ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 3079–3091
Published online 24 June 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13979

ORIGINAL ARTICLE

Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Claudia Baratto[1,2], Sergio Caravita[1,3], Davide Soranna[4], Céline Dewachter[2], Antoine Bondue[2], Antonella Zambon[4,5], Luigi P. Badano[1,6], Gianfranco Parati[1,6] and Jean-Luc Vachiéry[2]*

[1]*Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milan, Italy;* [2]*Department of Cardiology, Hopital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070, Bruxelles, Belgium;* [3]*Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy;* [4]*Biostatistics Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy;* [5]*Department of Statistic and Quantitative Methods, University of Milano-Bicocca, Milan, Italyl and* [6]*Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*

Abstract

Aims Exercise right heart catheterization (RHC) is considered the gold-standard test to diagnose heart failure with preserved ejection fraction (HFpEF). However, exercise RHC is an insufficiently standardized technique, and current haemodynamic thresholds to define HFpEF are not universally accepted. We sought to describe the exercise haemodynamics profile of HFpEF cohorts reported in literature, as compared with control subjects.

Methods and results We performed a systematic literature review until December 2020. Studies reporting pulmonary artery wedge pressure (PAWP) at rest and peak exercise were extracted. Summary estimates of all haemodynamic variables were evaluated, stratified according to body position (supine/upright exercise). The PAWP/cardiac output (CO) slope during exercise was extrapolated. Twenty-seven studies were identified, providing data for 2180 HFpEF patients and 682 controls. At peak exercise, patients with HFpEF achieved higher PAWP (30 [29–31] vs. 16 [15–17] mmHg, $P < 0.001$) and mean right atrial pressure ($P < 0.001$) than controls. These differences persisted after adjustment for age, sex, body mass index, and body position. However, peak PAWP values were highly heterogeneous among the cohorts (I^2 = 93%), with a relative overlap with controls. PAWP/CO slope was steeper in HFpEF than in controls (3.75 [3.20–4.28] vs. 0.95 [0.30–1.59] mmHg/L/min, *P* value < 0.0001), even after adjustment for covariates ($P = 0.007$).

Conclusions Despite methodological heterogeneity, as well as heterogeneity of pooled haemodynamic estimates, the exercise haemodynamic profile of HFpEF patients is consistent across studies and characterized by a steep PAWP rise during exercise. More standardization of exercise haemodynamics may be advisable for a wider application in clinical practice.

Keywords Heart failure; Cardiac catheterization; Haemodynamics; Exercise testing; Meta-analysis

Received: 8 December 2021; Revised: 8 April 2022; Accepted: 8 May 2022
**Correspondence to: Jean-Luc Vachiéry, Department of Cardiology, Hopital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070 Brussels, Belgium. Tel: +32 (0) 2 555 5602; +32 (0) 2 555 4866. Email: jeanluc.vachiery@erasme.ulb.ac.be*

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent condition. Additionally, patients may present with lifestyle-limiting effort symptoms but no clinical evidence of hypervolemia.[1] Therefore, in case of non-conclusive exams and normal haemodynamics at rest, exercise right heart catheterization (RHC) has been claimed as the gold-standard diagnostic test for HFpEF, potentially overcoming several limitations of non-invasive examinations and algorithms.[2–4]

However, exercise RHC is a costly and time-consuming test with a limited availability. Moreover, the procedural approach, including patients' body position and exercise protocol as well as the haemodynamic measurements and their interpretation, has not been widely standardized. This non-negligible limitation could impact on the reproducibility and generalizability of the results.[5,6]

To address these issues, we conducted a systematic review and meta-analysis of studies on exercise haemodynamics in patients with HFpEF, taking into account potential heterogeneity of these populations and exercise RHC methodology. Our aim was to describe the exercise haemodynamic profile of a large population of patients diagnosed as HFpEF and to compare it with control subjects. It is important to mention that pulmonary artery wedge pressure (PAWP) is influenced by several factors, including the patient's body position and the timing of measurement during the respiratory and cardiac cycle. Therefore, the reading of pressure traces may differ across investigators, especially during exercise, and lead to heterogeneity of interpretations when a standardized procedure is not universally adopted by all laboratories. However, the impact of body position and of respiratory swings might be minimized when normalizing the exercise-induced changes of pulmonary pressures for cardiac output (CO) increase.[5,7] Additionally, and recent evidence suggests that flow-corrected PAWP during exercise might be a more sensitive marker of HFpEF than absolute PAWP values at peak effort,[5] with proven prognostic value.[4] Thus, we also sought to build and compare the PAWP/CO slope of HFpEF and controls for all studies, to test the validity of this composite variable in a large HFpEF cohort.

Methods

We followed the PRISMA statement[8] for reporting systematic reviews and meta-analysis. A comprehensive literature research on PubMed was updated to December 2020, and the search terms included: ('right heart catheterization' OR 'hemodynamics' OR 'cardiac catheterization' OR 'haemodynamics') AND ('exercise' OR 'effort') AND ('heart failure with preserved ejection fraction' OR 'HFPEF' OR 'dyspnea' OR 'diastolic dysfunction' OR 'diastolic heart failure' OR 'left heart disease') AND ('PAWP' OR 'PCWP' OR 'wedge pressure' OR 'occlusion pressure').

We included papers that met the following criteria: (i) published in peer-reviewed journal, (ii) designed to evaluate the exercise haemodynamics in the HFpEF population, and (iii) reporting PAWP at rest and at peak exercise (main endpoint measure).

We excluded case reports, editorials, reviews, not pertinent studies (e.g. not including HFpEF or not reporting exercise invasive haemodynamics data), and studies reporting follow-up data of HFpEF patients who had undergone implant of an interatrial septal device within a clinical trial. When the same patients were included in more than one study, the larger one was considered.

Two investigators independently reviewed the search results to select the studies based on the inclusion criteria. Additionally, we performed a manual search of secondary sources including references of initially identified articles, reviews, and commentaries to minimize missing relevant studies. Any discrepancy in the process of study selection and data extraction was resolved by discussion between the investigators, and all disagreements were solved by consulting with a third investigator. Study design was reported according to Participant, Intervention, Comparison, Outcome Study. Risk of bias was assessed by two reviewers, using a scale adapted from the Newcastle-Ottawa Quality Assessment Scale for cross-sectional studies.

For each study, non-invasive data (clinical, echocardiography, & blood tests) as well as haemodynamics (e.g. PAWP & CO) at rest and at peak exercise were extracted. Additionally, for all studies reporting PAWP and CO at rest and at peak exercise, we calculated the slope of their relationship during effort.

Statistical analysis

Clinical characteristics of HFpEF and control patients of each study were reported as mean and standard deviation (for continuous variables) or proportions (for categorical variables). A summary estimate of each clinical characteristic, for HFpEF and control patients, was reported as median and interquartile range of study-specific values and jointly represented with a radar plot.

