscle diffusion (Dm)			
Mitochondrial respiration (vmax)		O2 diffusion and/or distraction ↓	Skeletal muscle dysfunction — Structural: capillary density↓, intermuscular fat↑, shift muscle fiber type Functional: anabolism↓, mitochondria size and function↓, oxidative capacity↓, inflammation↑

HFpEF | exercise intolerance

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VOL. 80, NO. 12, 2022

JACC FOCUS SEMINAR: EXERCISE, CARDIOVASCULAR DISEASE, AND THE ATHLETE'S HEART

Heart Failure With Preserved Ejection Fraction as an Exercise Deficiency Syndrome

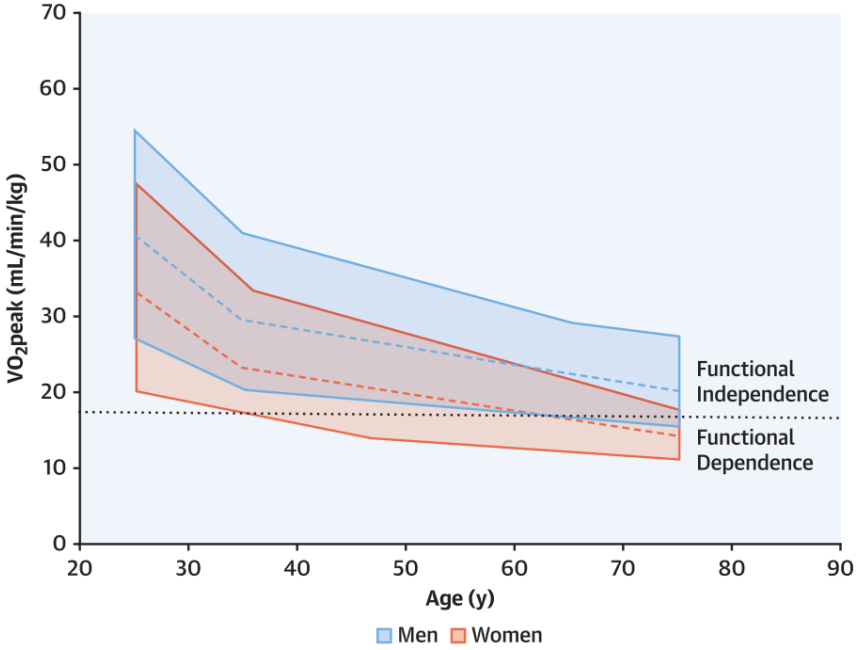
JACC Focus Seminar 2/4

Andre La Gerche, MBBS, PhD,[a,b,c] Erin J. Howden, PhD,[a] Mark J. Haykowsky, PhD,[d,e] Gregory D. Lewis, MD,[e] Benjamin D. Levine, MD,[f,g] Jason C. Kovacic, MBBS, PhD[h,i,j]

HIGHLIGHTS

- Physical activity is associated with increases in cardiac mass, stroke volume, cardiac output, and peak oxygen consumption, and reduction of clinical events. As a corollary, inactivity results in cardiac atrophy, reduced cardiac output and chamber size, and impaired augmentation of cardiac performance during exercise.
- A chronic lack of exercise is a risk factor for HFpEF in certain individuals.
- Lifelong physical activity improves cardiorespiratory fitness in middle-life and can allow for normal age-related declines in cardiac function without disability.

FIGURE 4 Age-Related Decrease in Cardiorespiratory Fitness and Functional Independence



Peak oxygen consumption (VO_2peak) falls by approximately 0.5 to 1 mL/min/kg with each year of aging. Average cardiorespiratory fitness in women is less than men for all age groups. Thus, greater cardiorespiratory fitness in younger and middle-age years is critical in providing the reserve required to avoid functional disability in later years.

HFpEF | exercise benefits

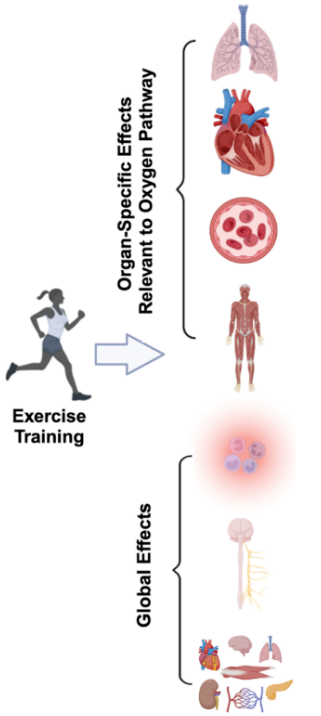
Circulation Research

COMPENDIUM ON CARDIOPULMONARY DISEASE AND EXERCISE: MOLECULAR TO CLINICAL MECHANISMS

Exercise Training in Heart Failure: Clinical Benefits and Mechanisms

Louisa A. Mounsey, Meihan Guo, Emily S. Lau, Jennifer E. Ho

Circulation Research. 2025;137:273–289. DOI: 10.1161/CIRCRESAHA.124.325533



Organ System	Physiologic Effects of Exercise Training	Potential Molecular Mechanisms
Respiratory System	Peak and reserve VO_2 ↑ V_E/VCO_2 slope ↓ Inspiratory muscle strength ↑ Diffusion capacity & pulmonary blood flow ↑	Diaphragm contractile dysfunction ↓ with less oxidative modification of actin and creatine kinase, ↓ proteolytic pathways
Cardiac Structure and Function	LV size ↓ Systolic function improved (LVEF, SV, CO) ↑ Diastolic function improved (E/e', IVRT) ↑	Myocardial stiffness ↓ with increased titin compliance (via PEVK domain phosphorylation)
Systemic Vasculature	Rest and peak systemic vascular resistance ↓ Endothelial function ↑	Endothelial vasodilation ↑ via ↑ eNOS, NO pathways, expansion of endothelial progenitor cells
Skeletal Muscle	Muscle atrophy ↓ Oxidative stress ↓ Mitochondrial content ↑	↑ Oxidative (type I) and ↓ glycolytic (type II) fibers, enhanced mitochondrial activity and biogenesis, ↑ angiogenesis in skeletal muscle
Global effects	**Physiologic Effects of Exercise Training**	**Potential Molecular Mechanisms**
Inflammation, oxidative stress	Anti-inflammatory & anti-oxidant effects Skeletal myopathy ↓ Endothelial function ↑	↓ Pro-inflammatory cytokines including TNF-α , IL-6 and soluble IL-6 receptor ↑ Radical scavenger enzymes (glutathione peroxidase, catalase)
Autonomic nervous system & neurohormones	Sympathetic activity ↓ Arterial baroreflex sensitivity ↑ Muscle metaboreflex ↓ and mechanoreflex ↑	Balance ACE and ACE2 Norepinephrine, vasopressin, angiotensin II, aldosterone ↓ ↓ COX-2 expression and ↓ NFκB/IκB ratio
Multi-Organ Crosstalk	*Extrapolated from healthy populations:* Inter-organ communication ↑ with diverse effects on molecular pathways involved in inflammation, fatty acid metabolism, endothelial function, among others	Release of exerkines ↑ Release of extracellular vesicles ↑

Figure 2. Organ-specific and global effects of 1, exercise training.

