

Review

Impact of exercise on the 21st century epidemic of heart failure

Michael J. LaMonte

Department of Epidemiology & Environmental Health, School of Public Health and Health Professions, University at Buffalo – SUNY, Buffalo, NY, 14214, USA

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ABSTRACT

Heart failure (HF) poses a serious threat to public health in an aging population. HF with reduced ejection fraction (HFrEF) historically was the focus for developing prevention and management strategies, including exercise training in HFrEF patients. However, HF with preserved ejection fraction (HFpEF) is increasingly common among older adults. There are no well-established treatment options making its primary prevention critical. This article reviews the role of exercise in the prevention and management of HF. Selected published articles informed discussion of HF etiology, evidence for the role of exercise in HF, and the biologic mechanisms linking exercise with HF development and prognosis. HF is a complex syndromic condition that manifests with severe exercise intolerance. Several causes of HF-related exercise intolerance respond to exercise training and two randomized controlled exercise interventions in HFrEF patients have demonstrated safety and efficacy for improved physical work capacity, quality of life, and mortality endpoints in medically stable HF patients. At present, only epidemiological cohort data are available for HFpEF outcomes, but the data are generally consistent in supporting lower risk of HFpEF development with levels of lifestyle physical activity meeting recommended amounts. Clinical trial evidence is needed to support this observation in HFpEF. Exercise training is established as part of guideline directed treatment of HFrEF patients. Lifestyle physical activity at guideline recommended amounts appears to be associated with lower risk of developing both HFrEF and HFpEF. There has yet to be a definitive clinical trial on exercise training and HFpEF treatment.

1. Introduction

Cardiovascular disease (CVD) mortality among adults living in the United States (US) rose to an all-time high by the middle of the 20th century, with age-standardized CVD mortality of ≈ 315 and ≈ 440 deaths per 100 000 in 1900 and 1960, respectively.¹ This was followed by a steady decline in CVD mortality of about 60% by 1999. Several factors contributed to the impressive downward temporal trend in CVD mortality, notably improved recognition and management of acute myocardial infarction and the identification of major modifiable CVD risk factors and implementation of community strategies for their control.² Together these achievements resulted in less coronary heart disease, which accounts for the largest proportion of CVD deaths annually in U.S. adults. Coronary heart disease had been considered the CVD epidemic of the 20th century,² and its reduction over the past 50 years is considered one of the most significant public health accomplishments ever.¹ However, the reductions in age-standardized CVD mortality may provide somewhat of a false sense of security given the rapidly increasing size of the population ages 65 and older.

As the U.S. population average age continues to increase, and with greater proportions of women and men living into their 80s and 90s, the absolute number of CVD deaths might increase despite any apparent decline in CVD mortality based on age-standardized data. Indeed, during the time interval 1960–2000 while age-standardized mortality declined by 60%, the absolute number of CVD deaths stayed between 800 000 and 900 000 annually.³ Not only will an aging baby-boomer generation contribute to the community burden of CVD during the 21st century, but so too will emergence of another CVD epidemic – *heart failure*.

2. Heart failure overview

Heart failure (HF) is a disease of aging with more than 80% of existing HF cases in adults aged 65 and older.⁴ HF is a syndromic condition with complex etiologic progression involving systolic (e.g., impaired myocardial contraction and reduced ejection of blood) and diastolic (e.g., impaired myocardial relaxation and increased filling pressures) cardiac dysfunction, microvascular inflammation and endothelial dysfunction (e.g., oxidative stress, impaired vasodilation, myocardial stunning,

E-mail address: mlamonte@buffalo.edu.

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List of abbreviations:

ADL,	Activities of daily living
AMPK	5' adenosine monophosphate-activated protein kinase
CI	confidence interval
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVD	cardiovascular disease
GLUT-4	glucose transporter type 4
HF	heart failure
HF-ACTION	Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training
HFpEF	heart failure with preserved ejection fraction
HFrfEF	heart failure with reduced ejection fraction
h	hour
IGF-1	insulin-like growth factor 1
IL-6	interleukin 6

LVEF	left ventricular ejection fraction
MET	metabolic equivalent
MET-h/week	metabolic equivalent hours per week
Min	minute
OPACH	Objective Physical Activity and Cardiovascular Health in Older Women Study
QOL,	quality of life
PPAR	peroxisome proliferator-activated receptor
Reps	repetitions
RPE	rate of perceived exertion
REHAB-HF	Rehabilitation Therapy in Older Acute Heart Failure Patients
SD	standard deviation
WHI	Women's Health Initiative
Wk	week
VO _{2peak}	peak oxygen uptake

microvascular stiffening), impaired myocardial energy transfer, and maladaptive peripheral responses.⁵ Typical symptoms that lead to HF diagnosis are dyspnea, fatigue, exercise intolerance, orthopnea, and peripheral edema. At present, about 7 million U.S. adults have HF with an expected increase to 9 million by 2030.⁴ HF accounted for 45% of all CVD mortality (85 855 deaths) in 2020 and is the number one reason for hospitalization in adults 65 and older, in 2019: 1 297 000 hospital discharges.³ At age 50, an adult without prior HF has a lifetime residual risk of developing HF close to 50%. HF progresses over defined stages (Table 1) from development of HF risk factors (Stage A) to cardiac structural abnormalities (Stage B) to overt clinical disease (Stage C) and end-stage decompensation (Stage D).⁴ HF is broadly classified into two subtypes based on left ventricular ejection fraction: HF with preserved ejection fraction (HFpEF)⁶ or with reduced ejection fraction (HFrfEF),⁷ the former $\geq 50\%$ EF and the latter $\leq 40\%$ EF. About half of acute HF hospitalizations are HFpEF. Fig. 1 contrasts HFpEF and HFrfEF structural, functional, and clinical characteristics. A key difference is the history of prior myocardial infarction is common in HFrfEF but not HFpEF.