When only median and interquartile range of haemodynamic variable were available in included studies, they were transformed in mean and standard deviation value[9] before applying the meta-analytic procedure. Summary estimates of each haemodynamic variable were separately evaluated for HFpEF and control cohorts. Additionally, summary estimates of PAWP and delta CO were separately evaluated also for exercise body position. The random effect summary mean estimate and the corresponding 95% confidence intervals (95% CI) were calculated according to the DerSimonan and Laird's method.[10] Between-studies' heterogeneity was quantified using the I^2 index. Values of this index more than 75% suggest high heterogeneity.[11] Homogeneity between summary mean estimates stratified for body position during exercise was performed by a χ^2 statistic. In order to account for potential populations' heterogeneity, reflecting differences in inclusion criteria of individual studies, we performed a stratified analysis. In particular, we subdivided studies defining HFpEF based on haemodynamic criteria only, from studies defining HFpEF based on clinical criteria or including patients with LVEF $<$ 50%.

Finally, univariate and multivariate meta-regression models were implemented for each haemodynamic variable, including status (HFpEF or control) as independent variable, and age, sex, body mass index (BMI), and body position as dependent variables. Meta-regression is a linear weighted mixed model including study as random effect and standard error of published mean as weight.[12] The estimated

coefficient related to status variable gives information about the summary means difference.

Results were considered statistically significant when two-tailed *P* value was lower than 0.05. All analyses were performed with R Version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection

One hundred and thirty-eight studies were identified. After preliminary screening based on the title and the abstract, 48 studies were selected for full-text review. Other studies were excluded because either reporting duplicate patients' data with other larger studies (19 studies) or not reporting the exercise haemodynamic variables (*Figure 1*). Study design of included manuscripts and the Newcastle-Ottawa Quality Assessment Scale are reported in Supporting Information, *Tables S1* and *S2*.

Characteristics of included studies

The 27 selected studies[2–4,13–36] included 2180 HFpEF patients and 682 controls. Characteristics of individual studies are reported in *Table 1*. Thirteen studies (48%) had a prospective design,[3,4,17,19,23,25–27,29–31,34] 13 (48%) were retrospective,[2,13–15,18,20–22,24,28,33,35,36] and 1 study (4%) was a randomized controlled trial.[32]

Of the 27 selected studies, 17 were performed in three centres of the United States,[2–4,13–18,21,24,26,28,30,33,34,36] 5 in one Australian centre,[19,22,25,27,31] and 2 in Europe.[29,35] Three studies were multicentric, with patients coming from American, Australian, and European centres.[20,23,32]

Overall, the selected studies included 35 cohorts of HFpEF patients and 21 cohorts of control subjects, whose clinical characteristics are reported in *Tables S3* and *S4*, respectively. Control subjects were mainly individuals who underwent a clinically indicated invasive cardiopulmonary evaluation for unexplained dyspnoea and who did not satisfy the haemodynamic diagnostic criteria for HFpEF. Healthy volunteers (n = 8) served as control group only in one study.[31]

A symptom-limited exercise testing protocol was used in all studies. Patients underwent supine exercise in 21 studies[2,13,15–23,25,27,29–34] and upright exercise in 6 studies.[3,4,14,24,26,28] Exercise PAWP was measured at end-expiration in almost all studies (25 of 27). Only in seven studies (26%) high-fidelity catheters were employed.[2,17,23,30,33,34,36] CO was measured by direct Fick method in most studies (n = 16, 59%).[2–4,13–18,21,23,24,26,28,30,36]

Only four studies used non-invasive diagnostic criteria to define HFpEF, including either clinical parameters, echocardiographic data, or reduced peak oxygen consumption at cardiopulmonary exercise test.[13,23,29,31] In all the other studies, the diagnosis of HFpEF was confirmed based on rest or peak PAWP. A peak PAWP cut-off of ≥25 mmHg was used in all but one of the studies performing the effort in supine position.[35] In four of the six studies evaluating patients exercising in the upright position, a peak PAWP > 20 mmHg or a PAWP/CO slope > 2 mmHg/L/min was considered as a pathological threshold to define HFpEF.[3,4,24,28]

Notably, six studies focused on specific HFpEF subpopulations, such as those with obesity, recent myocardial infarction, non-obstructive coronary artery disease, or patients included in an interventional trial.[20,24,29,32,34,36] Only in four studies the left ventricular ejection fraction to define

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. HFpEF, heart failure with preserved ejection fraction; RHC, right heart catheterization.

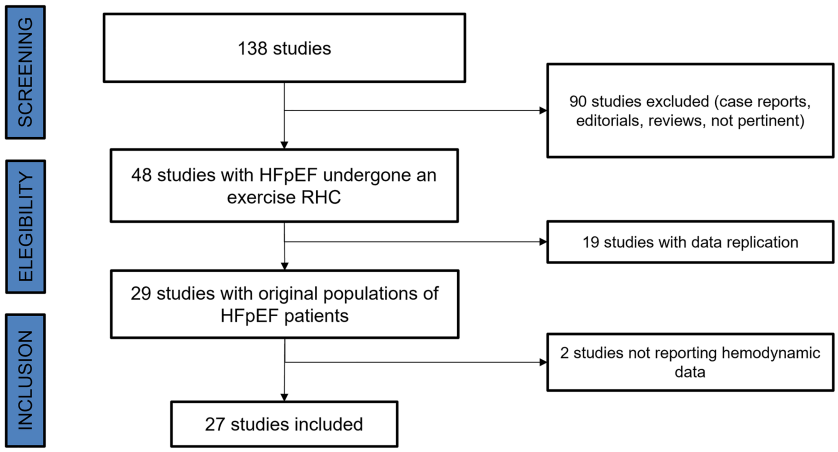


Table 1 Characteristics of the included studies

Author	Country	Centre	*n* HFpEF	*n* controls	Timing of enrolment
Tschöpe *et al.*[35]	Germany	Campus Benjamin Franklin	15	15	2003
Borlaug *et al.*[2]	USA	Mayo Clinic	32	23	2005–2009
Maeder *et al.*[31]	Australia	Alfred Hospital	14	8	2008–2009
Abudiab *et al.*[13]	USA	Mayo Clinic	109	73	2002–2011
Andersen *et al.*[29]	Denmark	Rigshospitalet & Copenhagen University	61		2010–2012
Santos *et al.*[28]	USA	Brigham and Women's Hospital	31	31	2011–2013
Houstis *et al.*[14]	USA	Massachusetts General Hospital	79	55	2006–2016
Obokata *et al.*[15]	USA	Mayo Clinic	195	71	2000–2014
Reddy *et al.*[30]	USA	Mayo Clinic	98	22	
Nanayakkara *et al.*[25]	Australia	Alfred Hospital	21	19	
Eisman *et al.*[3]	USA	Massachusetts General Hospital	77	98	
Gorter *et al.*[14]	USA	Mayo Clinic	161		2006–2013
McCabe *et al.*[24]	USA	Brigham and Women's Hospital	8	14	
Platz *et al.*[26]	USA	Brigham and Women's Hospital	13	12	
Ho *et al.*[4]	USA	Massachusetts General Hospital	243		2006–2017
Obokata *et al.*[17]	USA	Mayo Clinic	38	20	
Reddy *et al.*[18]	USA	Mayo Clinic	238	125	
Van Empel *et al.*[19]	Australia	Alfred Hospital	9	21	
Wolsk *et al.*[20]	USA, Europa, Australia	Multicentre	108	42	2013–2016
Beale *et al.*[22]	Australia	Alfred Hospital	161		2008–2018
Chen *et al.*[23]	Taiwan	Taiwan University Hospital	34		2018
Telles *et al.*[27]	Australia	Alfred Hospital	49	22	2016–2018
Obokata *et al.*[32]	USA, Europe, Australia	Multicentre	79		2014–2016
Fermoyle *et al.*[21]	USA	Mayo Clinic	30		2009–2012
Sorimachi *et al.*[33]	USA	Mayo Clinic	105	51	2007–2018
Ahmad *et al.*[34]	USA	Mayo Clinic	22	29	2010–2019
Houston and Tedford[37]	USA	Mayo Clinic	169		2000–2014