HFpEF | pathophysiology

- Muscle (cardiac & peripheral)
  - aging
  - inflammation
  - metabolism
- Toxic adiposity (adipokines)
- Lung (dynamic hyperinflation)
- Peripheral circulation (stiffness)

HFpEF | etiology | muscle aging

JACC: ADVANCES VOL. 4, NO. 12, 2025

STATE-OF-THE-ART REVIEW

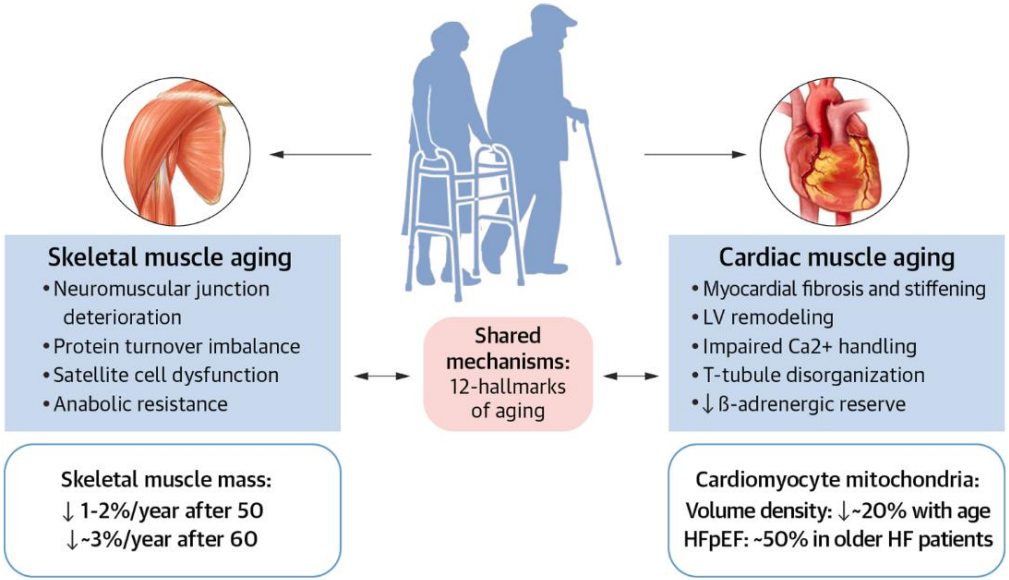
Skeletal Muscle-Cardiac Muscle Aging

Shared Mechanisms and Multimodal Interventions

Kriti Kalra, MD,[a] Patrick Berchie, MD,[b] Sahib Singh, MD,[c] Yasser Jamil, MD,[d] Nishok Karthikeyan, MD,[e] Oliver Glen Ancheta, DO, MS, MPH,[e] Ardeshir Hashmi, MD,[e] Trejeeve Martyn, MD, MSc,[e] Samir Kapadia, MD,[e] Venu Menon, MD,[e] David A. Zidar, MD, PhD,[e] Abdulla A. Damluji, MD, PhD, MBA[d,e,f]

HIGHLIGHTS

- Age-related cardiac and skeletal muscle deterioration share fundamental molecular pathways that synergistically accelerate functional decline.
- Chronic inflammation, mitochondrial dysfunction, and anabolic resistance represent key therapeutic targets for preserving muscle integrity and function.
- Combined exercise, optimized nutrition, and targeted pharmacological approaches offer the most promising strategy for muscle preservation.
- Future interventions must address muscle-heart crosstalk mechanisms and deploy integrated care models with personalized, multimodal approaches.



HFpEF | etiology | muscle metabolism

Circulation: Heart Failure

ORIGINAL ARTICLE

Skeletal Muscle Quantity Versus Quality in Heart Failure: Exercise Intolerance and Outcomes in Older Patients With HFpEF Are Related to Abnormal Skeletal Muscle Metabolism Rather Than Age-Related Skeletal Muscle Loss

Sabra C. Lewsey, MD, MPH; T. Jake Samuel, PhD; Michael Schär, PhD; Joevin Sourdon, PhD; Joseph R. Goldenberg, MD, PhD; Lisa R. Yanek, MPH; Shenghan Lai, MD; Angela M. Steinberg, MSN; Paul A. Bottomley, PhD; Gary Gerstenblith, MD; Robert G. Weiss, MD

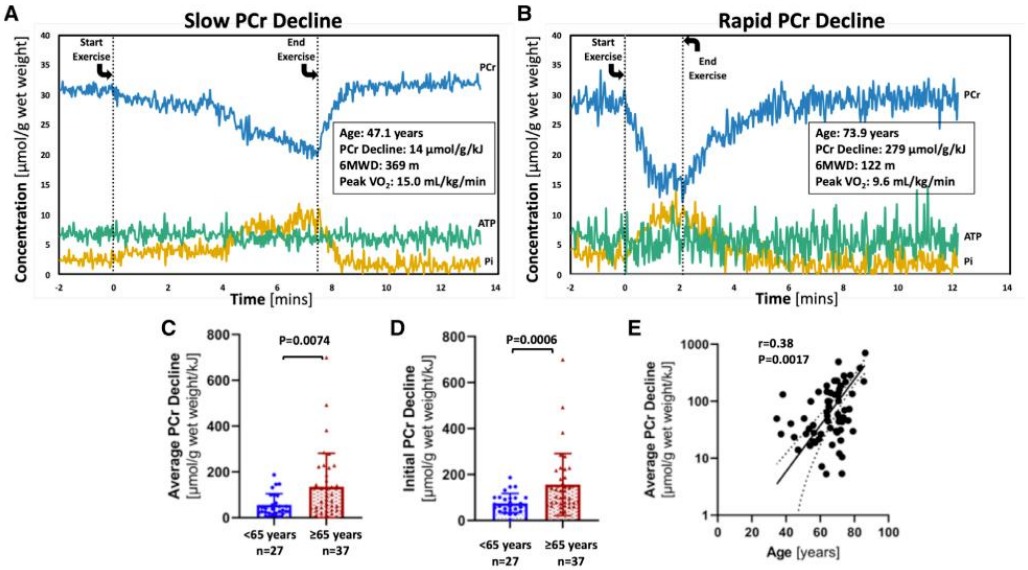
BACKGROUND: Heart failure with preserved ejection fraction (HFpEF) is a systemic process with contributions from peripheral factors, including skeletal muscle (SM). Age-associated SM loss and impaired energy metabolism occur without heart failure, but the relative importance of changes in SM quantity versus metabolic quality in patients with HFpEF for exercise intolerance (EI) or outcomes has not been studied. We hypothesized that EI and subsequent clinical outcomes across the adult lifespan in patients with HFpEF are related to impaired SM energy metabolism rather than age-associated SM loss.

METHODS: Patients with HFpEF (n=64; aged 34–86 years) with left ventricular ejection fraction ≥50% were stratified by age in a prospective study. They underwent 3T magnetic resonance imaging to measure calf muscle quantity and ^{31}P magnetic resonance spectroscopy to measure muscle high-energy phosphate metabolism during plantar flexion exercise.

