CJC Open 7 (2025) 367–379

Systematic Review/Meta-analysis

Unraveling Heart Failure Phenotypes: A Systematic Review and Meta-analysis of Peak Oxygen Uptake and Its Determinants

Corey R. Tomczak, PhD,[a,‡] Stephen J. Foulkes, PhD,[b,c,‡] Christopher Weinkauf, BSc,[b] Devyn Walesiak, BSc,[b] Jing Wang, PhD,[d] Veronika Schmid, MSc,[e] Sarah Paterson, BSc,[b] Wesley J. Tucker, PhD,[f] Michael D. Nelson, PhD,[g] Simon Wernhart, MD, PhD,[e] Jan Vontobel, MD,[h] David Niederseer, MD, PhD,[h,i,j] and Mark J. Haykowsky, PhD[b]

[a] *College of Kinesiology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*

[b] *iCARE Laboratory, Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada*

[c] *Heart, Exercise and Research Trials (HEART) Lab, St Vincent's Institute of Medical Research, Fitzroy, Victoria, Australia*

[d] *Division of Public Health, School of Medicine, University of Utah, Salt Lake City, Utah, USA*

[e] *Department of Sports Medicine and Sports Cardiology, TUM University Hospital, School of Medicine and Health, Technical University of Munich, Munich, Germany*

[f] *Nutrition and Food Sciences, Texas Woman's University, Houston, Texas, USA*

[g] *College of Nursing and Health Innovation, University of Texas at Arlington, Arlington, Texas, USA*

[h] *Hochgebirgsklinik, Medicine Campus Davos, Davos, Switzerland*

[i] *Christine-Kühne-Centre for Allergy Research and Education (CK-CARE), Davos, Switzerland*

[j] *Centre of Translational and Experimental Cardiology (CTEC), Department of Cardiology, University Heart Centre Zurich, University of Zurich, Zurich, Switzerland*

ABSTRACT

Background: Understanding the impact of heart failure (HF) phenotype on peak oxygen uptake (peak $\dot{V}O_2$) is essential for advancing personalized treatment strategies and enhancing patient outcomes. Therefore, we conducted a systematic review and meta-analysis of the evidence examining differences in peak $\dot{V}O_2$ (primary objective) and its determinants (secondary objectives) between patients with HF with reduced (HFrEF) or preserved ejection fraction (HFpEF).

Methods: Studies comparing peak $\dot{V}O_2$ in HFrEF vs HFpEF were found through PubMed (1967-2024), Scopus (1981-2024), and Web of Science (1985-2024). Data extraction and methodologic quality assessment were completed by 2 independent coders. Differences between HFrEF and HFpEF were compared using weighted mean difference (WMD) and 95% confidence intervals (95% CIs) derived from random effects meta-analysis.

RÉSUMÉ

Contexte : Il est essentiel de comprendre l'effet du phénotype de l'insuffisance cardiaque (IC) sur la consommation maximale d'oxygène ($\dot{V}O_2$max) pour améliorer les stratégies de traitement personnalisées et le pronostic des patients. Nous avons donc procédé à une revue systématique et réalisé une méta-analyse des données probantes portant sur les différences au niveau de la $\dot{V}O_2$max (objectif principal) et de ses déterminants (objectifs secondaires) entre des patients présentant une IC avec fraction d'éjection réduite (ICFER) et préservée (ICFEP).

Méthodologie : Nous avons identifié les études comparant la $\dot{V}O_2$max chez des patients atteints d'ICFER et d'ICFEP dans PubMed (1967-2024), Scopus (1981-2024) et Web of Science (1985-2024). L'extraction des données et l'évaluation qualitative de la méthodologie des études ont été confiées à deux programmeurs indépendants. Les différences entre l'ICFER et l'ICFEP ont été comparées à partir de la

Received for publication December 21, 2024. Accepted January 15, 2025.

‡These authors contributed equally to this work as first authors.

Corresponding author: Prof. Mark J. Haykowsky, iCARE Laboratory, Room 5-246, ECHA University of Alberta, Edmonton, Alberta T6G 1C9, Canada. Tel.: 780-263-9959.

E-mail: mhaykows@ualberta.ca

@S_FoulkesAEP, @iCARE_lab_UofA, @UAlbertaNursing

See page 377 for disclosure information.

Heart failure (HF) is a significant global health issue, affecting more than 64 million individuals worldwide.[1] Despite advancements in treatment, it remains associated with high rates of morbidity and mortality and reduced quality of life.[1] Traditionally, HF has been characterized as 2 main phenotypes—heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)—

https://doi.org/10.1016/j.cjco.2025.01.012

Results: After screening 3107 articles, 25 unique studies were included in the analysis for the primary outcome (HFrEF n = 3783; HFpEF n = 3279). Peak $\dot{V}O_2$ (WMD: −1.6 mL/kg/min, 95% CI: −2.3 to −0.8 mL/kg/min), and peak exercise measures of cardiac output (WMD: −1.1 L/min, 95% CI: −2.1 to −0.2 L/min), stroke volume (WMD: −10.1 mL, 95% CI: −16.6 to −3.7 mL), heart rate (WMD: −4 bpm, 95% CI: −6 to −2 bpm), and left ventricular ejection fraction (WMD: −28.2%, 95% CI: −32.6% to −23.8%) were significantly lower while peak exercise arterial-venous oxygen difference was significantly higher in HFrEF compared with HFpEF (2.3 mL/dL, 95% CI: 1.6-2.9 mL/dL).

Conclusions: Our findings highlight distinct physiological impairments along the oxygen cascade in HFrEF compared with HFpEF, with direct implications for the management and treatment strategies of these HF subtypes.

différence moyenne pondérée (DMP) et des intervalles de confiance (IC) à 95 % estimés à l'aide d'une méta-analyse à effets aléatoires.

Résultats : Nous avons passé en revue 3 107 articles et sélectionné 25 études individuelles pour les besoins de l'analyse du paramètre principal (ICFER, n = 3 783; ICFEP, n = 3 279). La $\dot{V}O_2$max (DMP : -1,6 ml/kg/min; IC à 95 % : -2,3 à -0,8 ml/kg/min), de même que les mesures du débit cardiaque maximal à l'effort (DMP : -1,1 L/min; IC à 95 % : -2,1 à -0,2 L/min), le volume d'éjection systolique (DMP : -10,1 ml; IC à 95 % : -16,6 à -3,7 ml), la fréquence cardiaque (DMP : -4 bpm; IC à 95 % : -6 à -2 bpm) et la fraction d'éjection ventriculaire gauche (DMP : -28,2 %; IC à 95 % : -32,6 à -23,8 %) étaient nettement moindres tandis que la différence artérioveineuse maximale en oxygène à l'effort était nettement plus élevée en présence d'une ICFER, comparativement à l'ICFEP (2,3 ml/dl; IC à 95 % : 1,6 à 2,9 ml/dl).

Conclusions : Nos résultats mettent en évidence des altérations physiologiques distinctes le long de la cascade de l'oxygène en présence d'une ICFER comparativement à l'ICFEP, une différence qui a des implications directes pour les stratégies de prise en charge et de traitement de ces sous-types d'IC.

where HFrEF has been extensively studied, leading to better understanding and established treatments, and HFpEF remains more challenging to study and treat because of its heterogeneous nature, resulting in fewer targeted therapies.[2,3]

A hallmark feature of HF is reduced exercise tolerance, objectively measured by peak oxygen uptake (peak $\dot{V}O_2$).[4] Emerging evidence indicates that the degree of impairment in peak $\dot{V}O_2$ and the mechanisms that contribute to this may be associated with the specific HF phenotype. Indeed, exercise intolerance in HFrEF patients are typically considered a result of more significant "central" (cardiac output [CO]) limitations, whereas "noncardiac" peripheral factors (oxygen extraction, measured as arterial-venous oxygen difference [a-vO_2 difference]) may more prominently limit exercise tolerance in HFpEF.[5,6] Currently, however, a large-scale analysis of the evidence base examining peak $\dot{V}O_2$ and its determinants in HFrEF and HFpEF has not been undertaken. Therefore, the aim of our meta-analysis was to (1) compare peak $\dot{V}O_2$ between patients with HFrEF and HFpEF (primary outcome) and (2) compare the Fick determinants of peak $\dot{V}O_2$ (ie, CO and a-vO_2 difference) between these phenotypes.