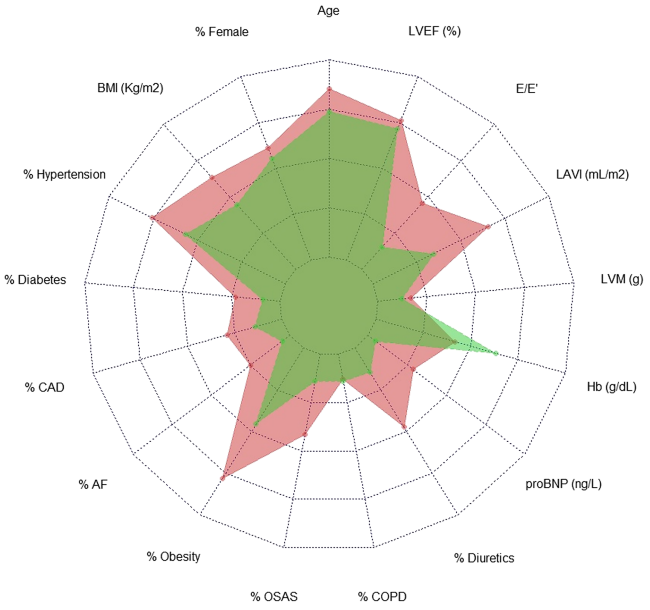
BMI, body mass index; CAD, coronary artery disease; CPCPH, combined post-capillary pulmonary hypertension; EAT, epicardial adipose tissue; END-EXP, end-expiratory phase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFpEFphys, physiological definition of heart failure with preserved ejection fraction; IPCPH, isolated post-capillary pulmonary hypertension; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Table 1 (continued)

Author	Exercise position	PAWP (end-exp/avg)	PAWP (mean/mid-A)	HFpEF diagnosis	Other remarks
Tschöpe *et al.*[35]	Supine			Haemodynamic (rest and/or exercise), echo	restPAWP > 12, peakPAWP > 20
Borlaug *et al.*[2]	Supine	End-exp		Haemodynamic (exercise)	
Maeder *et al.*[31]	Supine	End-exp	Mean	↓ ex capacity	
Abudiab *et al.*[13]	Supine	End-exp		Clinical	
Andersen *et al.*[29]	Supine	Avg		Echo	LVEF > 45% and post-STEMI
Santos *et al.*[28]	Upright	End-exp		Haemodynamic (exercise)	PAWP peak > 20
Houstis *et al.*[14]	Upright	End-exp		Haemodynamic (rest and/or exercise), ↓ ex capacity	
Obokata *et al.*[15]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Reddy *et al.*[30]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Nanayakkara *et al.*[25]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Eisman *et al.*[3]	Upright	End-exp		Haemodynamic (exercise)	
Gorter *et al.*[14]	Supine	End-exp		Haemodynamic (rest)	
McCabe *et al.*[24]	Upright	Avg		Haemodynamic (rest and/or exercise)	PAWP rest > 15, peak > 20 mmHg
Platz *et al.*[26]	Upright	End-exp		Haemodynamic (rest)	
Ho *et al.*[4]	Upright	End-exp		Haemodynamic (exercise)	
Obokata *et al.*[17]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Reddy *et al.*[18]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Van Empel *et al.*[19]	Supine	End-exp	Mean	Haemodynamic (exercise), echo	LVEF > 45%
Wolsk *et al.*[20]	Supine	End-exp	Mean	Haemodynamic (rest and/or exercise), BNP, echo	LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP
Beale *et al.*[22]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Chen *et al.*[23]	Supine	End-exp	Mid-A	Clinical, BNP, echo	
Telles *et al.*[27]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Obokata *et al.*[32]	Supine			Haemodynamic (rest and/or exercise), BNP, echo	LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP
Fermoyle *et al.*[21]	Supine	End-exp	Mid-A	Haemodynamic (rest and/or exercise)	
Sorimachi *et al.*[33]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Ahmad *et al.*[34]	Supine	End-exp	Mid-A	Haemodynamic (rest and/or exercise)	Non-obstructive CAD
Houston and Tedford[37]	Supine	End-exp		Haemodynamic (rest and/or exercise)	BMI ≥ 30

BMI, body mass index; CAD, coronary artery disease; CPCPH, combined post-capillary pulmonary hypertension; EAT, epicardial adipose tissue; END-EXP, end-expiratory phase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFpEFphys, physiological definition of heart failure with preserved ejection fraction; IPCPH, isolated post-capillary pulmonary hypertension; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Figure 2 Radar plot with the clinical characteristics of HFpEF patients (pink) and control subjects (green). AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin; LAVI, left atrial volume indexed; LVM, left ventricular mass; NT-proBNP, N terminal pro brain natriuretic peptide; OSAS, obstructive sleep apnoea syndrome.



HFpEF was >40% or >45%, rather than the currently adopted cut-off of ≥50%.[19,20,29,32]

Clinical characteristics of heart failure with preserved ejection fraction patients and controls

A graphical joint comparison of clinical characteristics of HFpEF patients and controls is reported in *Figure 2* and in *Table S5*. The HFpEF group was slightly older than the control group (median age 67 vs. 60 years), with more women (61% vs. 56%), and higher BMI (32.0 vs. 27.9 kg/m^2). Moreover, the HFpEF group had a larger burden of comorbidities (prevalence of arterial hypertension was 76% vs. 56%, and prevalence of diabetes was 23% vs. 9%), higher N terminal pro brain natriuretic peptide (NT-proBNP) (340 vs. 83 pg/mL), larger left atrial volume index (39 vs. 29 mL/m^2), and higher E/E' (13 vs. 9). The prevalence of atrial fibrillation was 25% in HFpEF vs. 5% in controls, but this information was reported only in about half of the cohorts.