RESULTS: Older patients with HFpEF exhibited more severe EI, less calf muscle, faster exercise-induced high-energy phosphate decline, and worse SM energetics at fatigue than younger patients. EI correlated closely with muscle metabolic quality, not quantity. Neither magnetic resonance imaging exercise time, 6-minute walk distance, nor peak oxygen uptake at cardiopulmonary exercise testing on cardiopulmonary bicycle exercise testing correlated with calf SM area. In contrast, the 6-minute walk distance or peak oxygen uptake at cardiopulmonary exercise testing were inversely related to rapid exercise-induced high-energy phosphate decline and worse SM energetic profile at fatigue. Rapid exercise-induced high-energy phosphate decline and lower ATP at fatigue were associated with increased cardiovascular death or heart failure hospitalizations in univariate analysis over a median of 39.3 months.

CONCLUSIONS: EI in older patients with HFpEF is closely linked to age-associated abnormalities in SM energy metabolism, namely, rapid exercise-induced energetic decline and worse energetic profile at fatigue, and not SM quantity. Abnormal SM energy metabolism is associated with worse outcomes in patients with HFpEF in unadjusted analysis. These findings support SM energy metabolism as a barometer of systemic HFpEF severity and the pursuit of new SM metabolic modulators to reduce disabling EI and possibly adverse outcomes in patients with HFpEF.

Key Words: aging ■ exercise ■ heart failure ■ magnetic resonance spectroscopy ■ metabolism ■ muscle, skeletal



HFpEF | etiology| muscle atrophy & inflammation

JACC: ADVANCES VOL. 4, NO. 2, 2025

ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Skeletal Muscle Mass and Mortality in Heart Failure

Mediation Role of Systemic Immune-Inflammatory Index

Xiaojie Cai, MD,[a,b,*] Menghui Liu, MD,[a,b,*] Peng Qin, MBBS,[c] Sanhua Tang, MBBS,[d] Lixiang He, MD,[a,b] Jiangjie Lei, MD,[a,b] Yi Zhou, MD,[a,b] Zemeihong Xu, MBBS,[a,b] Yue Guo, PhD,[a,b] Chong Feng, MD,[a,b] Xiaodong Zhuang, PhD,[a,b] Xinxue Liao, PhD[a,b]

ABSTRACT

BACKGROUND Heart failure (HF)-related skeletal muscle wasting inversely affects the prognosis of HF, in which systemic inflammation may be involved. The relationships among skeletal muscle mass (SMM), systemic inflammation, and cardiovascular outcomes have not been clarified.

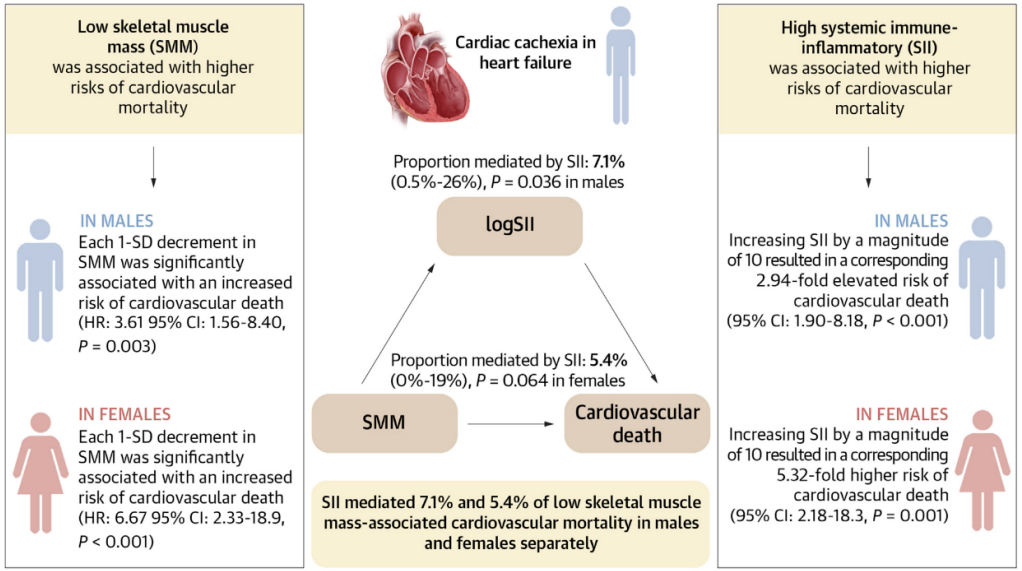
OBJECTIVES This study evaluated the associations of SMM with cardiovascular outcomes, systemic immune-inflammatory index (SII) with cardiovascular outcomes, and the mediation role of SII in the relationship between SMM and outcomes.

METHODS We included inpatients from the RED-CARPET trial (Real-world Data of Cardiometabolic ProtEcTion trial) with a definitive diagnosis of HF. We explored the associations of SMM with prognosis and SII with prognosis stratified by sex. Mediation analysis was applied for the role of SII in the association of SMM and the prognosis.

RESULTS With a median follow-up of 4.9 years, 1402 patients with HF had 208 all-cause deaths and 106 cardiovascular deaths. Each 1-SD decrement in SMM was significantly associated with an increased risk of all-cause death (HR: 2.17; 95% CI: 1.20-3.91; $P = 0.01$ in males and HR: 2.90; 95% CI: 1.27-6.67; $P = 0.012$ in females). For cardiovascular death, the HR was 3.61 (95% CI: 1.56-8.40; $P = 0.003$) in males and 6.67 (95% CI: [2.33, 18.9]; $P < 0.001$) in females. Higher SII was associated with adverse outcomes. In the mediation analyses, SII was partially mediated in the relationship between SMM and cardiovascular death (7.1% [proportion-mediated 95% CI: 0.5%-26%]; $P = 0.036$ for males, and 5.4% [proportion mediated 95% CI: 0%-18.8%]; $P = 0.064$ for females).

CONCLUSIONS Both low SMM and increased SII were significantly associated with unfavorable outcomes in HF. SII was partially mediated in the relationship between low SMM and cardiovascular death in HF. (JACC Adv. 2025;4:101553)

CENTRAL ILLUSTRATION The Relationship Between Skeletal Muscle Mass, SII, and Cardiovascular Mortality in Heart Failure



Cai X, et al. JACC Adv. 2025;4(2):101553.

Skeletal muscle mass and mortality in heart failure: mediation role of systemic immune-inflammatory index.