Methods

Data sources and search strategy

A comprehensive, systematic search was performed in the following bibliographic databases: PubMed (1967-2024), Scopus (1981-2024), and Web of Science (1985-2024). Additional Google Scholar searches were performed through references cited from the studies that met our inclusion criteria. The search strategy for each database used a combination of natural language keywords and subject headings, such as MeSH, wherever they were available. The search strategy was structured using 3 main concepts: (1) heart failure and preserved ejection fraction; (2) heart failure and reduced ejection fraction; and (3) oxygen consumption. A list including all search terms used and the search strategy for each database is provided in the Supplementary Material (Supplemental Appendix S1). Records identified through the database searches were exported in complete batches and imported into the Covidence review software (Covidence, Melbourne, Australia). Ethical approval was not sought as all data were sourced from previously published studies and did not involve any individually identifiable or re-identifiable data.

Data synthesis and statistical analysis

Differences in the primary and secondary outcomes were quantified using meta-analysis based on random effects models using the R metacont package (R Core Team 2016, R Foundation for Statistical Computing, Vienna, Austria). From these models, the weighted average effect size, defined as weighted mean difference (WMD) with 95% confidence intervals (CIs), was calculated for each outcome between the HFrEF and HFpEF groups. The weight assigned to each study was the inverse of the variance within study. The larger the sample size and smaller variance of the study, the higher was the assigned weight. Heterogeneity within individual effect sizes was calculated by the I^2. Forest plots were created to show individual effect sizes, standard deviations, weights, the weighted average effect size, and the associated P value for testing the significance of the weighted average effect size at the alpha significance level of 0.05.

Study selection, inclusion and exclusion criteria

After the removal of duplicate citations, 2 study authors (D.W., C.W.) independently screened the titles and abstracts to identify studies comparing HFrEF vs HFpEF. The inclusion criteria consisted of (1) direct comparison of HFrEF and HFpEF patients who were 18 years of age or older and (2) peak $\dot{V}O_2$ measured during a cardiopulmonary exercise test with gas analysis. Studies were excluded if (1) there was no original or duplicate data, (2) it was published in a non-English language, or (3) it was a nonhuman study. The full text of potentially relevant

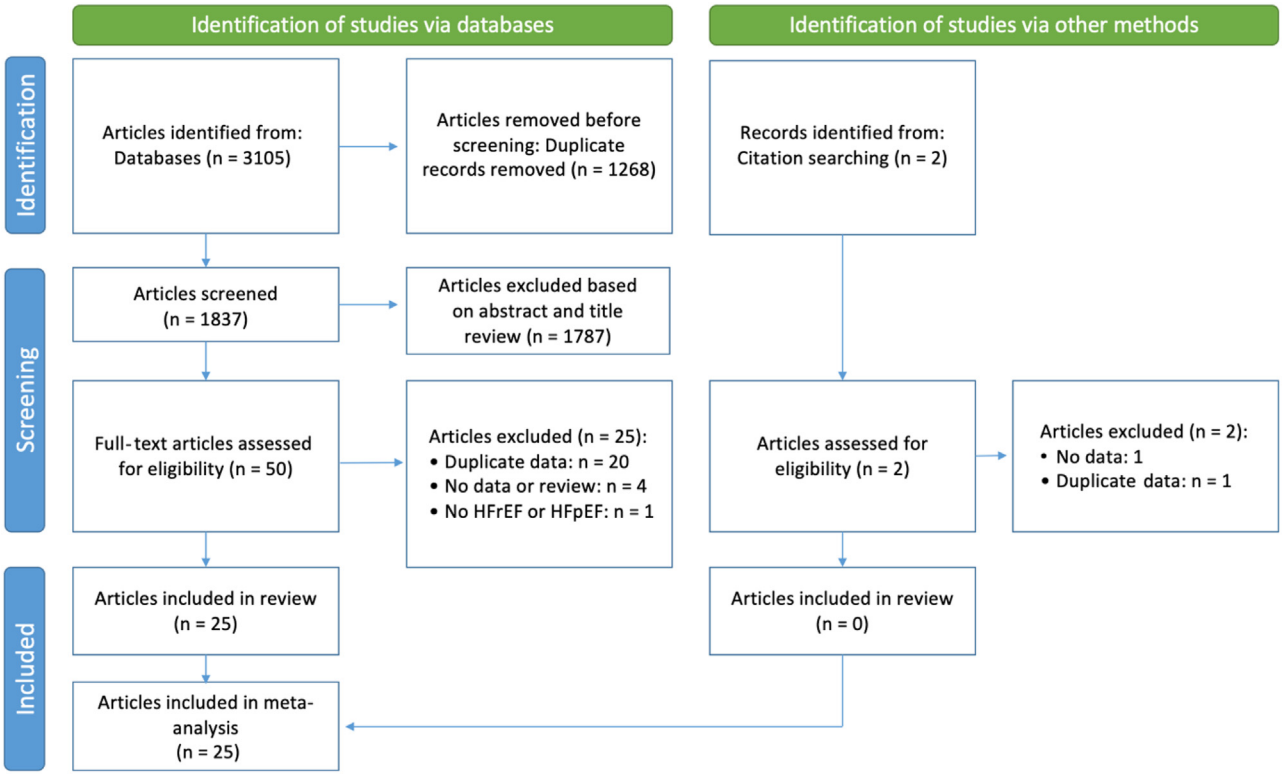

Figure 1. Study selection. PRISMA (**P**referred **R**eporting **I**tems for **S**ystematic reviews and **M**eta-**A**nalyses) diagram for selection of studies included in the meta-analysis.

articles was independently reviewed by 2 reviewers (D.E., C.W.) and any discrepancies during the study selection process were resolved by a third adjudicator (M.H.).

Study quality assessment

The quality of the included studies was evaluated using the AXIS appraisal tool,[7] a validated 20-point tool designed to assess the quality of cross-sectional studies. According to this tool, a score of 0 to 8 indicates very low quality, whereas a score of 17 to 20 indicates high quality.[7]

Results

The initial database search and identification of studies from other methods included 3107 articles. Following full-text screening, 25 unique studies were included in this meta-analysis[6,8-31] (Fig. 1). In the studies included, based on left ventricular ejection fraction (LVEF), HFrEF was primarily defined by a value below 35% to 50%, with some studies using a more stringent cutoff of $\leq$40%, whereas HFpEF was characterized by an LVEF $\geq$50% (Table 1). Additionally, some studies incorporated clinical symptoms, physical signs, and biomarker measurements alongside LVEF assessments to define HF subtypes.