Haemodynamics at rest

The summary estimates of PAWP at rest in HFpEF and controls are reported in *Figure S1*. The summary mean of PAWP was 15 (95% CI: 14–16) mmHg in HFpEF cohorts and 9 (95% CI: 8–9) mmHg in control cohorts. High heterogeneity, especially in HFpEF cohorts, was observed (I^2 = 97% and I^2 = 82%, respectively). This heterogeneity as well as the PAWP summary estimates did not show relevant differences at a stratified data analysis subdividing studies adopting pure haemodynamic definitions for HFpEF, as opposed to those adopting only non-invasive, clinical definitions of HFpEF, or including patients with LVEF < 50% (*Figure S2*). Notably, in all the studies adopting non-invasive or atypical HFpEF definitions, exercise was performed in the supine position. Similar to PAWP, also right atrial pressure at rest was higher in HFpEF than in control subjects (8, 95% CI: 7–10 mmHg vs. 4, 95% CI: 3–5 mmHg, respectively, *P* value < 0.0001).

In HFpEF, both CO and cardiac index (5.13; 95% CI: 4.95–5.31 L/min and 2.61; 95% CI: 2.53–2.68 L/min/m^2, respectively), even if within normal limits, were slightly lower than those of controls (5.41; 95% CI: 5.19–5.63 L/min and 2.76; 95% CI 2.61–2.91 L/min/m^2).

We compared the summary estimates of HFpEF and controls cohorts by meta-regression analysis without and with adjustment for age, sex, BMI, and body position (*Table 2*). In the meta-regression analysis without adjustment, we observed a statistically significant difference for all haemodynamic variables, except CO, between HFpEF and control cohorts. After adjustment, CO and cardiac index were no more different between the two groups.

Exercise haemodynamics

Complete rest and exercise haemodynamics of HFpEF patients and control subjects from each included study are reported in *Tables S6–S9*.

Table 2 Rest and exercise haemodynamics of heart failure with preserved ejection fraction and control subjects

Outcome	HFpEF		Controls		Unadjusted meta-regression models		Adjusted meta-regression models	
	Mean (95% CI)	*N* of cohorts	Mean (95% CI)	*N* of cohorts	*P* value	*N* of cohorts	*P* value	*N* of cohorts
REST								
PAWP (mmHg)	14.98 (13.84–16.13)	35	8.70 (8.16–9.24)	22	<0.0001	57	<0.0001	54
CO (L/min)	5.13 (4.95–5.31)	15	5.41 (5.19–5.63)	11	0.068	26	0.103	26
CI (L/min/m^2)	2.61 (2.53–2.68)	18	2.76 (2.61–2.91)	10	0.083	28	0.413	25
RAP (mmHg)	8.35 (7.25–9.82)	26	4.05 (3.23–4.87)	16	<0.0001	42	0.012	42
PEAK								
PAWP (mmHg)	29.99 (28.93–31.06)	34	15.76 (14.75–16.78)	21	<0.0001	55	<0.0001	54
CO (L/min)	9.50 (8.97–10.03)	18	12.95 (10.00–15.90)	13	<0.0001	31	0.128	31
CI (L/min/m^2)	4.60 (4.22–5.01)	20	6.75 (5.93–7.56)	9	<0.0001	29	0.047	26
RAP (mmHg)	17.73 (16.32–19.14)	25	8.18 (7.53–8.84)	15	<0.0001	40	<0.0001	40
DELTA PEAK-REST								
PAWP (mmHg)	15.00 (14.16–15.84)	34	7.15 (6.27–8.02)	21	<0.0001	55	<0.0001	52
CO (L/min)	4.38 (3.73–5.03)	15	8.15 (6.71–9.59)	11	<0.0001	26	0.096	26

95% CI, 95% of the confidence interval; CI, cardiac index; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; *N*, number; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.
Adjustment was performed using meta-regression models including age, sex, body mass index, and body position as covariates. Data are reported as mean (95% confidence interval).
The *P* value reflects the comparison between the two groups, both unadjusted, and after adjustment for age, sex, BMI, and body position.

During exercise, HFpEF cohorts showed markedly higher filling pressures than controls (*Table 2* and *Figure 3*). Similarly to resting data, these results were characterized by high heterogeneity (I^2 = 93% and 83%, respectively). This heterogeneity, as well as the PAWP summary estimates, did not show relevant differences at a stratified data analysis subdividing studies adopting pure haemodynamic definitions for HFpEF as opposed to studies adopting only non-invasive, clinical definitions of HFpEF, or including patients with LVEF < 50% (*Figure S3*). This wide dispersion of PAWP values among the cohorts led to a zone of partial overlap between HFpEF and controls at values between 20 and 25 mmHg. Nonetheless, HFpEF cohorts showed a summary estimate of PAWP at peak which was twice as high as compared with control cohorts (30; 95% CI: 29–31 mmHg and 16; 95% CI: 15–17 mmHg, respectively), as well as of delta PAWP (15; 95% CI: 14–16 mmHg and 7; 95% CI: 6–8 mmHg, respectively), and of right atrial pressure (18; 95% CI: 16–19 mmHg and 8; 95% CI: 8–9 mmHg, respectively). All these differences remained statistically significant after adjustment for the covariates (*P* value < 0.0001).

Additionally, summary estimates of PAWP at peak performed during supine exercise was slightly higher than those obtained in upright position only for HFpEF cohorts (supine position: 31; 95% CI:30–32 mmHg vs. upright position; 26; 95% CI: 25–27 mmHg, respectively, *P* value < 0.01; *Figure 3*).

Another relevant difference in the haemodynamic response to exercise between HFpEF and controls concerned the exercise-induced increase in CO (*Table 2*). Both CO and cardiac index at peak resulted significantly lower in HFpEF than in controls (*P* < 0.001). Moreover, the increase in CO during exercise was significantly lower in HFpEF than in controls (4.38; 95% CI: 3.73–5.02 L/min and 8.15; 95% CI: 6.71–9.59 L/min respectively, *P* value < 0.0001) although high heterogeneity was present (I^2 = 94% and I^2 = 96%), as shown in *Table 2* and *Figure 4*. However, this difference was no longer statistically significant after adjustment for the covariates. Finally, summary estimate of delta CO in the supine position resulted lower than in upright position only for HFpEF cohorts (*P* value < 0.01, *Figure 4*).

Because there were more cohort studies per centre with overlapped recruitment period, we performed a sensitivity analysis including only one cohort per centre[3,4,17,21,22,26–28,30,34] to verify the robustness of results. As shown in *Table S10*, summary point and interval estimates of each exercise haemodynamic variable in this subset of studies were comparable with those obtained on the entire dataset.

Pulmonary artery wedge pressure/circuit output slope

Figure 5 represents PAWP/CO slopes for cohorts reporting rest and at peak values for both haemodynamic variables.