HFpEF | etiology | adipokine hypothesis

JACC
VOL. 86, NO. 16, 2025

JACC STATE-OF-THE-ART REVIEW

The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction

A Novel Framework to Explain Pathogenesis and Guide Treatment

Milton Packer, MD

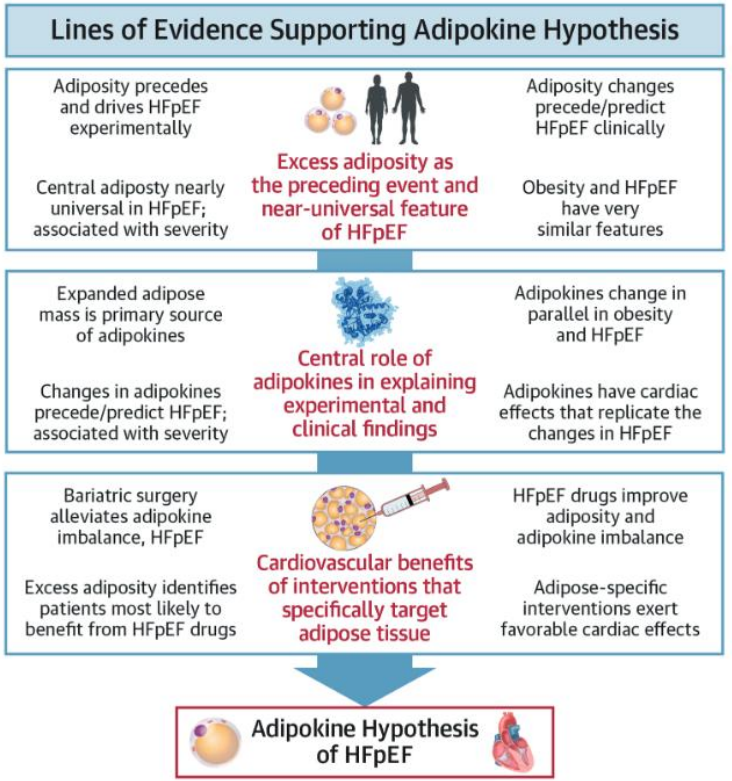
ABSTRACT

HYPOTHESIS The paper proposes a novel unifying hypothesis—that heart failure with preserved ejection fraction (HFpEF) arises primarily from the expansion and dysfunctional transformation of visceral adipose tissue, leading to the secretion of altered suite of signaling molecules (adipokines), which causes systemic inflammation, plasma volume expansion, and cardiac hypertrophy and fibrosis.

ELEMENTS OF THE FRAMEWORK The framework groups adipokines into 3 domains. Domain I adipokines are cardioprotective molecules but are suppressed in patients with excess adiposity. Domain II adipokines are cardioprotective molecules that are up-regulated by adiposity as a compensatory response mechanism. Domain III adipokines, whose secretion is heightened in adiposity, have proinflammatory, prohypertrophic, profibrotic, and antinatriuretic effects. HFpEF results from an adiposity-driven imbalance that promotes Domain III adipokines but suppresses Domain I adipokines, with Domain II adipokines representing an inadequate counter-regulatory response.

KEY LINES OF EVIDENCE 1) Obesity and dietary nutrient excess are the major drivers of experimental HFpEF; 2) changes in visceral adiposity and circulating adipokines are observed years before and predict the diagnosis of HFpEF (but not heart failure with a reduced ejection fraction) in the general community; 3) central obesity or visceral adiposity is present in >95% of patients with HFpEF and tracks with disease severity; 4) obesity and HFpEF exhibit striking parallelism in their molecular, pathophysiological, and clinical features; 5) characteristic changes in the adipokine profile occur in parallel in central obesity and heart failure and are correlated with disease severity; 6) adipokines have established effects on cardiac structure and function that can lead to HFpEF; 7) bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots (disproportionate to changes in body weight), while simultaneously increasing Domain I adipokines and decreasing Domain III adipokines; 8) excess adiposity appears to identify patients most likely to respond to current treatments for HFpEF; and 9) experimental interventions that target only adipose tissue to selectively increase or decrease its secretion of specific adipokines cause distant effects on the heart to modulate cardiac structure and the evolution of cardiomyopathy.

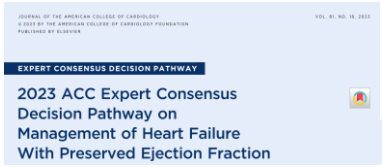
CONCLUSIONS The totality of evidence suggests that HFpEF evolves—not as a heterogenous disorder related to diverse comorbidities and not as a primary disorder of cardiomyocytes—but as an adipose-driven derangement that is disseminated (through endocrine-paracrine signaling) to the heart. (JACC. 2025;86:1269-1373) © 2025 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).



Packer M, JACC. 2025;86(16):1269-1373.

The evidences …

HFpEF | non-pharmacological interventions



Nonpharmacological Interventions in HFpEF

Study	Sample Size (HFpEF only)	Intervention	Outcome
WEIGHT LOSS AND/OR EXERCISE TRAINING			
Edelmann et al[84]	64	3 months of endurance/resistance training	■ Peak Vo_2 increased by 3.3 mL/kg/min ■ Improved quality of life ■ Improvement in E/e' and left atrial volume index
Mueller et al[85]	176	12 weeks of high-intensity interval training and moderate continuous training	■ Improved peak Vo_2 at 3 months
Kitzman et al[86]	63	16 weeks of exercise training	■ Peak Vo_2 increased by 2 mL/kg/min ■ Improved quality of life
Kitzman et al[87]	100	20 weeks of caloric restriction, aerobic exercise, or both	Increase in peak Vo_2 by: ■ Exercise: 1.2 mL/kg/min ■ Diet: 1.3 mL/kg/min ■ Both (additive): 2.5 mL/kg/min
Brubaker et al[88]	88	20 weeks of (caloric restriction and aerobic exercise) ± resistance training	Addition of resistance training to caloric restriction and aerobic exercise ■ increase in leg strength and muscle quality ■ no additive increase in peak Vo_2 or QOL
Mikhalkova et al[89]	12 (all women)	Gastric bypass	■ Improvement in Minnesota Living with Heart Failure score ■ Improved diastolic relaxation on echocardiogram

HFpEF | mixed HF exercise trials outcomes

Circulation Research

COMPENDIUM ON CARDIOPULMONARY DISEASE AND EXERCISE: MOLECULAR TO CLINICAL MECHANISMS

Exercise Training in Heart Failure: Clinical Benefits and Mechanisms

Louisa A. Mounsey, Meihan Guo, Emily S. Lau, Jennifer E. Ho

Trial	Population	Study design and training protocol	Short result summary	Outcomes reported			
				Exercise capacity	Echocardiogram	Mortality/ readmission	Quality of life
HFrEF and HFpEF							
EJECTION-HF[15]	275 participants with a recent heart failure admission 62 with HFpEF, 213 with HFrEF	RCT 2 groups: 23 wk of supervised center-based exercise training vs multidisciplinary HF disease management program plus an individualized home exercise program aiming to achieve moderate aerobic exercise for 30 min 5×/wk	No difference in all-cause 1 y mortality or readmission between groups (60% intervention, 65% control; *P*=0.37). Trend toward greater benefit in participants <70 y (OR, 0.56 [95% CI, 0.30–1.02] vs OR, 1.56 [95% CI, 0.67–3.64]; *P* for interaction=0.05)	✓		✓ only < 70 y	✓
HEART Camp[16,17]	204 participants 145 with HFrEF, 59 with HFpEF	RCT 2 groups: if attended ≥6 of 9 initial exercise training sessions, randomized to 18-month structured program consisting of educational sessions for 6 mo and training sessions for 12 mo followed by 6 mo of independent exercise vs enhanced usual care with paid access to a hospital-based exercise training facility for 18 mo	At 18 mo, there was greater adherence (defined by ≥120 min of moderate-intensity exercise per week) to exercise in the intervention group compared with the usual care group (35% vs 19%). In the HFpEF group, significantly higher 6MWD among the exercise group (446±113 m vs 372±95 m in the usual care) at 18 mo, yet no significant change in the HFrEF group	✓			✓
Fu et al 2016[18]	120 participants 60 with HFrEF, 60 with HFpEF	Nonrandomized 4 groups: HFpEF or with 3 sessions per week of hospital-based bicycle training for 12 wk vs HFrEF or HFpEF with general care (home-based health care program, prompted to exercise via oral commands from case manager)	Significant improvement in peak VO_2 in both HFrEF and HFpEF groups	✓	✓		✓