Cardiopulmonary exercise testing was conducted to quantify peak $\dot{V}O_2$ using various modes: 21 studies employed cycle ergometry, 3 studies used treadmill exercise, and 1 study did not report the specific exercise testing mode. Finally, 4 studies measured peak exercise CO[6,24,25,31] using different techniques (ie, invasive right heart catheterization, echocardiography, or impedance cardiography) and a-vO_2 difference, whereas 1 study only reported the latter parameter.[16]

Peak oxygen uptake and hemodynamics

Compared with HFpEF, peak $\dot{V}O_2$ indexed to body mass or as an absolute value (Fig. 2) was lower in HFrEF (n = 7205, WMD: −1.6 mL/kg/min, 95% CI: −2.3 to −0.8 mL/kg/min, I^2: 90%; and n = 690, −0.1 L/min, 95% CI: −0.2 to 0.0 L/min, I^2: 28%). Analysis of studies assessing central hemodynamics showed that patients with HFrEF had a significantly lower peak exercise CO and cardiac index (n = 814, WMD: −1.1 L/min, 95% CI: −2.1 to −0.2 L/min, I^2: 80%, Fig. 3A; and, n = 224, WMD: −1.4 L/min/m^2, 95% CI: −1.8 to −1.0 L/min/m^2, I^2: 0%), heart rate (n = 5697, WMD: −4.2 beats/min, 95% CI: −6.4 to −2.0 beats/min, I^2: 41%, Supplemental Fig. S1A), stroke volume and stroke volume index (n = 637, WMD: −10.1 mL, 95% CI: −16.6 to −3.7 mL, I^2: 60%; n = 541, −6.4 mL/m^2, 95% CI: −8.9 to −3.8 mL/m^2, I^2: 27%, Supplemental Fig. S1, B and C). Moreover, in individuals with HFrEF, LVEF (n = 814, WMD: −28.2%, 95% CI: −32.6% to −23.8%, I^2: 86%, Supplemental Fig. S2A) and systolic and diastolic blood pressure (n = 5467, WMD: −23.8 mm Hg, 95% CI: −27.6 to −20.0 mm Hg, I^2: 70%; and, n = 2784, WMD: −3.2 mm Hg, 95% CI: −4.8 to −1.6 mm Hg, I^2: 44%, respectively, Supplemental Fig. S3, A and B) were also lower during exercise, whereas end-diastolic volume (absolute and indexed) was significantly higher compared with HFpEF

Table 1. Demographic data and details of included studies

Author	Group	Number (% Female)	Age (yr)	LVEF (%)	BMI	Resting SBP (mm Hg)	HF-RF (n)	HF-Med (n)
Katz[7]	HFrEF	41 (12)	61	21	NR	NR	NR	DIU (40)
	HFpEF	12 (33)	63	70	NR	NR	NR	ACEI (37)
								CCB (3)
								BB (3)
								DIG (32)
								DIU (7)
								ACEI (2)
								CCB (8)
								BB (3)
								DIG (0)
Kitzman[8]	HFrEF	60 (35)	70	31	26	136	HYP (29)	DIU (52)
	HFpEF	59 (86)	70	60	30	147	DM (16)	ACEI (49)
							HYP (47)	CCB (14)
							DM (10)	BB (10)
								DIG (44)
								NIT (18)
								DIU (35)
								ACEI (18)
								CCB (24)
								BB (14)
								DIG (11)
								NIT (6)
Chung[9]	HFrEF	20 (15)	64	31	28	131	HYP (10)	DIU (16)
	HFpEF	20 (30)	64	66	30	141	DM (6)	ACEI (20)
							SM (3)	CCB (3)
							HYP (20)	BB (17)
							DM (8)	NIT (7)
							SM (2)	STAT (18)
								ASP (17)
								DIU (6)
								ACEI (7)
								CCB (12)
								BB (11)
								NIT (5)
								STAT (10)
								ASP (10)
Farr[10]	HFrEF	185 (21)	63	30	29	NR	NR	ACEI (185)
	HFpEF	43 (47)	67	56	31	NR	NR	BB (139)
								ACEI (43)
								BB (28)
Guazzi[11]	HFrEF	211 (12)	62	33	NR	NR	NR	DIU (91)
	HFpEF	42 (69)	61	55	NR	NR	NR	ACEI (171)
								BB (120)
								INO (106)
								DIU (12)
								ACEI (33)
								BB (28)
								INO (8)
Kou[12]	HFrEF	23 (17)	51	33	24	NR	NR	DIU (16)
	HFpEF	28 (36)	56	57	23	NR	NR	ACEI (14)
								CCB (2)
								BB (23)
								ARB (9)
								DIU (10)
								ACEI (19)
								CCB (4)
								BB (24)
								ARB (4)

Table 1. Continued.

Author	Group	Number (% Female)	Age (yr)	LVEF (%)	BMI	Resting SBP (mm Hg)	HF-RF (n)	HF-Med (n)
Jehn[13]	HFrEF	30 (23)	57	30	29	NR	NR	DIU (26)
	HFpEF	20 (25)	67	55	27	NR	NR	ACEI (27)
								BB (30)
								STAT (27)
								ARB (3)
								DIG (8)
								DIU (6)
								ACEI (11)
								BB (13)
								STAT (15)
								ARB (7)
								DIG (0)
Dhakal[5]	HFrEF	56 (20)	59	29	28	123	HYP (34)	DIU (48)
	HFpEF	48 (58)	63	62	34	150	DM (12)	ACEI/
							HYP (29)	ARB (45)
							DM (14)	BB (51)
								DIG (28)
								MA (3)
								DIU (30)
								ACEI/
								ARB (14)
								BB (25)
								DIG (6)
								MA (4)
Konishi[14]	HFrEF	173 (51)	66	31	29	NR	HYP (133)	DIU (135)
	HFpEF	76 (16)	69	55	31	NR	DM (73)	ACEI (116)
							HYP (70)	BB (164)
							DM (34)	ARB (52)
								MA (97)
								DIU (48)
								ACEI (40)
								BB (59)
								ARB (27)
								MA (17)
Fu(a)[15]	HFrEF	30 (30)	60	28	25	131	HYP (18)	DIU (20)
	HFpEF	30 (33)	61	58	26	138	DM (14)	ACEI/
							HYP (25)	ARB (28)
							DM (19)	CCB (5)
								BB (24)
								STAT (13)
								DIU (22)
								ACEI/
								ARB (28)
								CCB (8)
								BB (22)
								STAT (15)
Fu(b)[15]	HFrEF	30 (37)	60	28	27	132	HYP (20)	DIU (21)
	HFpEF	30 (40)	63	57	24	139	DM (11)	ACEI/
							HYP (13)	ARB (25)CCB (6)
							DM (6)	BB (24)
								STAT (9)
								DIU (21)
								ACE/
								ARB (27)
								CCB (8)
								BB (23)
								STAT (8)

Continued

Table 1. Continued.

Author	Group	Number (% Female)	Age (yr)	LVEF (%)	BMI	Resting SBP (mm Hg)	HF-RF (n)	HF-Med (n)
Sato[16]	HFrEF	498 (16)	59	30	23	105	DM (142)	DIU (376)
	HFpEF	438 (23)	62	60	24	119	DM (117)	ACEI/ ARB (455)
								CCB (59)
								BB (485)
								STAT (220)
								DIG (85)
								MA (345)
								DIU (163)
								ACEI/ ARB (349)
								CCB (124)
								BB (348)
								STAT (187)
								DIG (24)
								MA (124)
Van Iterson[17]	HFrEF	32 (6)	55	22	28	NR	NR	DIU (29)
	HFpEF	27 (41)	71	61	33	NR	NR	ACEI (25)
								CCB (1)
								BB (28)
								DIG (23)
								NIT (9)
								ARB (2)
								ASP (22)
								AA (10)
								DIU (11)
								ACEI (12)
								CCB (6)
								BB (17)
								DIG (2)
								NIT (10)
								ARB (7)
								ASP (21)
								AA (5)
Nadruz[18]	HFrEF	630 (27)	56	25	28	114	HYP (370)	DIU (477)
	HFpEF	195 (47)	56	55	29	123	DM (185)	ACEI/ ARB (518)
							HYP (119)	CCB (24)
							DM (37)	BB (565)
								STAT (328)
								MA (223)
								AA (259)
								AC (249)
								AP (357)
								DIU (100)
								ACEI/ ARB (137)
								CCB (34)
								BB (134)
								STAT (78)
								MA (23)
								AA (20)
								AC (45)
								AP (79)
Kato[19](a)	HFrEF	112 (12)	45	26	25	109	HYP (46)	BB (78)
	HFpEF	264 (25)	45	65	24	118	DM (26)	BB (69)
							HYP (82)	
							DM (37)	
Kato[19](b)	HFrEF	146 (16)	62	27	24	110	HYP (77)	BB (98)
	HFpEF	494 (28)	63	66	23	123	DM (72)	BB (168)
							HYP (267)	
							DM (138)	
Kato[19](c)	HFrEF	56 (25)	76	28	22	115	HYP (37)	BB (39)
	HFpEF	285 (44)	76	68	22	126	DM (21)	BB (100)
							HYP (177)	
							DM (91)	

Table 1. Continued.