Figure 3 Forest plots with pooled standardized mean pulmonary artery wedge pressure values at peak exercise both in heart failure with preserved ejection fraction and in controls. HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

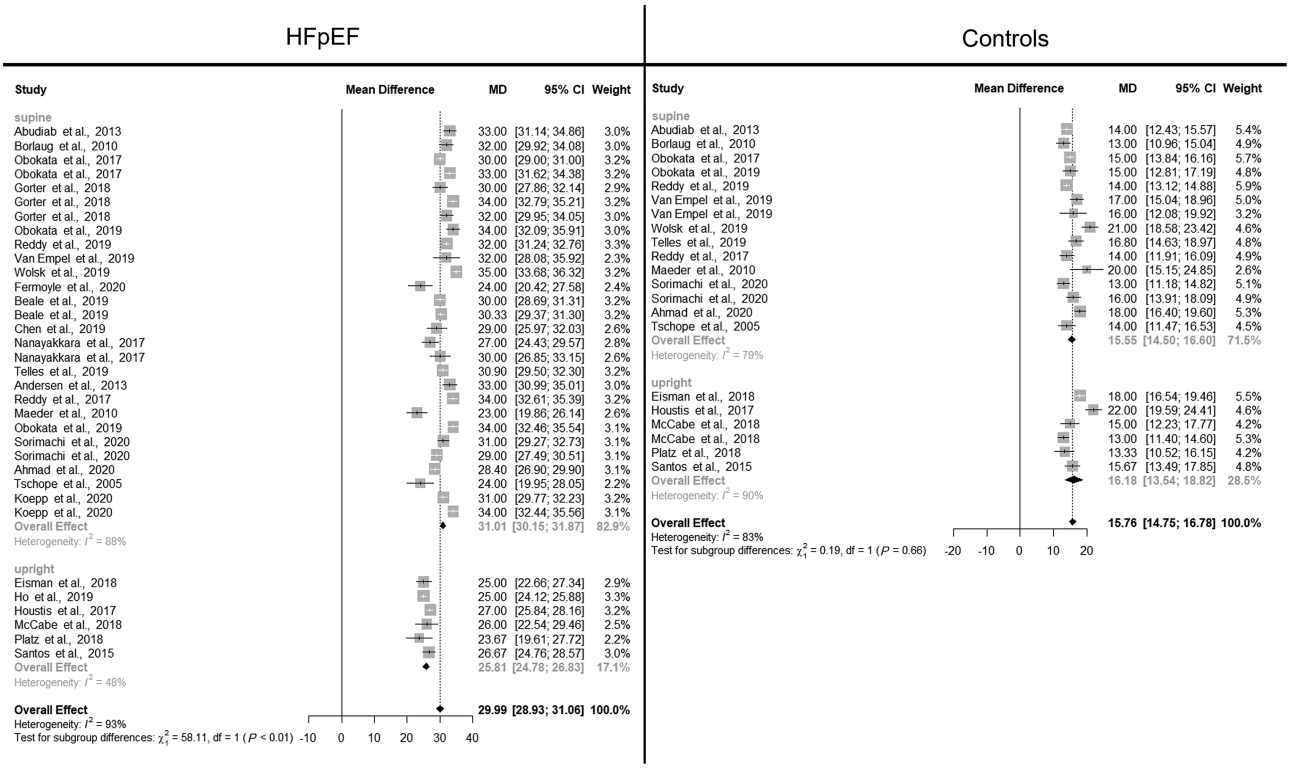
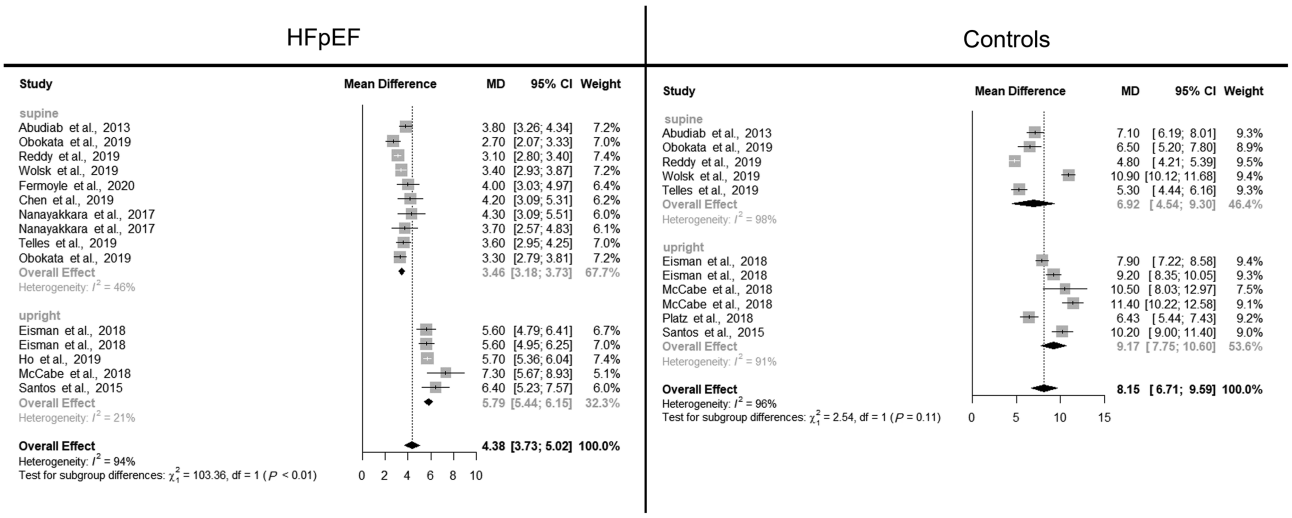
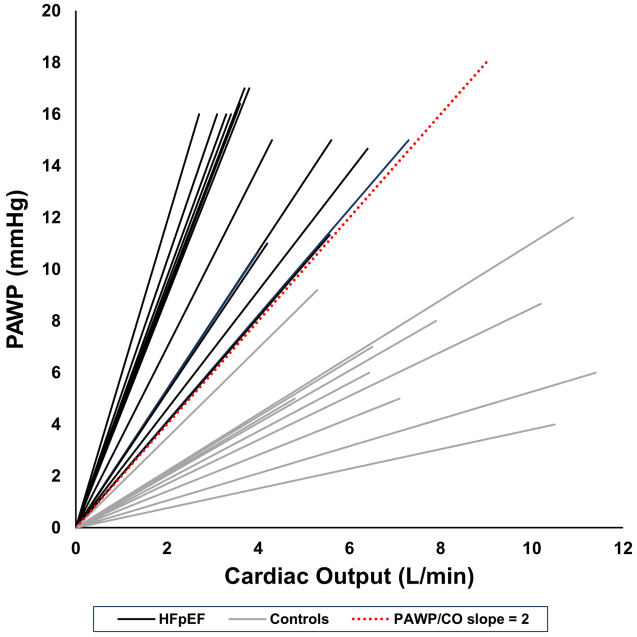


Figure 4 Forest plots with pooled standardized cardiac output increase during exercise both in heart failure with preserved ejection fraction and in the controls. CO, cardiac output; HFpEF, heart failure with preserved ejection fraction.