Circulation Research. 2025;137:273–289. DOI: 10.1161/CIRCRESAHA.124.325533

HFpEF | specific exercise trials

Circulation Research

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Louisa A. Mounsey, Meihan Guo, Emily S. Lau, Jennifer E. Ho

Trial	Population	Study design and training protocol	Short result summary	Outcomes reported			
				Exercise capacity	Echocardiogram	Mortality/ readmission	Quality of life
HFpEF							
OptimEx-Clin[11]	180 sedentary participants with chronic, stable HFpEF (EF ≥50%) and NYHA class II–III	RCT 3 groups: high-intensity interval training vs moderate continuous training for 12 mo vs control group of advice on guideline-based physical activity	Change in peak VO_2 was significantly different between exercise vs control groups at 3 mo (HIIT vs control: 1.5 mL/kg per minute [95% CI, 0.4–2.5], P=0.01; MCT vs control: 2.0 mL/kg per minute [95% CI, 0.9–3.1]; P=0.001), neither group met the prespecified clinical important difference of 2.4 mL/kg per minute. No difference in peak VO_2 between groups at 12 mo	✓	✓		✓
PARIS[12]	53 elderly (mean age 70 y±6) participants with HFpEF	RCT 2 groups: 16 wk of supervised 3× weekly training vs attention control with telephone calls every 2 wk not addressing exercise behaviors	At 16 wk, peak VO_2 significantly increased by 2.7 mL/kg per minute (95% CI, 1.4–4.0) in the exercise group compared with control group. No significant difference in resting echocardiographic measures	✓	✓		✓

Circulation Research. 2025;137:273–289. DOI: 10.1161/CIRCRESAHA.124.325533

HFpEF | HF Stage B trial

Circulation

ORIGINAL RESEARCH ARTICLE

One-Year Committed Exercise Training Reverses Abnormal Left Ventricular Myocardial Stiffness in Patients With Stage B Heart Failure With Preserved Ejection Fraction

Michinari Hieda, MD, MS, PhD; Satyam Sarma, MD; Christopher M. Hearon Jr, PhD; James P. MacNamara, MD; Katrin A. Dias, PhD; Mitchel Samels, MS; Dean Palmer, MS; Sheryl Livingston, MSN, RN; Margot Morris, RN; Benjamin D. Levine, MD

Circulation. 2021;144:934–946. DOI: 10.1161/CIRCULATIONAHA.121.054117

BACKGROUND: Individuals with left ventricular (LV) hypertrophy and elevated cardiac biomarkers in middle age are at increased risk for the development of heart failure with preserved ejection fraction. Prolonged exercise training reverses the LV stiffening associated with healthy but sedentary aging; however, whether it can also normalize LV myocardial stiffness in patients at high risk for heart failure with preserved ejection fraction is unknown. In a prospective, randomized controlled trial, we hypothesized that 1-year prolonged exercise training would reduce LV myocardial stiffness in patients with LV hypertrophy.

METHODS: Forty-six patients with LV hypertrophy (LV septum >11 mm) and elevated cardiac biomarkers (N-terminal pro-B-type natriuretic peptide [>40 pg/mL] or high-sensitivity troponin T [>0.6 pg/mL]) were randomly assigned to either 1 year of high-intensity exercise training (n=30) or attention control (n=16). Right-heart catheterization and 3-dimensional echocardiography were performed while preload was manipulated using both lower body negative pressure and rapid saline infusion to define the LV end-diastolic pressure-volume relationship. A constant representing LV myocardial stiffness was calculated from the following: $P=S\times[\mathrm{Exp}\ \{a\ (V-V_0)\}-1]$, where "P" is transmural pressure (pulmonary capillary wedge pressure – right atrial pressure), "S" is the pressure asymptote of the curve, "V" is the LV end-diastolic volume index, "V_0" is equilibrium volume, and "a" is the constant that characterizes LV myocardial stiffness.

RESULTS: Thirty-one participants (exercise group [n=20]: 54±6 years, 65% male; and controls (n=11): 51±6 years, 55% male) completed the study. One year of exercise training increased $\dot{V}o_2$ max by 21% (baseline 26.0±5.3 to 1 year later 31.3±5.8 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, $P<0.0001$, interaction $P=0.0004$), whereas there was no significant change in $\dot{V}o_2$ max in controls (baseline 24.6±3.4 to 1 year later 24.2±4.1 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, $P=0.986$). LV myocardial stiffness was reduced (right and downward shift in the end-diastolic pressure-volume relationship; LV myocardial stiffness: baseline 0.062±0.020 to 1 year later 0.031±0.009), whereas there was no significant change in controls (baseline 0.061±0.033 to 1 year later 0.066±0.031, interaction $P=0.001$).

CONCLUSIONS: In patients with LV hypertrophy and elevated cardiac biomarkers (stage B heart failure with preserved ejection fraction), 1 year of exercise training reduced LV myocardial stiffness. Thus, exercise training may provide protection against the future risk of heart failure with preserved ejection fraction in such patients.

HFpEF | HF Stage B trial

Circulation

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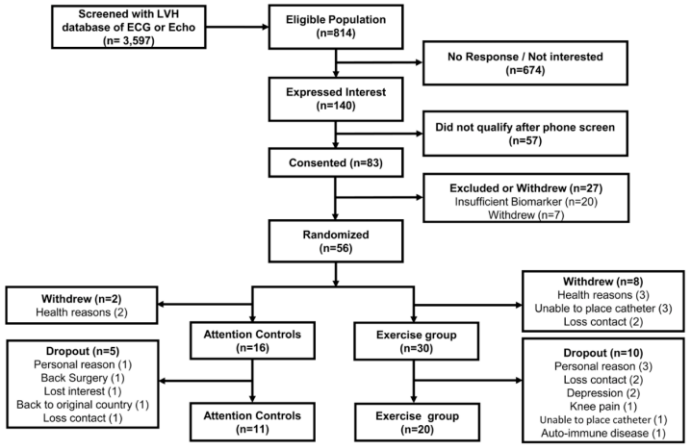

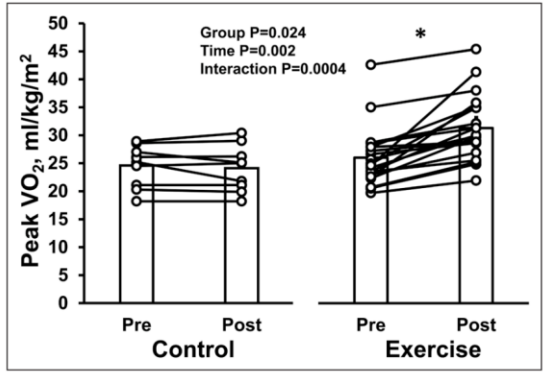

Figure 2. Effect of high-intensity exercise training on peak oxygen consumption in patients with left ventricular hypertrophy.
The individual change and group mean response for peak oxygen uptake are shown for the control and exercise group. *P<0.05 denotes significantly different from pre. Post indicates 1 year later; and pre, baseline.