Author	Group	Number (% Female)	Age (yr)	LVEF (%)	BMI	Resting SBP (mm Hg)	HF-RF (n)	HF-Med (n)
Tanaka[20]	HFrEF	30 (40)	67	33	33	NR	HYP (12)	DIU (29)
	HFpEF	30 (43)	69	60	37	NR	DM (13)	ACEI/
							HYP (18)	ARB (26)
							DM (20)	CCB (2)
								BB (27)
								MA (14)
								DIU (27)
								ACE
								ARB (26)
								CCB (12)
								BB (18)
								MA (7)
Kondo[21]	HFrEF	37 (8)	66	31	24	123	HYP (21)	DIU (29)
	HFpEF	28 (29)	70	58	23	126	DM (24)	ACEI/
							HYP (22)	ARB (32)
							DM (13)	BB (34)
								MA (24)
								DIU (14)
								ACE/
								ARB (22)
								BB (24)
								ALDA (10)
van Wezenbeek[22]	HFrEF	109 (28)	57	36	34	NR	NR	NR
	HFpEF	57 (67)	53	58	40	NR	NR	NR
Pugliese[23]	HFrEF	205 (35)	65	33	27	120	HYP (135)	DIU (29)
	HFpEF	188 (52)	72	56	32	135	DM (51)	ACEI/
							HYP (160)	ARB (146)
							DM (73)	CCB (33)
								BB (176)
								DIU (19)
								ACEI/
								ARB (132)
								CCB (51)
								BB (120)
Bandera[24]	HFrEF	137 (23)	67	30	26	120	HYP (96)	DIU (112)
	HFpEF	40 (70)	76	62	29	130	DM (48)	ACEI/
							SM (54)	ARB (110)
							HYP (32)	CCB (12)
							DM (14)	BB (118)
							SM (11)	DIU (32)
								ACEI/
								ARB (26)
								CCB (11)
								BB (23)
Adams[25]	HFrEF	20 (25)	61	29	30	125	HYP (17)	DIU (16)
	HFpEF	20 (75)	70	64	33	138	DM (7)	ACEI/
							HYP (20)	ARB (19)
							DM (6)	CCB (1)
								BB (20)
								DIU (14)
								ACEI/
								ARB (19)
								CCB (8)
								BB (15)
Gong[26]	HFrEF	598 (28)	58	25	28	114	HYP (425)	DIU (403)
	HFpEF	585 (51)	58	59	30	129	DM (167)	ACEI/
							SM (55)	ARB (422)
							HYP (376)	BB (527)
							DM (113)	DIU (357)
							SM (26)	ACEI/
								ARB (242)
								BB (365)

Continued

Table 1. Continued.

Author	Group	Number (% Female)	Age (yr)	LVEF (%)	BMI	Resting SBP (mm Hg)	HF-RF (n)	HF-Med (n)
Wernhart[27]	HFrEF	153 (15)	53	22	28	NR	HYP (68)	DIU (119)
	HFpEF	123 (41)	60	60	27	NR	DM (52)	ACEI/ARB
							SM (90)	/ARNI (143)
							HYP (68)	BB (147)
							DM (16)	DIU (34)
							SM (35)	ACEI/ARB
								/ARNI (54)
								BB (62)
Baccanelli[28]	HFrEF	126 (NR)	65	33	NR	119	NR	NR
	HFpEF	22 (NR)	64	58	NR	118	NR	NR
Ali[29]	HFrEF	11 (36)	79	27	30	115	HYP (8)	DIU (11)
	HFpEF	21 (62)	81	63	30	124	DM (3)	ACEI (5)
							OB (5)	BB (10)
							HYP (17)	CCB (1)
							DM (7)	ARB (1)
							OB (9)	DIU (19)
								ACEI (5)
								BB (8)
								CCB (7)
								ARB (5)
Rozenbaum[30] (a)	HFrEF	40 (0)	64	37	NR	127	NR	NR
	HFpEF	43 (0)	61	65	NR	127	NR	NR
Rozenbaum[30] (b)	HFrEF	22 (100)	63	37	NR	135	NR	NR
	HFpEF	35 (100)	62	64	NR	143	NR	NR

AA, antiarrhythmic; AC, anticoagulant; ACEI, angiotensin converting enzyme inhibitor; ALDA, aldosterone antagonist; ARB, angiotensin II receptor blocker; AP, antiplatelet; ARNI, angiotensin receptor-neprilysin inhibitor; ASP, Aspirin; BB, β-blocker; BMI, body mass index; CCB, calcium channel blocker; DIG, digoxin; DIU, diuretics; DM, diabetes mellitus, HF-Med, heart failure medications; HFrEF, heart failure and reduced ejection fraction; HF-RF, heart failure risk factors; HFpEF, heart failure and preserved ejection fraction; HYP, hypertension; INO, inotropes; LVEF, left ventricular ejection fraction; NIT, nitrate; MA, mineralocorticoid receptor antagonist; NR, not reported; OB, obese; SBP, systolic blood pressure; SM, smoker; STAT, statin.

(n = 244, WMD: 73 mL, 95% CI: 21-125 mL, I^2: 93%; n = 421, 42.5 mL/m^2, 95% CI: 27.2-57.8 mL/m^2, I^2: 90%, Supplemental Fig. S2, B and C). Finally, peak a-vO_2 difference was significantly higher in HFrEF vs HFpEF (n = 934, WMD: 2.3 mL/dL, 95% CI: 1.6-2.9 mL/dL, I^2: 70%, Fig. 3B).

Study quality and bias

The average AXIS score was 14, reflecting a moderate quality level.[7] Publication bias was assessed using the both the funnel plot and Egger test. The funnel plot shows approximate symmetry, and the Egger test is nonsignificant with a *P* value of 0.83, which implies that there is no evidence of publication bias (Supplemental Fig. S4). A high degree of heterogeneity (I^2 = 60%-90%) was observed in most outcomes in this analysis. To further explore and address the sources of this heterogeneity, 2 additional approaches were applied: outlier removal and meta-regression analysis. Jehn et al.[13] and Wernhart et al.[28] were identified as potential outliers because of their exceptionally large effect sizes, the 2 largest among all included studies. The removal of these studies led to a modest reduction in heterogeneity (I^2 decreased from 90.0% to 87.5%). Although this reduction in I^2 was not large, it demonstrates that these studies introduced some variability that was not consistent with the rest of the studies. Following the outlier removal, meta-regression was conducted to further investigate potential sources of heterogeneity using 3 key covariates: sample size, publication year (dichotomized as ≤2018 vs >2018), and hypertension status. Meta-regression explained 81% of the heterogeneity (R^2), reducing I^2 to 54%. This significant reduction indicates that these covariates account for a substantial portion of the variability between studies. Smaller studies ($P = 0.0009$), studies published after 2018 ($P = 0.02$), and those studies involving hypertensive patients reported larger effect sizes ($P = 0.01$). However, hypertension status was missing in 32% of the studies, suggesting that more heterogeneity might have been accounted for if complete data were available for this covariate. Other potential moderators, including age, resting systolic blood pressure, resting left-ventricular ejection fraction in the HFrEF group, diabetes status, and medication use (ie, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or β-blockers), were also explored. These covariates did not explain additional heterogeneity and reduced the model's explanatory power (R^2). This suggests that these factors may not have played a significant role in the variability of effect sizes in this meta-analysis. The role of sex could not be determined as few studies reported results subgrouped by sex.