Table 1
Stages of heart failure.

STAGE	DEFINITION	CHARACTERISTICS
A	At Risk	<ul style="list-style-type: none"> • Presence of HF risk factors^a • No current or prior HF signs/symptoms • No structural cardiac changes • No cardiac biomarker elevations
B	Pre-HF	<ul style="list-style-type: none"> • Current or prior HF signs/symptoms^b with ≥ 1 of: <ul style="list-style-type: none"> ✓ Structural cardiac abnormality^c ✓ Functional cardiac abnormality^d ✓ Elevated BNP or cardiac troponin
C	HF	<ul style="list-style-type: none"> • Current or prior HF signs/symptoms • Structural cardiac abnormality • Functional cardiac abnormality
D	Advanced HF	<ul style="list-style-type: none"> • Severe HF symptoms at rest • Recurrent hospitalization despite medical therapy • Requiring advanced therapies: <ul style="list-style-type: none"> • Cardiac transplantation • Mechanical circulatory support • Palliative care

HF, heart failure; BNP, brain natriuretic peptide.

^a Include obesity, hypertension, diabetes, sedentary lifestyle.

^b Include fatigue, unusual shortness of breath at rest or on exertion, exercise intolerance, swelling in the abdomen or extremities, inability to sleep lying flat.

^c Refers to abnormalities of the heart valves, chamber dimensions, or myocardium.

^d Refers to abnormalities in cardiac contraction, relaxation, chamber filling and emptying.

Furthermore, HFpEF is far more common in women at older ages, the most rapidly growing population age subgroup. In fact, the possibility has been raised that HFpEF could be one component of a broader *frailty phenotype* that results in accelerated biologic aging, physical and cognitive impairment, and premature mortality.⁸ Unlike HFrfEF where decades of scientific investigation fostered establishment of successful clinical management strategies, at present there are few available therapies for HFpEF making its primary prevention paramount to public health.

3. Exercise and HF

Exercise training and regular lifestyle physical activity are well-established in the prevention and management of clinical atherosclerotic CVD and in controlling several of its major modifiable risk factors.⁹ Evidence for the role of exercise and physical activity in HF treatment and prevention continues to evolve. Because many of the central and peripheral mechanisms of HF respond favorably to exercise, the use of exercise in HF management has been studied most rigorously.

3.1. Exercise and HF management

HF patients have severe exercise intolerance secondary to impaired oxygen delivery and/or use by contracting skeletal muscle. Fig. 2 summarizes the known or suspected central and peripheral mechanisms of exercise intolerance in HF patients. In addition to exercise intolerance, reduced independence and poorer overall quality life are typical in patients with worsening HF. Current clinical practice guidelines^{10,11} indicate that supervised exercise training is a safe and efficacious intervention as part of a holistic treatment plan in clinically stable HFrfEF and HFpEF patients. Several high-quality randomized secondary prevention trials support these practice guidelines.^{12,13} It is beyond the scope of the present manuscript to review in detail these previous studies, however, some salient features will be noted. Perhaps the two most recognized randomized trials of exercise in HF patients are HF-ACTION (Heat Failure and A Controlled Trial Investigating Outcomes of Exercise Training)^{14,15} and REHAB-HF (Rehabilitation Therapy in Older Acute HearT Failure Patients).^{16,17} Table 2 summarizes these landmark trials. In HF-ACTION, all randomized patients had HFrfEF whereas this was true of 47% of those randomized in REHAB-HF. Exercise training was exclusively aerobic walking or cycling in HF-ACTION, whereas REHAB-HF was multifaceted including aerobic, strengthening, mobility, and balance exercises. The primary outcome was all-cause mortality or hospitalization in HF-ACTION and was change in physical function score in REHAB-HF. Based on intent to treat primary analysis, HF-ACTION demonstrated a nonsignificant 7%