Circulation. 2021;144:934–946. DOI: 10.1161/CIRCULATIONAHA.121.054117

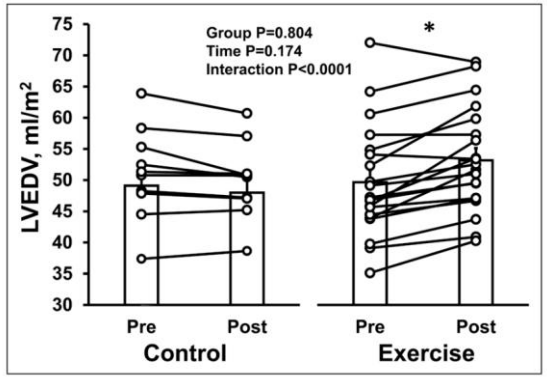

Figure 3. Effect of high-intensity exercise training on LVEDV.
The individual change and group mean response for LVEDV are shown for the control and exercise group. *P<0.05 denotes significantly different from pre. LVEDV indicates left ventricular end-diastolic volume; post, 1 year later; and pre, baseline.

HFpEF | exercise training in obese

Circulation: Heart Failure

ORIGINAL ARTICLE

A Randomized, Controlled Trial of Resistance Training Added to Caloric Restriction Plus Aerobic Exercise Training in Obese Heart Failure With Preserved Ejection Fraction

Peter H. Brubaker, PhD; Barbara J. Nicklas, PhD; Denise K. Houston, PhD; W. Gregory Hundley, MD; Haiying Chen, F Anthony J.A. Molina, PhD; W. Mary Lyles, MD; Benjamin Nelson, MS; Bharathi Upadhya, MD; Russell Newland, BS; Dalane W. Kitzman, MD

BACKGROUND: We have shown that combined caloric restriction (CR) and aerobic exercise training (AT) improve peak exercise O_2 consumption (VO_{2peak}), and quality-of-life in older patients with obese heart failure with preserved ejection fraction. However, ≈35% of weight lost during CR+AT was skeletal muscle mass. We examined whether addition of resistance training (RT) to CR+AT would reduce skeletal muscle loss and further improve outcomes.

METHODS: This study is a randomized, controlled, single-blind, 20-week trial of RT+CR+AT versus CR+AT in 88 patients with chronic heart failure with preserved ejection fraction and body mass index (BMI) ≥28 kg/m^2. Outcomes at 20 weeks included the primary outcome (VO_{2peak}); MRI and dual X-ray absorptiometry; leg muscle strength and quality (leg strength ÷ leg skeletal muscle area); and Kansas City Cardiomyopathy Questionnaire.

RESULTS: Seventy-seven participants completed the trial. RT+CR+AT and CR+AT produced nonsignificant differences in weight loss: mean (95% CI): −8 (−9, −7) versus −9 (−11, −8; P=0.21). RT+CR+AT and CR+AT had non-significantly differences in the reduction of body fat [−6.5 (−7.2, −5.8) versus −7.4 (−8.1, −6.7) kg] and skeletal muscle [−2.1 (−2.7, −1.5) versus −2.1 (−2.7, −1.4) kg] (P=0.20 and 0.23, respectively). RT+CR+AT produced significantly greater increases in leg muscle strength [4.9 (0.7, 9.0) versus −1.1 (−5.5, 3.2) Nm, P=0.05] and leg muscle quality [0.07 (0.03, 0.11) versus 0.02 (−0.02, 0.06) Nm/cm^2, P=0.04]. Both RT+CR+AT and CR+AT produced significant improvements in VO_{2peak} [108 (958, 157) versus 80 (30, 130) mL/min; P=0.001 and 0.002, respectively], and Kansas City Cardiomyopathy Questionnaire score [17 (12, 22) versus 23 (17, 28); P=0.001 for both], with no significant between-group differences. Both RT+CR+AT and CR+AT significantly reduced LV mass and arterial stiffness. There were no study-related serious adverse events.

CONCLUSIONS: In older obese heart failure with preserved ejection fraction patients, CR+AT produces large improvements in VO_{2peak} and quality-of-life. Adding RT to CR+AT increased leg strength and muscle quality without attenuating skeletal muscle loss or further increasing VO_{2peak} or quality-of-life.

HFpEF | exercise training in obese

Circulation: Heart Failure

ORIGINAL ARTICLE

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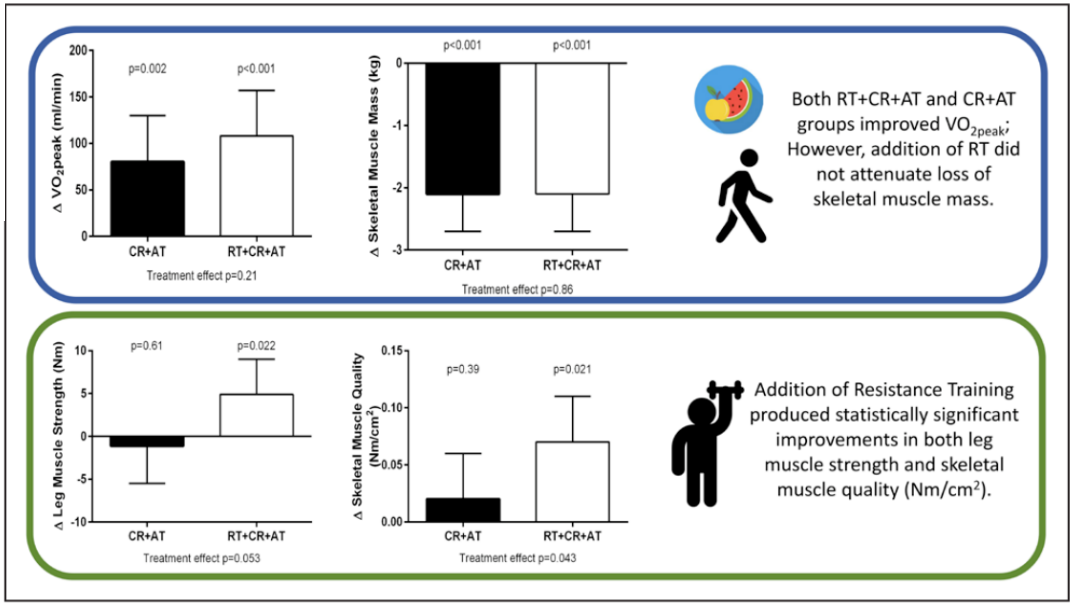

Figure 2. Effect sizes for the primary (peak VO_2) and key secondary outcomes (strength and body/muscle composition) from baseline to 20-week follow-up.