For all the studies, the Y-intercept of such relationship was fixed at 0, in order to focus on inter-studies differences in slopes, independent from baseline values. Coherent with what shown above for rest and peak PAWP as well as for CO data, HFpEF cohorts had a significantly larger impairment in the haemodynamic response to exercise compared with controls, witnessed by a steeper PAWP/CO slope. Indeed, in HFpEF cohorts, the summary PAWP/CO slope was higher

Figure 5 Pulmonary artery wedge pressure (PAWP)/cardiac output (CO) regression slopes in cohorts of patients with heart failure and preserved ejection fraction (HFpEF) and in control subjects cohorts. The red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.



than in control cohorts (3.75; 95% CI: 3.20–4.28 mmHg/L/min and 0.95; 95% CI: 0.30–1.59 mmHg/L/min, *P* value < 0.0001). This difference persisted even after adjustment for age, sex, BMI, and body position (*P* value = 0.007). All PAWP/CO slopes in HFpEF cohorts were found above the proposed pathological threshold of >2 mmHg/L/min while control cohorts showed slopes always <2 mmHg/L/min.

Finally, summary estimates of PAWP/CO slope were higher in HFpEF cohorts performing exercise in the supine position compared with those in upright position ($P < 0.0001$ and $P = 0.0002$ at non-adjusted and adjusted analysis, respectively), but not in control cohorts ($P = 0.135$ and $P = 0.966$ at non-adjusted and adjusted analysis, respectively). In *Figure S4*, the PAWP/CO slope in supine and upright position for HFpEF and control cohorts is presented.

Discussion

Our meta-analysis provides a thorough characterization of a large population of HFpEF and controls who underwent exercise RHC, highlighting (i) methodological heterogeneity in exercise haemodynamic protocols across centres; (ii) a quite typical clinical profile of HFpEF patients assessed through exercise haemodynamics, which differ from that of control subjects (even though clinical characterization was frequently incomplete as compared with what would be desired in order to apply current non-invasive HFpEF definitions); (iii) a high heterogeneity of haemodynamic responses to exercise across the different HFpEF cohorts; and (iv) the potential validity of a PAWP/CO slope cut-off value $>$ 2 mmHg/L/min to define HFpEF across laboratories independently from body position, as an alternative or as a complementary measure to absolute exercise PAWP supine or upright thresholds.

Published data on exercise RHC come mainly from retrospective analysis of relatively small contemporary cohorts of patients investigated in very few highly experienced centres in the world, albeit with methodological heterogeneity. In most studies, exercise was performed in the supine position (78%), CO was measured by direct Fick method (59%), and PAWP using fluid-filled catheters (74%). However, at variance from the suggestion from the European Respiratory Society to average pressure values over several respiratory cycles, in order to avoid PAWP overestimation during exercise,[6] in more than 90% of studies, PAWP was measured at end-expiration. Additionally, and despite the notion that PAWP values differ according to the phase of the cardiac cycle,[37] only 22% of studies reported such information, with mean PAWP value reported in half of them, and end-diastolic measurement (mid-A wave) in the other half. This underscores the need for more uniform standardization of the RHC procedure to obtain reproducible results across laboratories.

Heart failure with preserved ejection fraction patients were mostly elderly obese women, with a high burden of comorbidities associated with accelerated cardiovascular ageing,[38] an enlarged left atrium, and high NT-proBNP values. Only four studies included also patients with LVEF lower than 50% (LVEF $\geq$ 40–45%). However, many characteristics were not uniformly reported across the studies, precluding to determine whether these patients would fulfil the currently adopted diagnostic criteria for HFpEF in clinical practice (e.g. HFA-PEFF score and H2FPEF score).[39,40] Additionally, despite the non-invasive assessment might have overall suggested a quite typical HFpEF profile,[39] it was not deemed to be sufficient to allow per se for a definite diagnosis of HFpEF in the individual patient before the exercise invasive haemodynamic study. This might reflect the complexity of HFpEF, where comorbidities may act as confounders in explaining patients' complaints (i.e. exertional breathlessness) in the absence of sensitive non-invasive markers for early stages of disease.[2,5,41]

The haemodynamic phenotype of pooled HFpEF patients showed an increase of both left and right filling pressure as compared with control subjects, likely as a consequence of cardiovascular ageing with cardiac fibrosis and diastolic dysfunction[42] combined with dysfunctional preload (high stressed blood volume).[43] This observation was also made in a previous meta-analysis on 20 studies.[44] Filling pressures at rest in HFpEF were on average just at the upper limit of normal, but the difference between HFpEF and controls,

albeit being already present at rest, was greatly magnified by the physical stress, even after correction for age, sex, BMI, and body position. At a first glance, patients with HFpEF also seemed to have a reduced CO reserve, as compared with controls. However, the lower absolute CO response to exercise displayed by HFpEF lost statistical significance after adjustment for some relevant baseline differences in HFpEF and controls (age, sex, and BMI). This is at variance from the meta-analysis by Pandey *et al*.,[44] where both stroke volume and heart rate response to exercise were lower in HFpEF than in controls after adjustment for age or BMI, overall suggesting a reduced cardiac reserve during exercise. However, (i) cardiovascular responses may change as a function of ageing (in particular with lower chronotropic response),[45] potentially resulting in lower CO in older HFpEF patients than in controls—a difference that might reasonably disappear after correction for age; (ii) there is conflicting evidence on the role of cardiac reserve in exercise limitation of HFpEF patients, with arguments favouring a peripheral limitation[14]; (iii) our study, which was more focused on PAWP and PAWP/CO slope than on central vs. peripheral limit to exercise in HFpEF and conducted 3 years later, could include more than twice the patients studied by Pandey *et al*.,[44] potentially overcoming some limitations in the analysis related to the sample size. Thus, the above-mentioned haemodynamic characteristics (high filling pressures and normal age-corrected CO) are consistent with the definition of HFpEF as a clinical syndrome mainly characterized by the ability of the heart to accommodate blood flow for the increased metabolic needs at the expense of high filling pressures.[46]

However, the absolute thresholds of peak exercise PAWP to define HFpEF are not universally accepted and might be influenced by several factors, including exercise duration and intensity, the phase of the respiratory, or cardiac cycle in which measurements are taken,[5,6] and the body position in which exercise is performed. Indeed, as it would have been expected, stratification for body position confirmed that PAWP values in HFpEF were 5 mmHg higher in the supine compared with the upright position, somehow indirectly reinforcing the validity of previously proposed distinct PAWP cut-off for the two body positions (25 and 20 mmHg, respectively). Furthermore, the above-mentioned procedural factors, some of which were not systematically reported, as well as some non-invasive or atypical definitions of HfpEF in the included studies may, at least in part, account for both the heterogeneity of PAWP estimates across the studies, and for a partial overlap in PAWP estimates at peak exercise in some studies between HFpEF and controls.