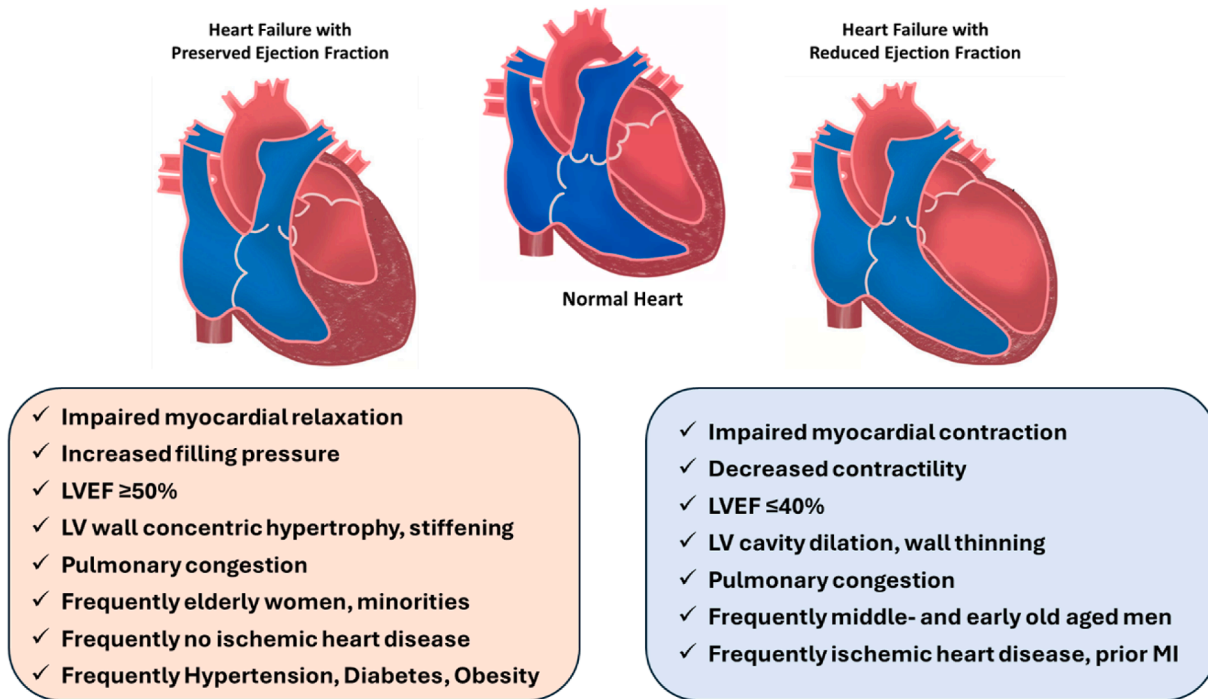


Fig. 1. Comparison of heart failure (HF) with preserved versus reduced ejection fraction. LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

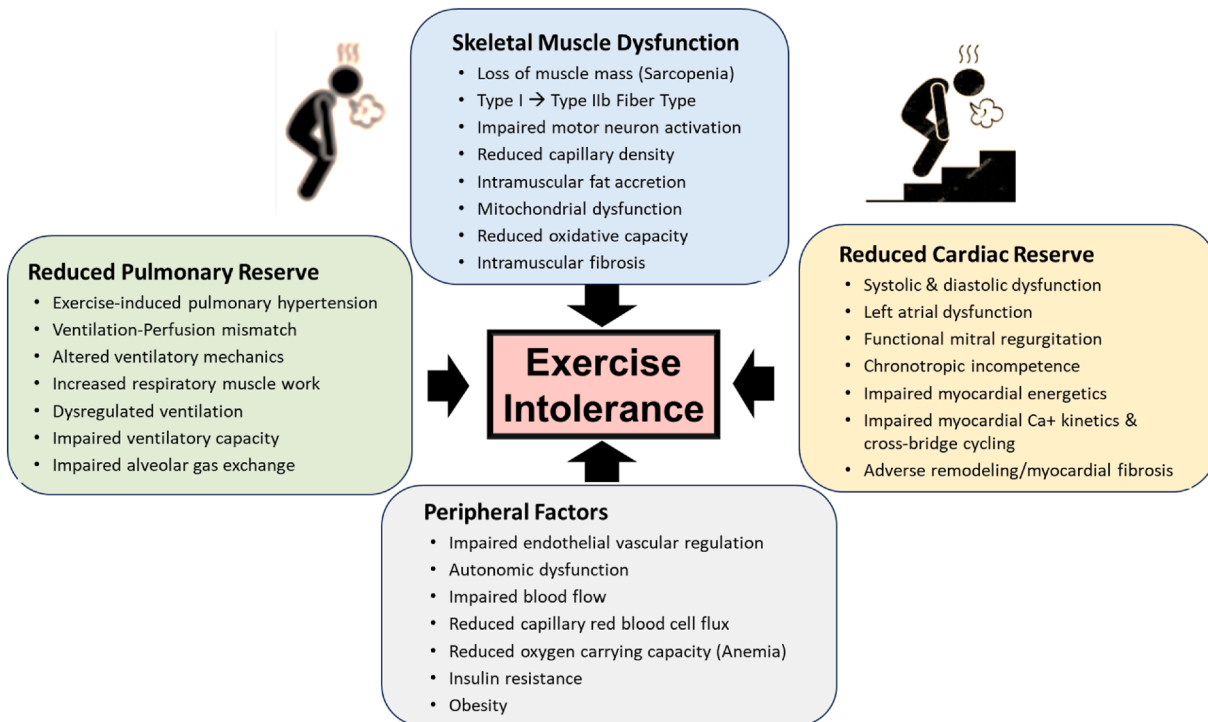


Fig. 2. Potential central and peripheral mechanisms underlying exercise intolerance in heart failure.

($p = 0.13$) reduction in clinical events; REHAB-HF demonstrated a significant improvement in physical function score (+ 1.5 units, $p < 0.001$). In secondary analyses, a significant reduction of 11% ($p = 0.03$) in all-cause mortality/hospitalization was evident in HF-ACTION when statistical models accounted for prognostic factors. Secondary analyses further demonstrated significant improvements in physical functioning (6-min walk distance) and QOL. In REHAB-HF, secondary analyses

showed significantly improved quality of life (QOL) and a nonsignificant 7% reduction in hospitalization. In both trials, there were no significant differences in major adverse (safety) events between intervention and comparison groups. Because REHAB-HF was a mix of both HFpEF and HFREF patients, secondary analyses compared the intervention effect accordingly.¹⁸ HFpEF patients had slightly better improvement in Short Physical Performance Battery (SPPB) score (+ 1.9 vs. + 1.1, $p = 0.20$)

Table 2
Overview of the HF-ACTION and REHAB-HF randomized trials on exercise training in HF patients.