AT indicates aerobic exercise training; CR, caloric restriction; RT, resistance training; and VO_{2peak} m/min, peak exercise oxygen consumption.

HFpEF | acute decompensated HF trial

JACC: HEART FAILURE
VOL. 9, NO. 10, 2021

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Rehabilitation Intervention in Older Patients With Acute Heart Failure With Preserved Versus Reduced Ejection Fraction

Robert J. Mentz, MD,[a] David J. Whellan, MD, MHS,[b] Gordon R. Reeves, MD, MPT,[c] Amy M. Pastva, PT, MA, PhD,[d] Pamela Duncan, PT, PhD,[e] Bharathi Upadhya, MD,[f] M. Benjamin Nelson, MS,[f] Haiying Chen, PhD,[g] Shelby D. Reed, PhD,[h] Paul B. Rosenberg, MD,[a] Alain G. Bertoni, MD, MPH,[i] Christopher M. O'Connor, MD,[j] Dalane W. Kitzman, MD[f,k]

ABSTRACT

OBJECTIVES This study assessed for treatment interactions by ejection fraction (EF) subgroup (≥45% [heart failure with preserved ejection fraction (HFpEF); vs <45% [heart failure with reduced ejection fraction (HFrEF)]).

BACKGROUND The REHAB-HF trial showed that an early multidomain rehabilitation intervention improved physical function, frailty, quality-of-life, and depression in older patients hospitalized with acute decompensated heart failure (ADHF).

METHODS Three-month outcomes were: Short Physical Performance Battery (SPPB), 6-min walk distance (6MWD), and Kansas City Cardiomyopathy Questionnaire (KCCQ). Six-month end points included all-cause rehospitalization and death and a global rank of death, all-cause rehospitalization, and SPPB. Prespecified significance level for interaction was $P \leq 0.1$.

RESULTS Among 349 total participants, 185 (53%) had HFpEF and 164 (47%) had HFrEF. Compared with HFrEF, HFpEF participants were more often women (61% vs 43%) and had significantly worse baseline physical function, frailty, quality of life, and depression. Although interaction *P* values for 3-month outcomes were not significant, effect sizes were larger for HFpEF vs HFrEF: SPPB +1.9 (95% CI: 1.1-2.6) vs +1.1 (95% CI: 0.3-1.9); 6MWD +40 meters (95% CI: 9 meters-72 meters) vs +27 (95% CI: −6 meters to 59 meters); KCCQ +9 (2-16) vs +6 (−2 to 14). All-cause rehospitalization rate was nominally lower with intervention in HFpEF but not HFrEF [effect size 0.83 (95% CI: 0.64-1.09) vs 0.99 (95% CI: 0.74-1.33); interaction $P = 0.40$]. There were significantly greater treatment benefits in HFpEF vs HFrEF for all-cause death [interaction $P = 0.08$; intervention rate ratio 0.63 (95% CI: 0.25-1.61) vs 2.21 (95% CI: 0.78-6.25)], and the global rank end point (interaction $P = 0.098$) with benefit seen in HFpEF [probability index 0.59 (95% CI: 0.50-0.68)] but not HFrEF.

CONCLUSIONS Among older patients hospitalized with ADHF, compared with HFrEF those with HFpEF had significantly worse impairments at baseline and may derive greater benefit from the intervention. (A Trial of Rehabilitation Therapy in Older Acute Heart Failure Patients [REHAB-HF]; NCT02196038) (J Am Coll Cardiol HF 2021;9:747-757)

HFpEF | acute decompensated HF trial

JACC: HEART FAILURE
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VOL. 9, NO. 10, 2021

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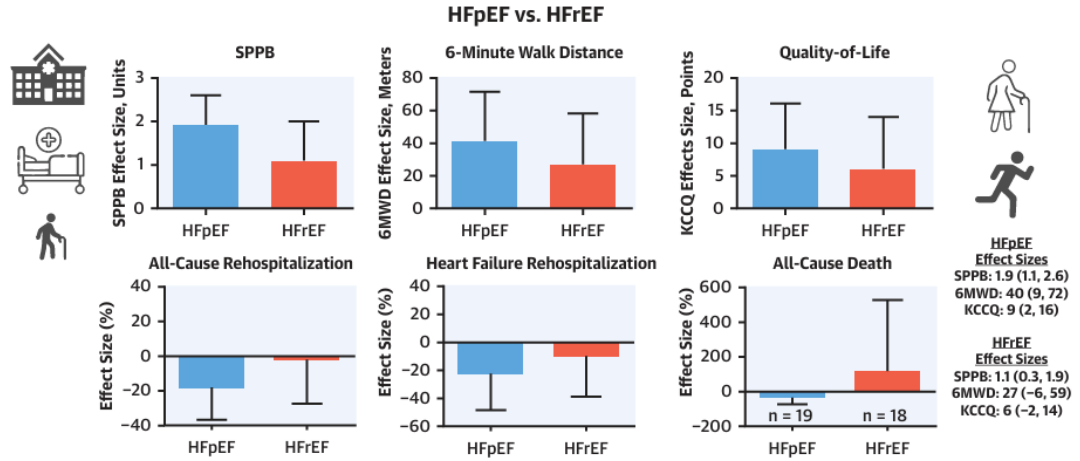
CENTRAL ILLUSTRATION Novel Rehabilitation Intervention in Older Patients With Acute Decompensated Heart Failure



Mentz, R.J. et al. J Am Coll Cardiol HF. 2021;9(10):747-57.

Effect of the novel REHAB-HF intervention in patients admitted with acute decompensated heart failure on outcomes at 3 months (SPPB, 6-min walk distance [6MWD], and quality of life [QOL]) and 6 months (all-cause rehospitalization, heart failure rehospitalization, all-cause death) in participants with HFpEF **(blue)** compared with HFrEF **(red)**. 6MWD = 6-min walk distance; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire (QOL); SPPB = Short Physical Performance Battery.