Discussion

The findings of this meta-analysis of exercise limitations in patients with HF, the largest conducted to date, identifies key differences in HF phenotypes related to peak $\dot{V}O_2$. Specifically, patients with HFrEF have significantly lower peak $\dot{V}O_2$ than those with HFpEF. In the few studies that measured the Fick determinants, patients with HFrEF showed greater "central" limitations secondary to a lower stroke volume and CO. In contrast, peripheral limitations are a more predominant feature of HFpEF, as peak exercise a-vO_2 difference was significantly lower in those with HFpEF vs HFrEF. These findings highlight the differential physiology driving reduced

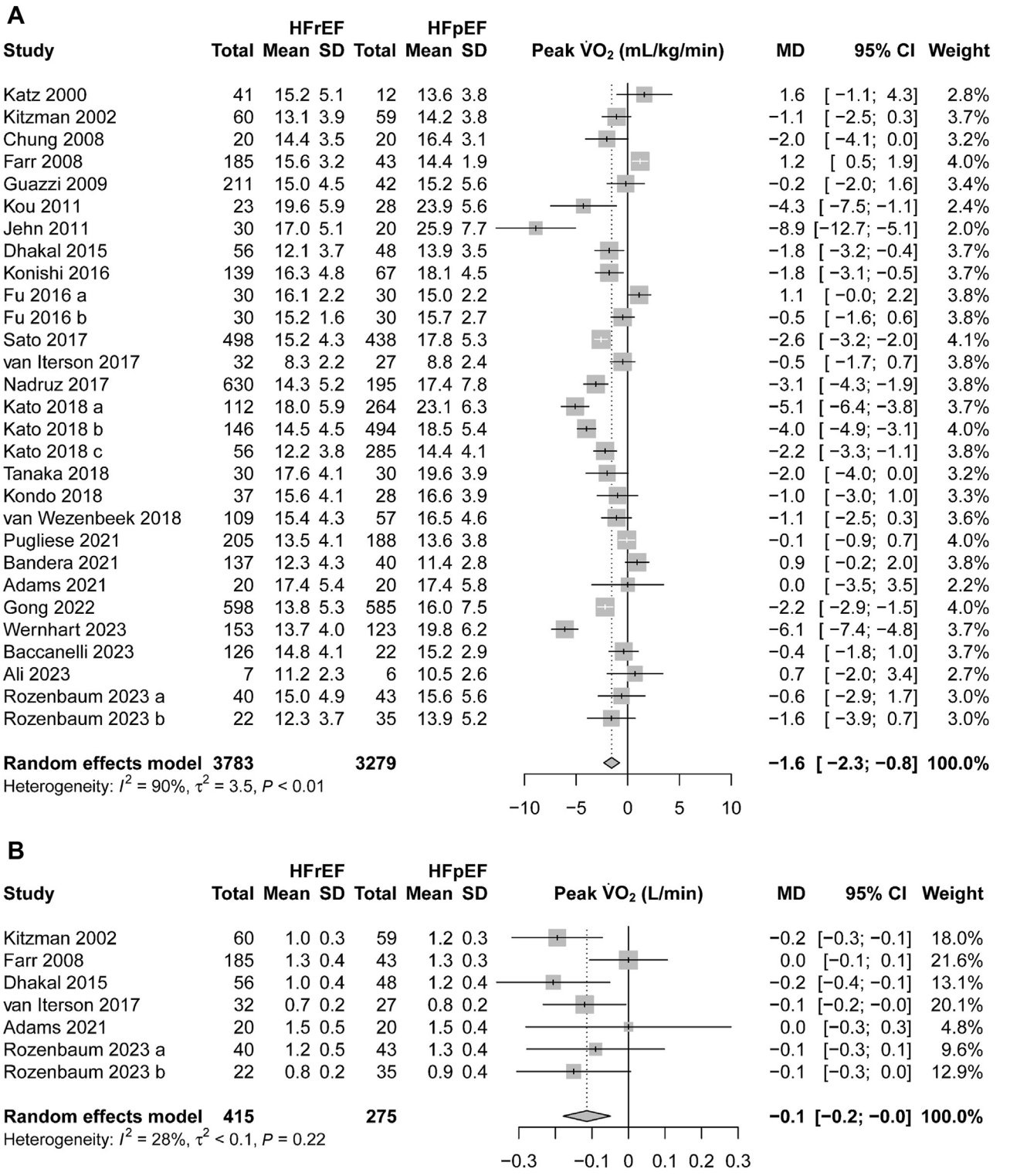

Figure 2. Peak in $\dot{V}O_2$ in patients with HFrEF vs HFpEF. Peak $\dot{V}O_2$ (**A**) indexed to body weight (mL/kg/min) or (**B**) in absolute values (L/min) in patients with heart failure with reduced ejection fraction (HFrEF) vs patients with heart failure with preserved ejection fraction (HFpEF) derived from a random effects meta-analysis. CI, confidence interval; MD, mean difference; SD, standard deviation.

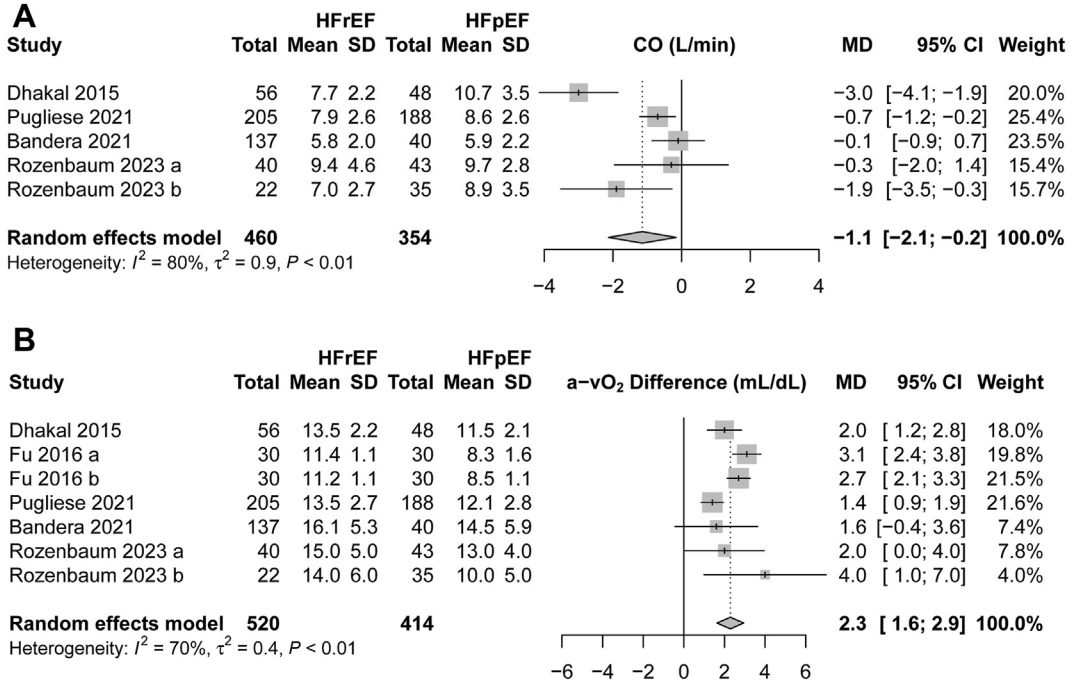

Figure 3. Fick's principle determinants of peak $\dot{V}O_2$ in patients with HFrEF vs HFpEF. Peak exercise (**A**) cardiac output (CO, L/min) and (**B**) arterio-venous oxygen content difference (a-vO_2 difference, mL/dL) in patients with heart failure with reduced ejection fraction (HFrEF) vs patients with heart failure with preserved ejection fraction (HFpEF) derived from a random effects meta-analysis. CI, confidence interval; MD, mean difference; SD, standard deviation.