TRIAL	TARGET ENROLLMENT	INCLUSION	EXERCISE INTERVENTION	OUTCOMES	RESULTS
HF-ACTION¹⁵	<i>n</i> = 3 000 Randomized 1:1 to intervention (exercise) or comparison (usual care). Stratified on clinical site and HF etiology (ischemic, nonischemic). <u>90% power:</u> 11% reduction primary outcome in 2.5 years.	LVEF ≤ 35% Chronic HF Age ≥ 18 years; Medically stable; NYHA class II-IV; Able to safely begin exercise program	Modality: Walk or cycle Phase 1: Clinic, Wk 1–2, 3 days/wk; 15–30 min/day; 60% HRR. Phase II/III: Clinic/Home, Wk 3–6/7–12, 3 days/wk; 30–35 min/day; 70% HRR Phase IV: Home, Wk 13 to end. 5 days/wk, 40 min/day, 60%–70% HRR.	Primary: All-cause mortality, All-cause hospitalization. Secondary: ̇V _{O_{2peak}} ; 6-Min Walk Distance; QOL.	<i>n</i> = 2 331 randomized. Median LVEF 25%; median age 59; 28% women; median follow-up 30 mo. Intent to Treat: HR 0.93 (95% CI: 0.84, 1.02), <i>p</i> = 0.13 Secondary analysis: Primary outcome adjusted for prognostic factors, HR 0.89 (95% CI: 0.81, 0.99), <i>p</i> = 0.03. Change ̇V _{O_{2peak}} + 0.7 vs. + 0.1, <i>p</i> < 0.001. Change 6-Min Walk Distance, + 20 m vs + 5 m, <i>p</i> < 0.001. Change QOL score, + 1.93, <i>p</i> < 0.001. <i>n</i> = 349 randomized. Mean age 72; 52% women; 53% LVEF ≥ 45%. Intent To Treat: + 1.5 SPPB units (95% CI: 0.9, 2.0), <i>p</i> < 0.001. Change 6-Min Walk distance, + 34 m, <i>p</i> < 0.05. Secondary analysis: HR 0.93 (95% CI: 0.66, 1.19). Change QOL, + 7.1 units, <i>p</i> < 0.05.
REHAB-HF¹⁷	<i>n</i> = 360 Randomized 1:1 to intervention or comparison. Stratified on clinic site and LVEF (< 45, ≥ 45). <u>80% power:</u> 1.1 unit increase in SPPB score at 3 mo. 25% reduction hospitalization at 6 mo.	LVEF = no restriction. Acute HF Age ≥ 60 years; Performing ADLs prior to HF admission; Able to walk 4 m.	Modality: Aerobic, Strengthening, Mobility, Balance exercises. 3 days/wk, 60 min/day. Intensity: RPE (6–20 scale) Wk 1–2: RPE ≤ 12. Wk 3: aerobic RPE 11–15, strength RPE 15–16. Wk 4 and beyond: RPE that results in heart rate ≥ 20 beats above resting.	Primary: SPPB function score (range: 0 to 12) at 3 months. 6-Min Walk distance. Secondary: All-cause hospitalization at 6 months. QOL at 3 months.	

ADL, aids to daily living; HF, heart failure; RPE, LVEF, left ventricular ejection fraction; HR, hazard ratio; mo, months; m, meters; min, minutes; wk, week; HRR, heart rate reserve; SPPB, Short Physical Performance Battery function test; QOL, quality of life score; RPE, rate of perceived exertion; ̇V_{O_{2peak}}, peak oxygen uptake.

and 6-min walk distance (+ 40 vs. + 27 m, $p = 0.54$) than did HFREF, though differences did not achieve statistical significance. A similar pattern of slightly better but nonsignificant intervention effect on clinical endpoints were evident in HFpEF for hospitalization (rate ratio 0.95, $p = 0.40$) and all-cause mortality (rate ratio 0.14, $p = 0.08$). These findings suggest HFpEF patients might benefit more from this multifaceted exercise intervention than do their HFREF counterparts, however, confirmation is required.

Given HF is increasingly common with older ages where frailty could impact exercise benefit, secondary analysis in HF-ACTION evaluated the intervention effect according to frailty status.¹⁹ About 29% of those randomized were classified as being frail (Rockwood frailty score > 0.21). There was a significant frailty by treatment interaction ($p = 0.02$) such that lower risk of the primary outcome was present in frail (HR 0.83) but not in nonfrail (HR 1.04) HFREF patients. A smaller randomized exercise intervention in mostly HFREF patients found no difference (interaction $p = 0.53$) in death or hospitalization based on the exercise treatment by frailty interaction.²⁰ How frailty influences exercise training benefit in HF patients deserves further investigation. Comprehensive meta-analyses of exercise intervention effects on physiologic measures, QOL, and clinical outcomes in HFpEF^{21,22} and HFREF²³ have generally agreed with the results of HF-ACTION and REHAB-HF.