As it could have been expected based on different peak PAWP and CO values, also PAWP/CO slope differed between HFpEF and controls. Notably, the slopes we could extrapolate from available studies were always >2 mmHg/L/min for HFpEF and <2 mmHg/L/min for controls, with non-overlapping confidence intervals, thus somehow confirming and extending the validity of such cut-off value, that has been generally reported only in upright studies. However, the steepness of the PAWP/CO slope was higher in the supine than in the upright position in HFpEF but not in control subjects cohorts. Thus, at variance from healthy subjects,[7] we might speculate that the flow-normalized behaviour of the pulmonary circulation is not independent from the body position, at least in patients with (occult) fluid overload, where dysfunctional preload could be magnified when laying down. Accordingly, even if the PAWP/CO slope cut-off of 2 mmHg/L/min might be valid to diagnose HFpEF irrespectively from body position (and from the phase of the respiratory cycle in which PAWP is measured),[5] its absolute value might not provide comparable results in patients performing supine or upright exercise.

Limitations

Most of the data used for this meta-analysis come from two US centres, potentially limiting the representativity of our results. However, as outlined above, clinical characteristics were overall in line with those of a typical HFpEF population. Furthermore, most studies selected patients based on rest and/or exercise haemodynamics rather than on clinical/non-invasive data. It is therefore possible that invasive haemodynamic criteria select a particular type or subgroup of HFpEF patients, and that these results might not be applicable to other cohorts.

Individual patients' data were not available, so that we drove conclusions based on pooled average of different populations. Accordingly, the results of our meta-analysis should be considered more hypothesis-generating than definitive, requiring further confirmation. Additionally, we plotted PAWP/CO slope based just on two PAWP/CO pairs (rest and peak) rather than building a multipoint PAWP/CO relationship throughout the whole exercise, as originally suggested.[3,4] However, in an ad hoc analysis, we performed on previously published exercise haemodynamic data from 57 patients from our laboratory,[5] the mean bias derived from such a methodological simplification was clinically negligible, that is, 3%. Indeed, the mean multipoint PAWP/CO slope in this cohort was 3.66 mmHg/L/min, while the PAWP/CO slope built based on rest and peak values only was 3.54 mmHg/L/min. Finally, in order to avoid further methodological confounders, control subjects were taken from the same studies of HFpEF patients. As declared, they were not healthy subjects but patients not qualifying as HFpEF based on exercise haemodynamics (non-cardiac dyspnoea), in most cases due to the retrospective nature of invasive, clinically indicated studies. Nonetheless, they sorted out to have different (and normal) haemodynamics as compared with HFpEF patients.

Conclusions

Despite methodological heterogeneity across highly experienced centres, the haemodynamic profile of HFpEF patients is consistent across studies and characterized by a higher left and right filling pressure at rest compared with controls, enhanced by physical exercise. A PAWP/CO slope cut-off $>$ 2 mmHg/L/min seems to retain validity also for studies conducted in the supine position, potentially overcoming the need of different supine and upright PAWP cut-offs. Rigorous methodological and interpretative requirements are advisable for a larger application of exercise haemodynamics in clinical practice, to provide consistent results across laboratories.

Acknowledgements

Dr Baratto is the recipient of a Research Grant from the European Society of Cardiology. Dr Caravita received the grant Vera Srebot from the Fondazione CNR/Regione Toscana per la Ricerca Medica e di Sanità Pubblica. Dr Bondue received support from the Belgian Fonds de la Recherche Scientifique (FRS-FNRS—grant J.0011.19), from the Erasme Foundation (ULB), and from the Belgian Cardiac Surgery Foundation. Dr Vachiéry is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department.

Conflict of interest

The authors have no conflict of interest to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. New-Castle Ottawa scale for quality assessment of cross-sectional studies.

Table S2. Participant, Intervention, Comparison, Outcome Study (PICOs).

Table S3. Clinical characteristics of heart failure with preserved ejection fraction cohorts as reported in individual studies.

Table S4. Clinical characteristics of control cohorts as reported in individual studies.

Table S5. Clinical characteristics of patients with heart failure with preserved ejection fraction and control subjects across included studies. Data are reported as median (interquartile range).

Table S6. Rest and exercise hemodynamics of heart failure with preserved ejection fraction cohorts in supine position as reported in individual studies.

Table S7. Rest and exercise hemodynamics of control cohorts in supine position as reported in individual studies.

Table S8. Rest and exercise hemodynamics of heart failure with preserved ejection fraction cohorts in upright position as reported in individual studies.

Table S9. Rest and exercise hemodynamics of control cohorts in upright position as reported in individual studies.

Table S10. Supporting Information.

Figure S1. Forest plots with pooled standardized mean pulmonary artery wedge pressure values at rest both in heart failure with preserved ejection fraction and in controls.

Figure S2. Forest plots with pooled standardized mean PAWP values at rest in patients with HFpEF, stratified by HFpEF definitions and body position.

Figure S3. Forest plots with pooled standardized mean PAWP values at peak exercise in patients with HFpEF, stratified by HFpEF definitions and body position.

Figure S4. Pulmonary artery wedge pressure (PAWP) /cardiac output (CO) regression slopes in cohorts of patients with heart failure and preserved ejection fraction (HFpEF) and in control subjects cohorts, stratified by body position. The panel on the top represents the mean PAWP/CO slope of cohorts (both HFpEF and control subjects) studied in the supine position. The panel on the bottom represents the mean PAWP/CO slope of cohorts (both HFpEF and control subjects) studied in the upright position. In both panels the red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.

References

1. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019; **124**: 1598–1617. PMID: 31120821; PMCID: PMC6534165.
2. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010; **3**: 588–595. Epub 2010 Jun 11. PMID: 20543134; PMCID: PMC3048586.
3. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R, Lewis GD. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail*. 2018; **11**: e004750. PMID: 29695381; PMCID: PMC5937988.

4. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation*. 2019; **140**: 353–365. Epub 2019 May 28. PMID: 31132875; PMCID: PMC6684250.
5. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati G, Vachiéry JL. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021; **14**: e007555. Epub ahead of print. PMID: 33951935.
6. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grünig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J*. 2017; **50**: 1700578.
7. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. *J Appl Physiol (1985)*. 2016; **121**: 1145–1150. Epub 2016 Oct 7. PMID: 27763874.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009; **62**: e1–e34.
9. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014; **14**: 135.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7**: 177–188.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; **21**: 1539–1558.
12. Stanley TD, Doucouliagos H. Neither fixed nor random: weighted least squares meta-analysis. *Stat Med*. 2015; **34**: 2116–2127.
13. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013; **15**: 776–785. Epub 2013 Feb 20. PMID: 23426022; PMCID: PMC3857919.
14. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O_2 pathway analysis. *Circulation*. 2018; **137**: 148–161. Epub 2017 Oct 9. PMID: 28993402; PMCID: PMC5760316.
15. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017; **136**: 6–19. Epub 2017 Apr 5. PMID: 28381470; PMCID: PMC5501170.
16. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J*. 2018; **39**: 2825–2835. PMID: 29947750; PMCID: PMC6093469.
17. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, Borlaug BA. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J*. 2019; **40**: 3707–3717. PMID: 31513270; PMCID: PMC7963136.
18. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; **21**: 891–900. Epub 2019 Mar 28. PMID: 30919562.
19. van Empel VP, Mariani J, Borlaug BA, Kaye DM. Impaired myocardial oxygen availability contributes to abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2014; **3**: e001293. PMID: 25468660; PMCID: PMC4338724.
20. Wolsk E, Kaye D, Komtebedde J, Shah SJ, Borlaug BA, Burkhoff D, Kitzman DW, Lam CSP, van Veldhuisen DJ, Ponikowski P, Petrie MC, Hassager C, Møller JE, Gustafsson F. Central and peripheral determinants of exercise capacity in heart failure patients with preserved ejection fraction. *JACC Heart Fail.* 2019; **7**: 321–332. Epub 2019 Mar 6. PMID: 30852235.
21. Fermoyle CC, Stewart GM, Borlaug BA, Johnson BD. Pulmonary vascular pressures and gas exchange response to exercise in heart failure with preserved ejection fraction. *J Card Fail*. 2020; **26**: 1011–1015. Epub 2020 Aug 1. PMID: 32750488; PMCID: PMC7704759.
22. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CSP, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail.* 2019; **7**: 239–249. PMID: 30819380.
23. Chen ZW, Huang CY, Cheng JF, Chen SY, Lin LY, Wu CK. Stress echocardiography-derived E/e' predicts abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *Front Physiol*. 2019; **10**: 1470. PMID: 31849715; PMCID: PMC6901703.
24. McCabe C, Oliveira RKF, Rahaghi F, Faria-Urbina M, Howard L, Axell RG, Priest AN, Waxman AB, Systrom DM. Right ventriculo-arterial uncoupling and impaired contractile reserve in obese patients with unexplained exercise intolerance. *Eur J Appl Physiol*. 2018; **118**: 1415–1426. Epub 2018 Apr 30. PMID: 29713818; PMCID: PMC6028899.
25. Nanayakkara S, Haykowsky M, Mariani J, Van Empel V, Maeder MT, Vizi D, Kaye DM. Hemodynamic profile of patients with heart failure and preserved ejection fraction vary by age. *J Am Heart Assoc*. 2017; **6**: e005434. PMID: 28939710; PMCID: PMC5634249.
26. Platz E, Merz A, Silverman M, Lewis E, Groarke JD, Waxman A, Systrom D. Association between lung ultrasound findings and invasive exercise haemodynamics in patients with undifferentiated dyspnoea. *ESC Heart Fail*. 2019; **6**: 202–207. Epub 2018 Nov 26. PMID: 30474936; PMCID: PMC6352886.
27. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, William J, Marwick TH, Kaye DM. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; **21**: 495–505. Epub 2019 Jan 16. PMID: 30652393.
28. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. *Circ Heart Fail*. 2015; **8**: 278–285. Epub 2014 Dec 30. PMID: 25550438; PMCID: PMC4936392.
29. Andersen MJ, Ersbøll M, Gustafsson F, Axelsson A, Hassager C, Køber L, Boesgaard S, Pellikka PA, Møller JE. Exercise-induced changes in left ventricular filling pressure after myocardial infarction assessed with simultaneous right heart catheterization and Doppler echocardiography. *Int J Cardiol*. 2013; **168**: 2803–2810. Epub 2013 Apr 28. PMID: 23628301.
30. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, Olson TP, Borlaug BA. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017; **70**: 136–148. PMID: 28683960; PMCID: PMC5520668.
31. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol*. 2010; **56**: 855–863. PMID: 20813283.
32. Obokata M, Reddy YNV, Shah SJ, Kaye DM, Gustafsson F, Hasenfuβ G,

Hoendermis E, Litwin SE, Komtebedde J, Lam C, Burkhoff D, Borlaug BA. Effects of interatrial shunt on pulmonary vascular function in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2019; **74**: 2539–2550. PMID: 31753198.
33. Sorimachi H, Obokata M, Takahashi N, Reddy YNV, Jain CC, Verbrugge FH, Koepp KE, Khosla S, Jensen MD, Borlaug BA. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur Heart J*. 2021; **42**: 1595–1605. Epub ahead of print. PMID: 33227126.
34. Ahmad A, Corban MT, Toya T, Verbrugge FH, Sara JD, Lerman LO, Borlaug BA, Lerman A. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020; **23**: 765–772. Epub ahead of print. PMID: 32949186.
35. Tschöpe C, Kasner M, Westermann D, Walther T, Gaub R, Poller WC, Schultheiss HP. Elevated NT-ProBNP levels in patients with increased left ventricular filling pressure during exercise despite preserved systolic function. *J Card Fail*. 2005; **11**: S28–S33. PMID: 15948097.
36. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020; **8**: 657–666. Epub 2020 Jul 8. PMID: 32653449; PMCID: PMC7395878.
37. Houston BA, Tedford RJ. What we talk about when we talk about the wedge pressure. *Circ Heart Fail*. 2017; **10**: e004450. PMID: 28912264.
38. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol*. 2020; **75**: 919–930.
39. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019; **40**: 3297–3317.
40. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018; **138**: 861–870.
41. Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, Farrell R, Shoenike MW, Sbarbaro J, Malhotra R, Nayor M, Tschöpe C, de Boer RA, Lewis GD, Ho JE. Evaluation of 2 existing diagnostic scores for heart failure with preserved ejection fraction against a comprehensively phenotyped cohort. *Circulation*. 2021; **143**: 289–291. Epub 2021 Jan 19. PMID: 33464963; PMCID: PMC8059354.
42. Senni M, Caravita S, Paulus WJ. Do existing definitions identify subgroup phenotypes or reflect the natural history of heart failure with preserved ejection fraction? *Circulation*. 2019; **140**: 366–369. Epub 2019 Jul 29. PMID: 31356132.
43. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc*. 2017; **6**: e006817. PMID: 28862947; PMCID: PMC5586477.
44. Pandey A, Khera R, Park B, Haykowsky M, Borlaug BA, Lewis GD, Kitzman DW, Butler J, Berry JD. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail*. 2018; **6**: 117–126. PMID: 29413366; PMCID: PMC8135913.
45. Wolsk E, Bakkestrøm R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, Hassager C, Møller JE, Gustafsson F. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. *JACC Heart Fail*. 2017; **5**: 337–346.
46. Braunwald E, Grossman W. Clinical aspects of heart failure. In Braunwald E., ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 4th ed. Philadelphia: Sunders; 1992. p 444–463.