exercise intolerance in HFrEF vs HFpEF and reinforce the importance of using exercise training and rehabilitation strategies that target the "weak links" in the O_2 pathway.[33]

Impaired peak $\dot{V}O_2$ in HFrEF and HFpEF: Implications for functional independence

Decreased exercise tolerance is a defining characteristic of HF, regardless of the phenotype. We observed that patients with HFrEF had a peak $\dot{V}O_2$ that was 10% lower than those with HFpEF. This difference holds clinical importance, as it exceeds previously established thresholds for a clinically meaningful difference in peak $\dot{V}O_2$,[34] and may contribute to important differences in disability and functional limitations. Indeed, the peak $\dot{V}O_2$ in HFrEF was 19% below the threshold required for full and independent living (18 mL/kg/min),[35] whereas in HFpEF, it was only 9% below this threshold. As a result, daily activities demand near-maximal or maximal effort, with more significant impairments expected in HFrEF patients. In addition, the combination of a lower peak exercise CO and lower peak $\dot{V}O_2$ may also explain the higher specific cardiovascular mortality in HFrEF compared with HFpEF.[1]

Peak exercise CO in HFrEF and HFpEF

In accordance with the Fick principle, several important pathophysiological differences may drive the markedly reduced peak $\dot{V}O_2$ values observed in both HF phenotypes. CO and its determinants are crucial in modulating peak $\dot{V}O_2$ in patients with HF. Our findings from the subgroup of studies assessing peak exercise hemodynamics show that CO at peak exercise is 1.1 L/min lower in HFrEF than in HFpEF, mainly because of a lower stroke volume, as the difference in maximal heart rate between groups was minimal (4 beats/min). Four studies included in our analysis measured the determinants of stroke volume during peak exercise[6,24,25,31] and consistently reported that HFrEF patients have higher peak exercise end-diastolic volume (index) and concomitantly lower LVEF. Taken together, despite a higher preload, the lower peak exercise stroke volume and LVEF in HFrEF is due to impaired contractility as peak exercise systemic vascular resistance was similar in the 2 studies where it was measured.[24,31] In turn, impaired contractility in HFrEF is most likely an effect of altered contractile properties of the myocardium secondary to damaged or necrotic tissue. Abnormal peripheral vascular endothelial function and increased muscle sympathetic nerve activity has been observed to a greater extent in HFrEF vs controls[3,36-38] and may also contribute to higher ventricular afterload during exercise. However, whether this contributes to the greater impairment in peak $\dot{V}O_2$, and CO observed in patients with HFrEF, requires further investigation.

Peak a-vO_2 difference in HFrEF and HFpEF

Our study found that the peak exercise a-vO_2 difference was 2.3 mL/dL higher in HFrEF compared to HFpEF, which suggests that patients in the latter group have a greater degree of peripheral impairment than those with HFrEF. However, because of a lower CO (and thus leg blood flow) at peak exercise, HFrEF patients will have a greater time for oxygen to be extracted by the active muscles.[33] Alternatively, the lower O_2 extraction in HFpEF may be due to heterogeneity in capillary transit time, muscle blood flow heterogeneity, and to abnormal muscle oxygen diffusive conductance (transport of O_2 from the red blood cell in the microvasculature to mitochondria in skeletal muscle) even when muscle venous O_2 pressure is low.[33,39-41] Indeed, Esposito et al.[42] previously

reported that muscle oxygen diffusive conductance is 22% to 32% lower in HFrEF patients compared with control subjects during peak cycle exercise or single-leg knee extension exercise where the limiting role of the heart is minimized.

No studies have specifically examined the impact of HF phenotype on peak exercise muscle oxygen diffusive conductance. However, comparing findings from several prior invasive hemodynamic studies suggests that the mean muscle oxygen diffusive conductance values for HFrEF are 41% higher than those reported for patients with HFpEF patients during single-leg knee extension exercise.[42,43] These differences may be influenced by variations in age (HFrEF: 53 years vs HFpEF: 70 years), sex (HFrEF: 0% females vs HFpEF: 70% females), and body mass (HFrEF: 96 kg vs HFpEF: 106 kg), which individually or collectively affect whole peak exercise VO_2 and O_2 extraction.[33]

Both HFrEF and HFpEF exhibit similar skeletal muscle abnormalities that include reductions in oxidative enzymes, percentage of type I (oxidative) muscle fibers, volume density of mitochondria, and surface density of mitochondrial cristae.[4,44-50] Additionally, there is impaired mitochondrial oxidative capacity, and a reduction in the capillary-to-fiber ratio.[3,47-49,51] Given these morphologic perturbations occur to a similar extent in both HF phenotypes, it is plausible that skeletal muscle quality plays a significant role in the greater impairment in O_2 extraction in HFpEF.[52] Indeed, patients with HFpEF display greater myosteatosis (increased intermuscular fat relative to skeletal muscle), which is related to a lower peak $\dot{V}O_2$, aerobic endurance, and physical function.[53-55] Furthermore, compared to HFrEF, patients with HFpEF show more rapid depletion of high-energy phosphate during small muscle mass exercise, indicating severe skeletal muscle bioenergetic impairment.[56] Thus, indicators associated with skeletal muscle composition and metabolism may be altered to a greater degree in patients with HFpEF, thereby attenuating the increase in a-vO_2 difference during peak exercise compared to patients with HFrEF.

Considerations

The heterogeneity in our meta-analyses warrants consideration when interpreting our findings. This variability may stem from the moderate quality of included studies—which is not uncommon for HF exercise studies[32,57]—and may be due to differences in study design, different testing protocols, modalities (upright or supine cycle, treadmill), and exercise termination criteria (often not reported) among the included studies. Moreover, there was variability in the criteria and cutoff points used to define HFrEF and HFpEF groups, which may also have contributed to heterogeneity. Meta-regression analysis revealed that studies with a smaller sample size, those published in 2018 or later, and hypertension status (greater in HFrEF) had a larger effect size. However, hypertension status was missing in 32% of studies, suggesting that more heterogeneity might have been accounted for if complete data were available for this covariate. Importantly, other covariates (diabetes, resting blood pressure, or HF medication) did not explain additional heterogeneity. Consequently, although not a direct aim of this meta-analysis, an important finding is the lack of standardization and insufficient reporting of key details related to the protocols and approaches for assessing peak $\dot{V}O_2$, diagnosing HF subtype, and reporting potential confounders (ie, medications, comorbidities) that needs to be addressed in future studies. However, despite the inherent variability in comparing exercise tests across independent research laboratories, our meta-analysis provides the most robust analysis to date regarding the HF phenotype—specific differences in peak $\dot{V}O_2$. Finally, despite the limited number of studies measuring peak exercise CO (each using different techniques with inherent limitations[58,59]), our analysis includes the largest sample size of HFrEF and HFpEF patients (n = 814 and n = 934, respectively) reported to date for these parameters.