3.2. Exercise and HF prevention

At present, there has not been a large-scale randomized trial evaluating exercise for primary HF prevention. Thus, available evidence derives from epidemiologic cohort studies. Interestingly, national guidelines on exercise for public health in the 1990s^{24–26} and 2008²⁷ did not include recommendations specific to HF because of insufficient evidence published during the time interval 1950 through 2006. However, the 2nd edition of Physical Activity Guidelines for Americans in 2018 did include a recommendation for HF.²⁸ Based on meta-analysis of available published prospective cohort data that met quality criteria for inclusion,

among adults without prior history of HF at baseline the relative risk of developing HF was 0.70 (95% CI: 0.67, 0.73) when comparing the highest to the lowest self-reported exercise groups. This suggests a 30% lower risk of HF associated with greater amounts of exercise. Moreover, unlike the curvilinear dose-response between exercise and CVD incidence where the greatest benefit is observed over the early portion of the dose-response curve, for HF incidence the dose-response appears to be fully linear over the range of self-reported exercise studied. The time interval between the 2008 and 2018 physical activity guidelines illustrates the recency of accumulated understanding about exercise and risk of developing HF, as reviewed elsewhere.^{29,30}

3.3. Exercise and HFpEF in women

Few studies to date have evaluated the relationship of exercise with HFREF and HFpEF separately. This was a major research gap identified in the 2018 revision of the Physical Activity Guidelines for Americans.²⁸ Findings from the Women's Health Initiative (WHI)³¹ were one of the first published studies to address this issue. Self-reported leisure activity was assessed by questionnaire in 161 808 postmenopausal women ages 50–79 years at WHI enrollment (1993–1998).³² Participants were then followed-up annually for hospitalized acute decompensated HF which was confirmed by physician medical record reviews. A subset of 44 000 women had expanded HF adjudication that involved imaging and biomarker information required to define HFpEF and HFREF. During a mean follow-up of 14 years there were 2 523 adjudicated cases of incident acute HF in which information was available to classify 734 cases of HFpEF and 452 cases of HFREF. Fig. 3 shows significant inverse associations ($p < 0.001$, each) between categories of total weekly physical activity and each HF endpoint controlling for age and other relevant factors. Risks of overall HF, HFpEF, and HFREF were 35%, 32%, and 32% lower when comparing the highest and lowest activity groups. Importantly, women who met current recommended amounts of physical activity (≥ 7.5 metabolic hours per week [MET-h/week]) had significant HF risk reduction. There were no significant differences in the

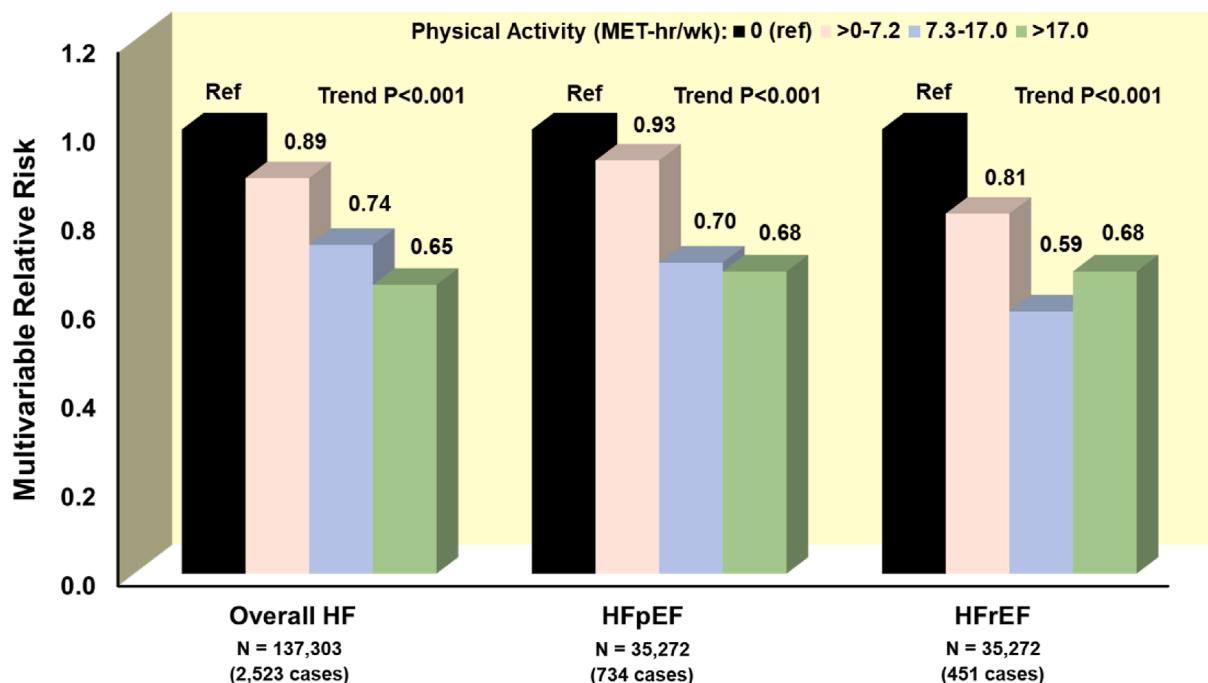


Fig. 3. Relative risks of overall heart failure and of heart failure with preserved or reduced ejection fraction according to levels of self-reported total recreational physical activity during an average follow-up of 14-years in the Women's Health Initiative.³² Relative risks are adjusted for age, race and ethnicity, education, income, smoking, alcohol, menopausal hormone therapy, parity, and hysterectomy status. MET-h/wk, metabolic equivalent hours per week. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; MET-h/wk, metabolic equivalent hours per week.