HFpEF | summary exercise training outcomes

Circulation Research

COMPENDIUM ON CARDIOPULMONARY DISEASE AND EXERCISE: MOLECULAR TO CLINICAL MECHANISMS

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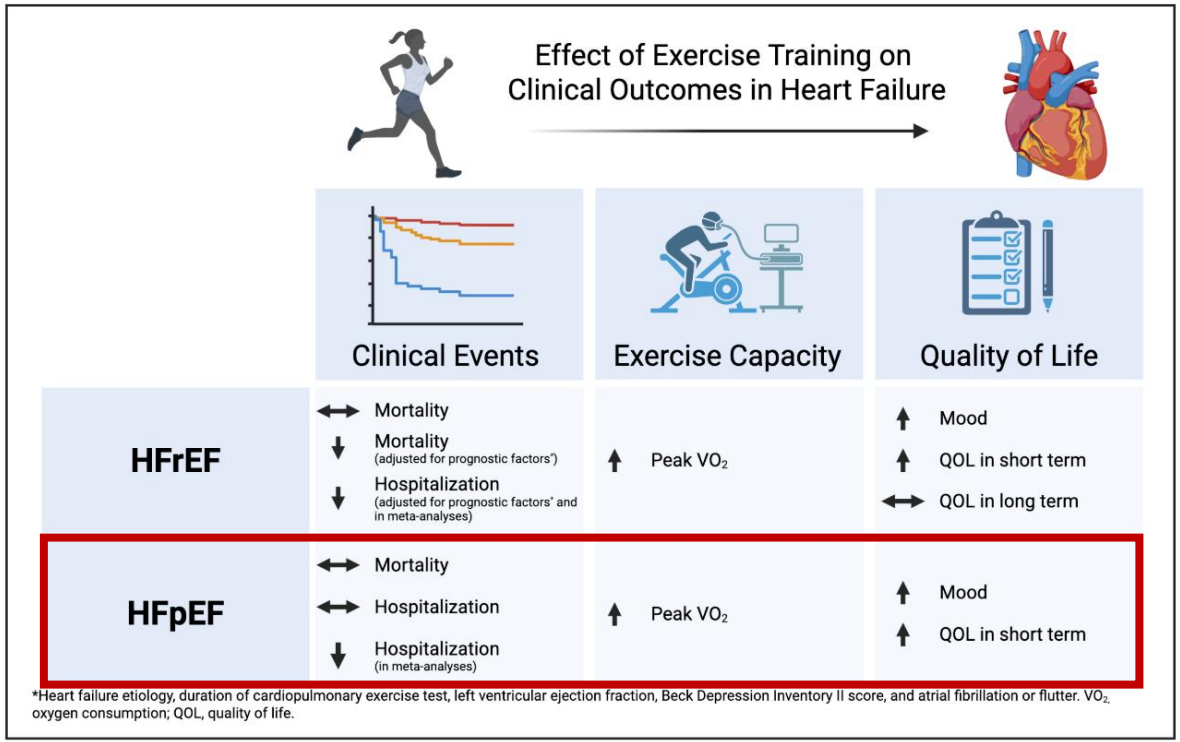
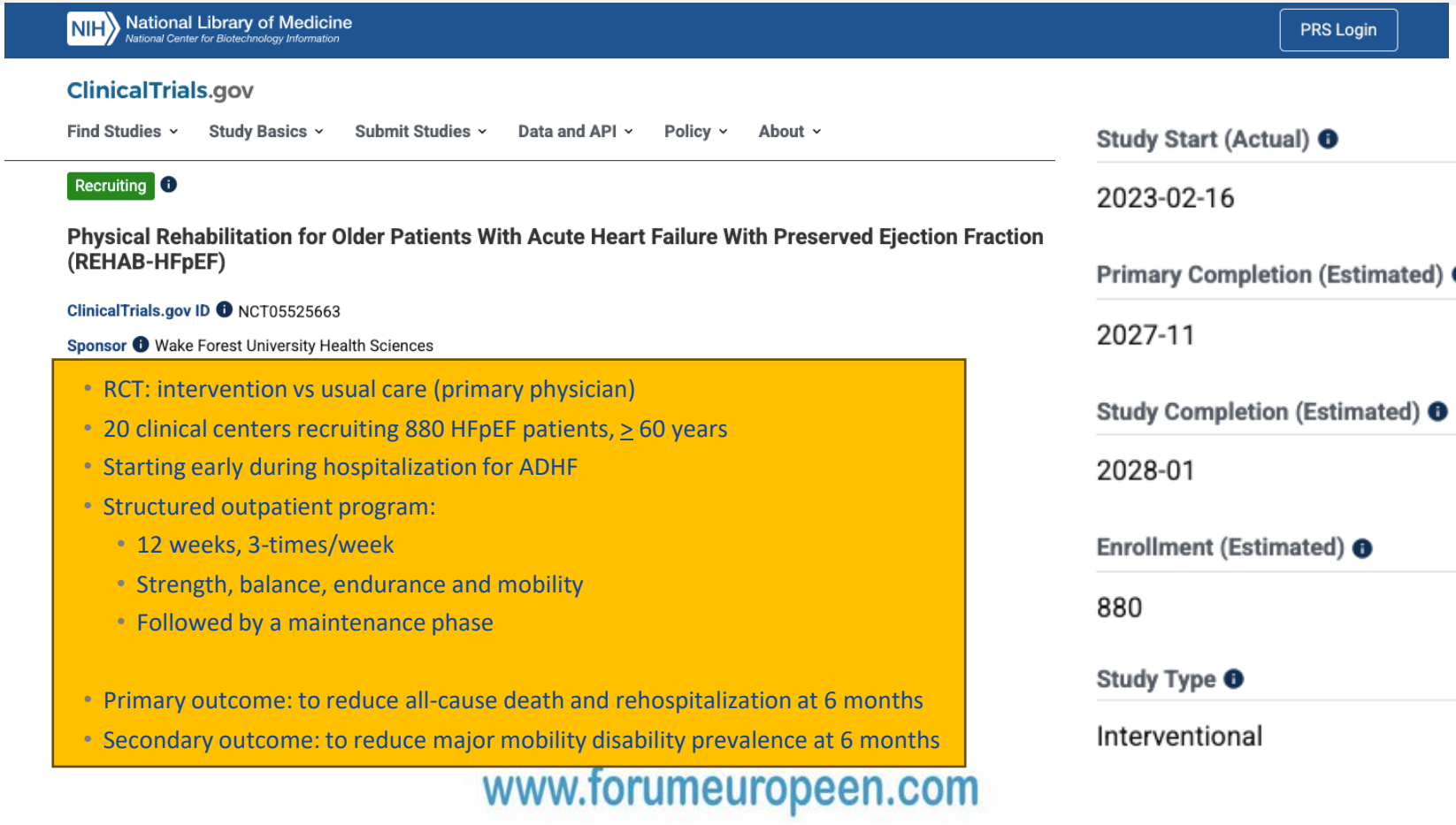


HFpEF | REHAB- HFpEF, ongoing



- RCT: intervention vs usual care (primary physician)
- 20 clinical centers recruiting 880 HFpEF patients, ≥ 60 years
- Starting early during hospitalization for ADHF
- Structured outpatient program:
  - 12 weeks, 3-times/week
  - Strength, balance, endurance and mobility
  - Followed by a maintenance phase
- Primary outcome: to reduce all-cause death and rehospitalization at 6 months
- Secondary outcome: to reduce major mobility disability prevalence at 6 months

HFpEF | take-home message

Exercise training, even without definitive evidence, seems interesting …

- to start early in the preclinical stage B and immediately after acute decompensation.
- to improve symptoms, exercise tolerance, and QoL.
- to confirm the positive trends regarding reducing hospitalizations and possibly mortality.