Conclusions

Our findings suggest that compared to patents with HFpEF, patients with HFrEF have greater impairment in peak $\dot{V}O_2$ that may contribute to increased functional limitations and disability. In the subset of studies investigating the determinants of reduced peak $\dot{V}O_2$ (encompassing 1,748 patients), we also demonstrated that decreased peak $\dot{V}O_2$ in HFrEF patients is primarily due to central factors, whereas HFpEF patients are more peripherally limited, with more impaired cardiac function playing a role in the former, and reduced skeletal muscle quality and metabolism likely playing a more significant role in the latter. Although at the individual level, patients may experience multiple limitations along the O_2 cascade, the above-mentioned salient phenotype-specific trends are evident. This highlights that instead of a one-size-fits-all approach, interventions such as exercise training and rehabilitation should be tailored to the specific HF phenotype: with a greater focus on improving cardiac function in patients with HFrEF and improving microvascular and skeletal muscle quality in patients with HFpEF. Understanding that addressing limitations along the entire O_2 cascade will result in the greatest improvement in peak $\dot{V}O_2$,[33,60] this targeted approach may offer the greatest benefit in alleviating the pronounced exercise intolerance characteristic of each HF phenotype.

Ethics Statement

Ethical approval was not sought as all data were sourced from previously published studies.

Patient Consent

Patient consent was not sought as the study did not involve any individually identifiable or reidentifiable data.

Funding Sources

Dr Haykowsky is supported by an endowed Research Chair in Aging & Quality of Life from the Faculty of Nursing at the University of Alberta.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2023;118:3272-87. https://doi.org/10.1093/cvr/cvac013.

2. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail 2015;8:33-40. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001615.

3. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. J Appl Physiol (1985) 2015;119:739-44. https://doi.org/10.1152/japplphysiol.00049.2015.

4. Tucker WJ, Haykowsky MJ, Seo Y, Stehling E, Forman DE. Impaired exercise tolerance in heart failure: role of skeletal muscle morphology and function. Curr Heart Fail Rep 2018;15:323-31. https://doi.org/10.1007/s11897-018-0408-6.

5. Haykowsky MJ, Kitzman DW. Exercise physiology in heart failure and preserved ejection fraction. Heart Fail Clin 2014;10:445-52. https://doi.org/10.1016/j.hfc.2014.04.001.

6. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286-94. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001825.

7. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open 2016;6:e011458. https://doi.org/10.1136/bmjopen-2016-011458.

8. Katz SD, Maskin C, Jondeau G, et al. Near-maximal fractional oxygen extraction by active skeletal muscle in patients with chronic heart failure. J Appl Physiol (1985) 2000;88:2138-42. https://doi.org/10.1152/jappl.2000.88.6.2138.

9. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144-50.

10. Chung I, Goyal D, Macfadyen RJ, Lip GY. The effects of maximal treadmill graded exercise testing on haemorheological, haemodynamic and flow cytometry platelet markers in patients with systolic or diastolic heart failure. Eur J Clin Invest 2008;38:150-8. https://doi.org/10.1111/j.1365-2362.2008.01909.x.

11. Farr MJ, Lang CC, Lamanca JJ, et al. Cardiopulmonary exercise variables in diastolic versus systolic heart failure. Am J Cardiol 2008;102:203-6. https://doi.org/10.1016/j.amjcard.2008.03.041.

12. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. Circ Heart Fail 2009;2:549-55. https://doi.org/10.1161/CIRCHEARTFAILURE.109.881326.

13. Kou S, Suzuki K, Akashi YJ, et al. Global longitudinal strain by two-dimensional speckle tracking imaging predicts exercise capacity in patients with chronic heart failure. J Echocardiogr 2011;9:64-72. https://doi.org/10.1007/s12574-010-0076-3.

14. Jehn M, Halle M, Schuster T, et al. Multivariable analysis of heart rate recovery after cycle ergometry in heart failure: exercise in heart failure. Heart Lung 2011;40:e129-37. https://doi.org/10.1016/j.hrtlng.2011.01.005.

15. Konishi M, Ebner N, Springer J, et al. Impact of plasma kynurenine level on functional capacity and outcome in heart failure—results from Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Circ J 2016;81:52-61. https://doi.org/10.1253/circj.CJ-16-0791.

16. Fu TC, Yang NI, Wang CH, et al. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. Am J Phys Med Rehabil 2016;95:15-27. https://doi.org/10.1097/PHM.0000000000000312.

17. Sato T, Yoshihisa A, Kanno Y, et al. Cardiopulmonary exercise testing as prognostic indicators: comparisons among heart failure patients with reduced, mid-range and preserved ejection fraction. Eur J Prev Cardiol 2017;24:1979-87. https://doi.org/10.1177/2047487317739079.

18. Van Iterson EH, Johnson BD, Borlaug BA, Olson TP. Physiological dead space and arterial carbon dioxide contributions to exercise ventilatory inefficiency in patients with reduced or preserved ejection fraction heart failure. Eur J Heart Fail 2017;19:1675-85. https://doi.org/10.1002/ejhf.913.

19. Nadruz W Jr, West E, Sengelov M, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. J Am Heart Assoc 2017;6:e006000. https://doi.org/10.1161/JAHA.117.006000.

20. Kato Y, Suzuki S, Uejima T, et al. Relationship between the prognostic value of ventilatory efficiency and age in patients with heart failure. Eur J Prev Cardiol 2018;25:731-9. https://doi.org/10.1177/2047487318758775.

21. Tanaka S, Sanuki Y, Ozumi K, Harada T, Tasaki H. Heart failure with preserved vs reduced ejection fraction following cardiac rehabilitation: impact of endothelial function. Heart Vessels 2018;33:886-92. https://doi.org/10.1007/s00380-018-1128-2.

22. Kondo T, Yamada S, Asai C, et al. Skeletal muscle pump function is associated with exercise capacity in patients with heart failure. Circ J 2018;82:1033-40. https://doi.org/10.1253/circj.CJ-17-0927.

23. van Wezenbeek J, Canada JM, Ravindra K, et al. C-reactive protein and N-terminal pro-brain natriuretic peptide levels correlate with impaired cardiorespiratory fitness in patients with heart failure across a wide range of ejection fraction. Front Cardiovasc Med 2018;5:178. https://doi.org/10.3389/fcvm.2018.00178.

24. Pugliese NR, Paneni F, Mazzola M, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. Eur J Heart Fail 2021;23:1858-71. https://doi.org/10.1002/ejhf.2337.

25. Bandera F, Barletta M, Fontana M, et al. Exercise-induced mitral regurgitation and right ventricle to pulmonary circulation uncoupling across the heart failure phenotypes. Am J Physiol Heart Circ Physiol 2021;320:H642-53. https://doi.org/10.1152/ajpheart.00507.2020.

26. Adams V, Wunderlich S, Mangner N, et al. Ubiquitin-proteasome-system and enzymes of energy metabolism in skeletal muscle of patients with HFpEF and HFrEF. ESC Heart Fail 2021;8:2556-68. https://doi.org/10.1002/ehf2.13405.

27. Gong J, Castro RRT, Caron JP, et al. Usefulness of ventilatory inefficiency in predicting prognosis across the heart failure spectrum. ESC Heart Fail 2022;9:293-302. https://doi.org/10.1002/ehf2.13761.

28. Wernhart S, Papathanasiou M, Rassaf T, Luedike P. Heart failure classification based on resting ejection fraction does not display a unique exercise response pattern. Int J Cardiol 2023;376:157-64. https://doi.org/10.1016/j.ijcard.2023.01.072.