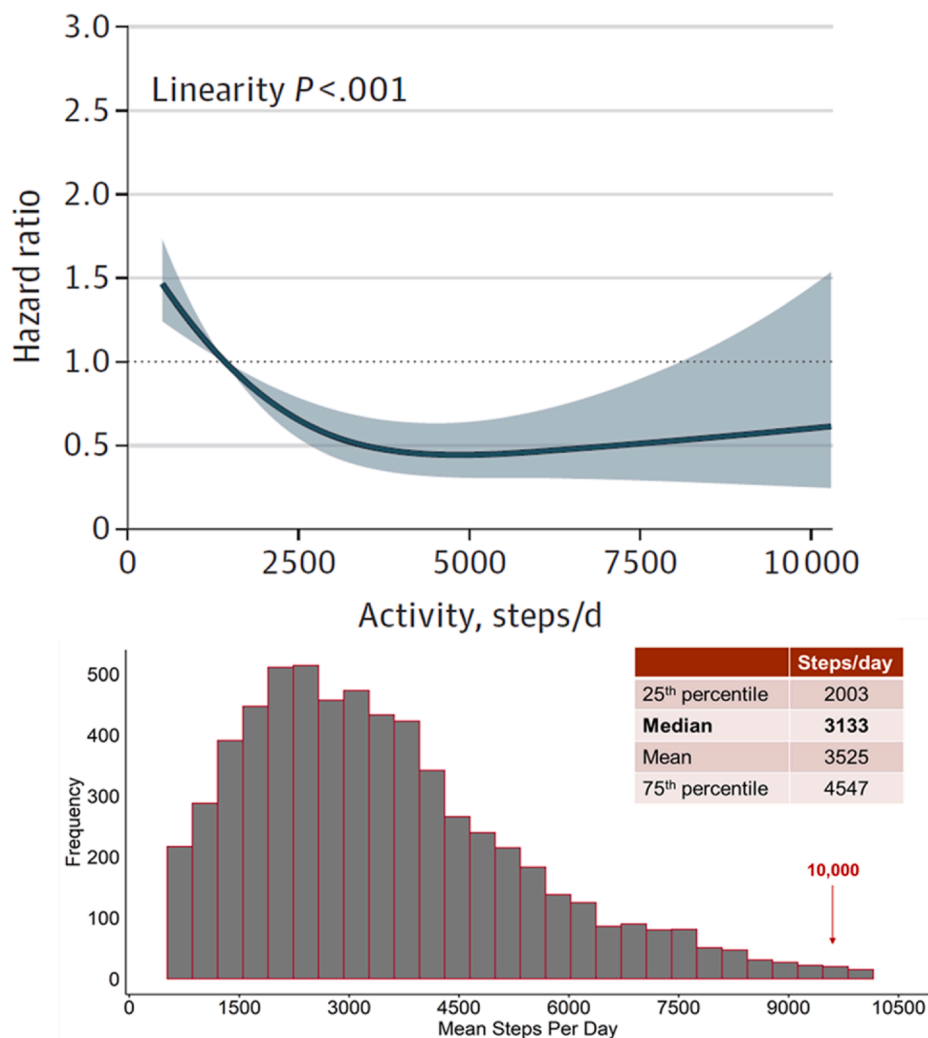


Fig. 4. Dose-response for HFpEF risk according to accelerometer-measured steps per day in ambulatory women ages 63–99 years in the OPACH Study.³⁴ The curve was estimated using restricted cubic spline regression with knots at the 10th, 50th, and 90th percentiles. Shaded area is the 95% confidence interval. Model covariates included age, race and ethnicity, education, alcohol, smoking, self-rated general health, walking device use, physical function score. History of hypertension, history of atrial fibrillation, and multimorbidity score.

inverse associations when stratified on subgroups defined by age or race and ethnicity. Because HFpEF preferentially afflicts older women and racial-ethnic minorities, these findings from the WHI were very encouraging regarding a potential role of lifestyle physical activity in primary prevention of HFpEF.

Self-reported physical activity is measured with error and can provide an incomplete assessment of daily movement especially for habitual light intensity activities that are typical of an older adult's life.³³ The WHI Objective Physical Activity and Cardiovascular Health (OPACH) Study in Older Women began to address this by deploying triaxial accelerometers to be worn at the hip 24-h/day for 7 consecutive days in more than 6 000 ambulatory women ages 63–91 years who were then followed during a mean 7.5 years for development of HF (407 cases), HFpEF (257 cases), and HFrEF (110 cases).³⁴ In this study, about 85% of total daily movement time was in light intensity activity. Controlling for age, sociodemographic, lifestyle, and clinical factors, a 1-standard deviation (*SD*) unit (72 min) increment in light intensity daily activity was associated with a significant 13% ($p = 0.01$) and 21% ($p = 0.001$) lower risk of overall HF and HFpEF. Light activity was not associated with HFrEF risk. Recent findings in the prospective United Kingdom (UK) Biobank accelerometer substudy showed similarly evidence for an inverse association between wrist-worn accelerometer-measured light intensity activity and risk of overall HF in younger and middle-aged adults.³⁵ This study did not evaluate HFpEF or HFrEF separately.

Translating physical activity levels to public health practice can be

challenging and there is increasing interest in using device-measured steps per day as a metric. Fig. 4 shows the dose-response curve for accelerometer-measured steps per day and risk of HFpEF.³⁴ Below the curve is the frequency distribution of steps per day in these older women, notice the median is about 3 100 steps. A significant inverse association ($p < 0.001$) is evident with a near linear relationship over the number of steps per day where the greatest frequency occurs (e.g., 1 500–3 000 steps). Each 2 500 steps per day increment was associated with a 30% lower risk of HFpEF ($p < 0.01$). A similar pattern of inverse association was evident for steps per day in light intensity and those in moderate-to-vigorous intensity activities. These findings suggest that even routine daily activity of sufficient amounts might favorably influence risk of developing HFpEF in later life. Indeed, walking 1 500–2 500 steps per day seems well within reach of many ambulatory older U.S. women, among whom the mean steps per day is about 2 340 steps based on public health surveillance data.³⁶ Thus, the population effect for preventing HFpEF at older ages through increased walking activity could be considerable.

4. Resistance activity in HF

The overwhelming number of published studies have evaluated aerobic exercise in relation to HF management or prevention. However, there is compelling evidence that skeletal muscle dysfunction is part of the peripheral component of HF.^{37,38} Compared to healthy controls, HF

patients have skeletal muscle atrophy (decreased myofibrillar cross-sectional area) and lower skeletal muscle strength and power, shifts in myofibril type from slow-twitch oxidative type I fibers to fast twitch glycolytic type IIb fibers, elevated myostatin-2 (inhibits muscle growth), smaller mitochondria and impaired oxidative function, impaired intrafibrillar calcium kinetics and excitation-contraction coupling, reduced myosin heavy chain protein content, reduced capillary recruitment during muscle contraction, increased sensitivity to sympathetic nervous activity and resulting intramuscular vasoconstriction, local myokine perturbation (increased skeletal muscle IL-6, reduced IGF-1) promoting catabolism, suppression of AMPK/GLUT4 signaling resulting in impaired glucose and fatty acid metabolic pathways. Evidence is accumulating that resistance exercise improves skeletal muscle mass, fiber morphology and histochemistry, and skeletal muscle functional measures in HF patients.^{39–41} In an exercise intervention, women 65 and older with medically managed stable HFrEF (mean LVEF 36%) were randomized to a 10 week resistance training program (3 days/week, 60 min/day, 80% 1-repetition maximum) or comparison group (stretching exercise only).⁴¹ Compared to controls, the resistance exercise group significantly increased 6-min walk distance (+ 49 vs. –3 m, $p < 0.05$) and this improvement in functional capacity was correlated ($p < 0.05$, all) with improved knee extensor muscle strength ($r = 0.59$) and endurance ($r = 0.63$), type I fiber area ($r = 0.61$), and oxidative enzyme capacity ($r = 0.57$). There were no significant differences in total body muscle mass (resistance group 13.6 vs. control 13.5 kg, $p = 0.30$) which suggests that muscle quality rather than quantity might be a key aspect connecting skeletal muscle dysfunction with HF. In the UK Biobank cohort of 468 941 adults without prior HF, low dominant hand grip strength was associated with an approximate 2-fold higher risk ($p < 0.05$) of developing HF after controlling for several demographic and clinical factors and aerobic exercise levels.⁴² In a study on 5-year survival in medically stable HFrEF patients (LVEF mean 21%), when included in a statistical model together with peak oxygen uptake and maximal workload achieved at peak cycle exercise, knee flexor strength was associated with longer survival ($p = 0.005$) whereas neither measure of aerobic capacity was associated with survival. There appears to be a role of skeletal muscle morphology and function in HF development and possibly prognosis. Given the relative paucity of published data on the topic, particularly differentiating HFpEF and HFrEF, additional research should be a high priority in the clinical and exercise research communities.

5. Mechanisms of exercise in HF prevention or management

As the ability to evaluate molecular aspects of responses to exercise stimulus has evolved in recent decades, there is a deeper understanding of both acute responses and chronic adaptations to exercise that might serve as mechanisms for preventing and treating HF. Three recent publications elegantly summarize current understanding.^{43–45} It is likely that aerobic and resistance exercise illicit direct or indirect beneficial responses in many of the underpinnings of HF-related exercise intolerance shown in Fig. 2 that manifests over the progression of HF stages A-C in Table 1. While an oversimplification, major mechanistic pathways include *metabolic*, *neurovascular*, and *structural* domains, briefly summarized below based on the aforementioned reviews.^{43–45}

5.1. Metabolic

Exercise, both acute and chronic, enhances skeletal and cardiac muscle non-oxidative and oxidative pathways via beta-adrenergic signaling and activation of 5' adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR- γ) cascades and nitric oxide synthase to increase mitochondrial biogenesis and maintain or improve metabolic integrity. Mitigating both oxidation of lipoproteins and the formation of advanced glycosylated end-products within skeletal and cardiac muscle also controls

local oxidative stress and inflammation which, left unchecked, is damaging to both muscle compartments. Exercise-related improvement in lipid and carbohydrate metabolism within skeletal and cardiac muscle also contributes to regulation of blood lipid profile, insulin receptor sensitivity, non-insulin mediated blood glucose clearance, and adiposity. These metabolic changes also would be anti-atherogenic and mitigate coronary artery disease progression.

5.2. Neurovascular

Arterial regulation, and its impact on tissue perfusion, is another focus where exercise has documented benefits that could impact HF. Increased sympathetic (adrenergic) activity is an important aspect of myocardial remodeling (stiffening) and impaired function (reduced contractility and/or relaxation). Heightened adrenergic tone activates the renin-angiotensin-aldosterone system which increases myocardial contractility (oxygen demand), renal sodium and water retention (volume overload), and systemic arterial remodeling (stiffening) and vasoconstriction (afterload). The combined effect of increased myocardial oxygen demand and myocardial volume overload lead to release of cardiac troponins (cTnT, cTnI) and natriuretic peptides (Atrial NP, Brain NP), each having demonstrated diagnostic and prognostic utility in HF. Overexpression of bioactive molecules locally and peripherally to the myocardium accelerates HF progression with a worsening clinical outlook.