29. Baccanelli G, Tomaselli M, Ferri U, et al. Effects of cardiac rehabilitation on cardiopulmonary test parameters in heart failure: a real world experience. Int J Cardiol Cardiovasc Risk Prev 2023;17:200178. https://doi.org/10.1016/j.ijcrp.2023.200178.

30. Ali D, Tran P, Ennis S, et al. Rising arterial stiffness with accumulating comorbidities associates with heart failure with preserved ejection fraction. ESC Heart Fail 2023;10:2487-98. https://doi.org/10.1002/ehf2.14422.

31. Rozenbaum Z, Granot Y, Sadeh B, et al. Sex differences in heart failure patients assessed by combined echocardiographic and cardiopulmonary exercise testing. Front Cardiovasc Med 2023;10:1098395. https://doi.org/10.3389/fcvm.2023.1098395.

32. Tucker WJ, Beaudry RI, Liang Y, et al. Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: a 10-year update. Prog Cardiovasc Dis 2019;62:163-71. https://doi.org/10.1016/j.pcad.2018.08.006.

33. Foulkes SJ, Wagner PD, Wang J, La Gerche A, Haykowsky MJ. Physiological determinants of decreased peak leg oxygen uptake in chronic disease: a systematic review and meta-analysis. J Appl Physiol (1985) 2024;136:1293-302. https://doi.org/10.1152/japplphysiol.00918.2023.

34. Kitzman DW. Exercise training in heart failure with preserved ejection fraction: beyond proof-of-concept. J Am Coll Cardiol 2011;58:1792-4. https://doi.org/10.1016/j.jacc.2011.07.024.

35. Paterson DH, Cunningham DA, Koval JJ, St Croix CM. Aerobic fitness in a population of independently living men and women aged 55-86 years. Med Sci Sports Exerc 1999;31:1813-20.

36. Seravalle G, Quarti-Trevano F, Dell'Oro R, et al. Sympathetic and baroreflex alterations in congestive heart failure with preserved, midrange and reduced ejection fraction. J Hypertens 2019;37:443-8. https://doi.org/10.1097/HJH.0000000000001856.

37. Hundley WG, Bayram E, Hamilton CA, et al. Leg flow-mediated arterial dilation in elderly patients with heart failure and normal left ventricular ejection fraction. Am J Physiol Heart Circ Physiol 2007;292:H1427-34. https://doi.org/10.1152/ajpheart.00567.2006.

38. Tucker WJ, Lijauco CC, Hearon CM Jr, et al. Mechanisms of the improvement in peak VO_2 with exercise training in heart failure with reduced or preserved ejection fraction. Heart Lung Circ 2018;27:9-21. https://doi.org/10.1016/j.hlc.2017.07.002.

39. Piiper J. Perfusion, diffusion and their heterogeneities limiting blood-tissue O_2 transfer in muscle. Acta Physiol Scand 2000;168:603-7. https://doi.org/10.1046/j.1365-201x.2000.00711.x.

40. Poole DC, Musch TI. Capillary-mitochondrial oxygen transport in muscle: paradigm shifts. Function (Oxf) 2023;4:zqad013. https://doi.org/10.1093/function/zqad013.

41. Del Torto A, Corrieri N, Vignati C, et al. Contribution of central and peripheral factors at peak exercise in heart failure patients with progressive severity of exercise limitation. Int J Cardiol 2017;248:252-6. https://doi.org/10.1016/j.ijcard.2017.07.071.

42. Esposito F, Mathieu-Costello O, Shabetai R, Wagner PD, Richardson RS. Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. J Am Coll Cardiol 2010;55:1945-54. https://doi.org/10.1016/j.jacc.2009.11.086.

43. Skow RJ, Sarma S, MacNamara JP, et al. Identifying the mechanisms of a peripherally limited exercise phenotype in patients with heart failure with preserved ejection fraction. Circ Heart Fail 2024:e011693. https://doi.org/10.1161/CIRCHEARTFAILURE.123.011693.

44. Magnusson G, Kaijser L, Rong H, et al. Exercise capacity in heart failure patients: relative importance of heart and skeletal muscle. Clin Physiol 1996;16:183-95. https://doi.org/10.1111/j.1475-097x.1996.tb00567.x.

45. Drexler H, Riede U, Munzel T, et al. Alterations of skeletal muscle in chronic heart failure. Circulation 1992;85:1751-9. https://doi.org/10.1161/01.cir.85.5.1751.

46. Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation 1990;81:518-27. https://doi.org/10.1161/01.cir.81.2.518.

47. Kitzman DW, Nicklas B, Kraus WE, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Physiol Heart Circ Physiol 2014;306:H1364-70. https://doi.org/10.1152/ajpheart.00004.2014.

48. Molina AJ, Bharadwaj MS, Van Horn C, et al. Skeletal muscle mitochondrial content, oxidative capacity, and Mfn2 expression are reduced in older patients with heart failure and preserved ejection fraction and are related to exercise intolerance. JACC Heart Fail 2016;4:636-45. https://doi.org/10.1016/j.jchf.2016.03.011.

49. Scandalis L, Kitzman DW, Nicklas BJ, et al. Skeletal muscle mitochondrial respiration and exercise intolerance in patients with heart failure with preserved ejection fraction. JAMA Cardiol 2023;8:575-84. https://doi.org/10.1001/jamacardio.2023.0957.

50. Schmid V, Foulkes SF, Wang J, et al. Impact of whole body and skeletal muscle composition on peak oxygen uptake in heart failure: a systematic review and meta-analysis. Eur Heart J Open 2024;4:oeae082.

51. Mettauer B, Zoll J, Sanchez H, et al. Oxidative capacity of skeletal muscle in heart failure patients versus sedentary or active control subjects. J Am Coll Cardiol 2001;38:947-54. https://doi.org/10.1016/s0735-1097(01)01460-7.

52. Pandey A, Shah SJ, Butler J, et al. Exercise intolerance in older adults with heart failure with preserved ejection fraction: JACC state-of-the-art review. J Am Coll Cardiol 2021;78:1166-87. https://doi.org/10.1016/j.jacc.2021.07.014.

53. Haykowsky MJ, Kouba EJ, Brubaker PH, et al. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Cardiol 2014;113:1211-6. https://doi.org/10.1016/j.amjcard.2013.12.031.

54. Haykowsky MJ, Brubaker PH, Morgan TM, et al. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. J Gerontol A Biol Sci Med Sci 2013;68:968-75. https://doi.org/10.1093/gerona/glt011.

55. Haykowsky MJ, Nicklas BJ, Brubaker PH, et al. Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. JACC Heart Fail 2018;6:640-9. https://doi.org/10.1016/j.jchf.2018.06.002.

56. Weiss K, Schar M, Panjrath GS, et al. Fatigability, exercise intolerance, and abnormal skeletal muscle energetics in heart failure. Circ Heart Fail 2017;10:e004129. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004129.

57. Haykowsky MJ, Liang Y, Pechter D, et al. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol 2007;49:2329-36. https://doi.org/10.1016/j.jacc.2007.02.055.

58. Warburton DE, Haykowsky MJ, Quinney HA, Humen DP, Teo KK. Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part II: Novel techniques and new advances. Sports Med 1999;27:241-60. https://doi.org/10.2165/00007256-199927040-00004.

59. Warburton DE, Haykowsky MJ, Quinney HA, Humen DP, Teo KK. Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part I: Conventional techniques. Sports Med 1999;27:23-41. https://doi.org/10.2165/00007256-199927010-00003.

60. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O_2 pathway analysis. Circulation 2018;137:148-61. https://doi.org/10.1161/CIRCULATIONAHA.117.029058.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2025.01.012