Exercise improves sympathetic nervous outflow as measured by circulating catecholamine concentration⁴⁶ and heart rate variability.⁴⁷ Exercise also is well-established in preserving or restoring endothelial function including nitric oxide vasomotor response.^{48,49} This contributes to enhanced blood pressure regulation which, in turn, reduces afterload and myocardial energy demand during systole. Recent post-hoc analysis in a randomized trial on exercise training in frail elderly adults showed a significantly lower circulating cardiac troponin-T concentration after 1-year in the intervention compared to control group.⁵⁰ This suggests that exercise could mitigate even sub-clinical cardiac aging and loss of resiliency in later life when HF susceptibility heightens.

5.3. Structural

Exercise also has demonstrated benefit on cardiac structure and function that may mitigate adverse myocardial remodeling and preserve both systolic and diastolic function.⁵¹ Starling mechanism preservation has been documented in HF patients following exercise training⁵² which could enhance efficiency of myocardial work. The hemodynamic stimulation by exercise enhances luminal shear stress and oblique wall stress which can foster beneficial changes in arterial wall architecture, peripherally and within the myocardium.⁵³ Larger coronary artery size has been documented in exercisers compared to their non-exercise peers.⁵⁴ These structural adaptations are likely mediated, in part, through insulin-like growth factor-1/phosphoinositide 3-kinase pathway activity and activation of endogenous cardiac stem and progenitor cells induced by exercise training. It is thought that enhanced cardiac structural integrity lends favorably to cardiac electrical stability and tolerance as well.^{55,56}

5.4. Psychological benefits of exercise in HF patients

HF is associated with substantial psychological distress that potentially affects the impact of therapies to improve long-term prognosis of HF patients.^{57,58} There is accumulating evidence that exercise could promote psychological well-being in adults with existing HF.^{59,60} In the HF-ACTION trial, aerobic exercise training resulted in a significant reduction in depressive symptoms as compared to the usual care control group at follow-up intervals of 3 months ($p = 0.002$) and 12 months ($p = 0.01$).⁶¹ In a 24-week randomized trial on combined moderate intensity aerobic and resistance exercise in adults (mean age 59 years)

Table 3
Potential exercise recommendations for HF management and prevention.

EXERCISE PURPOSE	EXERCISE PARAMETERS			KNOWLEDGE GAPS
	TYPE	INTENSITY	AMOUNT (VOLUME)	
HF Management (HF-ACTION)¹⁵	Aerobic (walking, cycling, stepping)	Moderate (titrate to 3–5 METs)	Moderate (titrate to 3.0–7.5 MET-h/wk)	Utility of “HIIT”? Utility of resistance exercise?
HF Prevention (PAGA 2018)²⁸	Aerobic (large muscle dynamic activities, e. g., walking, swimming, jogging, cycling) Resistance (large multi-joint muscles)	Moderate-to-vigorous (≥ 3 METs) Resistance than can be performed 8–12 reps	≥ 150 min/week moderate, or ≥ 75 min/week vigorous; combined energy expenditure of ≥ 7.5 MET-h/week 1–2 days/week	Need RCT evidence for primary HF prevention Utility of “HIIT”? Utility of resistance exercise?

MET, metabolic equivalent; PAGA, Physical Activity Guidelines for Americans; HIIT, high intensity interval training; RCT, randomized controlled trial; HF, heart failure; reps, repetitions; wk, week; h, hour.

with stable HF (mean LVEF 33%), self-efficacy significantly ($p < 0.05$) improved in the exercise compared to control group, and both depression and confusion indices improved with exercise ($p < 0.05$) but only in those with high adherence to intervention ($\geq 75\%$ session completion) as compared to worsening in those with low adherence.⁶² Another randomized trial in men (mean age 52 years) with chronic stable HF (NYHA class II and III) found significant decreases ($p < 0.05$) in anxiety and depression indices, and these psychological benefits were independent of improvements in measures of physical functioning and aerobic capacity.⁶³ Additional research is needed to better characterize the type and dose of exercise that favorably impacts specific psychological outcomes, separately and in combination with psycho-pharmacologic therapy, in HF patients.

6. Conclusion

HF is a major public health issue in an aging U.S. population. Exercise is a critical component of healthy aging and cardiovascular resiliency. Because several of the underlying mechanisms involved with HF development and progression respond favorably to exercise training and regular lifestyle physical activity, the role of exercise in HF management and prevention has become increasingly studied. At present, information on the recommended type, intensity, and amount of exercise in HF is limited. For HF management, the general approach to exercise prescription used in successful randomized trials on exercise in stable HF patients, such as HF-ACTION, could serve as a reasonable guide or at least a starting point for future research to build upon. For HF prevention, the current national guidelines for broad public health benefit are the principle evidence-based recommendations available and until a randomized primary HF prevention trial is completed, provides a general guide to practitioners and the communities served. Table 3 summarizes these exercise prescription parameters for potential use in HF management and prevention. As the 21st century moves onward, there will be greater need for safe and effective strategies to treat those afflicted with HF and to prevent its occurrence in those with prior history of HF. We may be in the early stages of the HF epidemic that was predicted at the conclusion of the previous century. As biomedical and clinical therapies continue development to meet the growing demand of HF in the community, so too must the exercise science community bring together streams of evidence from basic, clinical, and behavioral

research to advance the role of exercise as medicine, here, applied to the burgeoning toll that HF continues to inflict within the U.S. population and beyond.

Author's contribution

All the work was done by Michael J. LaMonte.

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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