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

Claudia Baratto¹,², Sergio Caravita¹,³, Davide Soranna⁴, Céline Dewachter², Antoine Bondue², Antonella Zambon⁴,⁵, Luigi P. Badano¹,⁶, Gianfranco Parati¹,⁶ and Jean-Luc Vachiéry²*

¹Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milan, Italy; ²Department of Cardiology, Hôpital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070, Bruxelles, Belgium; ³Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy; ⁴Biostatistics Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy; ⁵Department of Statistic and Quantitative Methods, University of Milano-Bicocca, Milan, Italy; and ⁶Department 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 (I² = 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

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*Correspondence to: Jean-Luc Vachiéry, Department of Cardiology, Hôpital 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. 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, with proven prognostic value. 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 for reporting systematic reviews and meta-analysis. A comprehensive literature search 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 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 DerSimonian and Laird’s method. Between-studies’ heterogeneity was quantified using the I² index. Values of this index more than 75% suggest high heterogeneity. Homogeneity between summary mean estimates stratified for body position during exercise was performed by a χ² 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. 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 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 and 1 study (4%) was a randomized controlled trial.2

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 \( \geq 25 \text{ mmHg} \) 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 \( > 20 \text{ mmHg} \) or a PAWP/CO slope \( > 2 \text{ mmHg/L/min} \) 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

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**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.

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| Author          | Country          | Centre                          | n HFpEF | n controls | Timing of enrolment |
|-----------------|------------------|---------------------------------|---------|------------|---------------------|
| Tschöpe et al.  | Germany          | Campus Benjamin Franklin        | 15      | 15         | 2003                |
| Borlaug et al.  | USA              | Mayo Clinic                     | 32      | 23         | 2005–2009           |
| Maeder et al.   | Australia        | Alfred Hospital                 | 14      | 8          | 2008–2009           |
| Abudiab et al.  | USA              | Mayo Clinic                     | 109     | 73         | 2002–2011           |
| Andersen et al. | Denmark          | Rigshospitalet & Copenhagen     | 61      |            | 2010–2012           |
| Santos et al.   | USA              | Brigham and Women’s Hospital    | 31      | 31         | 2011–2013           |
| Houstis et al.  | USA              | Massachusetts General Hospital   | 79      | 55         | 2006–2016           |
| Obokata et al.  | USA              | Mayo Clinic                     | 195     | 71         | 2000–2014           |
| Reddy et al.    | USA              | Mayo Clinic                     | 98      | 22         |                     |
| Nanayakkara et al. | Australia    | Alfred Hospital                 | 21      | 19         |                     |
| Eisman et al.   | USA              | Massachusetts General Hospital   | 77      | 98         |                     |
| Gor ter et al.  | USA              | Mayo Clinic                     | 161     |            | 2006–2013           |
| McCabe et al.   | USA              | Brigham and Women’s Hospital    | 8       | 14         |                     |
| Platz et al.    | USA              | Brigham and Women’s Hospital    | 13      | 12         |                     |
| Ho et al.       | USA              | Massachusetts General Hospital   | 243     |            | 2006–2017           |
| Obokata et al.  | USA              | Mayo Clinic                     | 38      | 20         |                     |
| Reddy et al.    | USA              | Mayo Clinic                     | 238     | 125        |                     |
| Van Empel et al.| Australia        | Alfred Hospital                 | 9       | 21         |                     |
| Wolsk et al.    | USA, Europa, Australia | Multicentre                  | 108     | 42         | 2013–2016           |
| Beale et al.    | Australia        | Alfred Hospital                 | 161     |            | 2008–2018           |
| Chen et al.     | Taiwan           | Taiwan University Hospital      | 34      |            | 2018                |
| Telles et al.   | Australia        | Alfred Hospital                 | 49      | 22         | 2016–2018           |
| Obokata et al.  | USA, Europe, Australia | Multicentre               | 79      |            | 2014–2016           |
| Fer moyle et al.| USA              | Mayo Clinic                     | 30      |            | 2009–2012           |
| Sorimachi et al.| USA              | Mayo Clinic                     | 105     | 51         | 2007–2018           |
| Ahmad et al.    | USA              | Mayo Clinic                     | 22      | 29         | 2010–2019           |
| Houston and Ted ford | 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.
| Author          | Exercise position | PAWP (end-exp/avg) | PAWP (mean/mid-A) | HFpEF diagnosis                              | Other remarks                      |
|-----------------|-------------------|--------------------|-------------------|----------------------------------------------|-----------------------------------|
| Tschöpe et al.  | Supine            | End-exp            | Mean              | Haemodynamic (rest and/or exercise), echo    | restPAWP > 12, peakPAWP > 20      |
| Borlaug et al.  | Supine            | End-exp            | Mean              | Haemodynamic (exercise)                      |                                    |
| Maeder et al.   | Supine            | End-exp            | Mean              | ↓ ex capacity                                 |                                    |
| Abudiaf et al.  | Supine            | End-exp            |                   | Clinical                                      |                                    |
| Andersen et al. | Supine            | Avg                |                   | Echo                                         | LVEF > 45% and post-STEMI          |
| Santos et al.   | Upright           | End-exp            |                   | Haemodynamic (exercise)                      | PAWP peak > 20                    |
| Houstis et al.  | Upright           | End-exp            |                   | Haemodynamic (rest and/or exercise), ↓ ex capacity |                                    |
| Obokata et al.  | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Reddy et al.    | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Nanayakara et al.| Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Eisman et al.   | Upright           | End-exp            |                   | Haemodynamic (exercise)                      |                                    |
| Gorter et al.   | Upright           | End-exp            |                   | Haemodynamic (rest)                           |                                    |
| McCabe et al.   | Upright           | Avg                |                   | Haemodynamic (rest and/or exercise)          | PAWP rest > 15, peak > 20 mmHg    |
| Platz et al.    | Upright           | End-exp            |                   | Haemodynamic (rest)                           |                                    |
| Ho et al.       | Upright           | End-exp            |                   | Haemodynamic (exercise)                      |                                    |
| Obokata et al.  | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Reddy et al.    | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Van Empel et al.| Supine            | End-exp            | Mean              | Haemodynamic (exercise), echo                | LVEF > 45%                         |
| Wolsk et al.    | Supine            | End-exp            | Mean              | Haemodynamic (rest and/or exercise), BNP, echo| LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP |
| Beale et al.    | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Chen et al.     | Supine            | End-exp            | Mid-A             | Clinical, BNP, echo                           |                                    |
| Telles et al.   | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          | LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP |
| Obokata et al.  | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Fermoyle et al. | Supine            | End-exp            | Mid-A             | Haemodynamic (rest and/or exercise)          | Non-obstructive CAD                |
| Sorimachi et al.| Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Ahmad et al.    | Supine            | End-exp            |                   | Haemodynamic (rest and/or exercise)          |                                    |
| Houston and Tedford| 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.
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/m²). 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/m²), 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/m², 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/m²).

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.
Exercise haemodynamics in HFpEF

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 | N of cohorts | P value | N of cohorts | P value | N of cohorts | P value |
|                              | PAWP (mmHg) |                        |                        |          |                        |          |                        |          |
| REST                         | 14.98 (13.84–16.13) | 35       | 22       | <0.0001 | 57       | <0.0001 | 54       | <0.0001 |
|                              | 8.70 (8.16–9.24) | 26       | 22       | 0.012   | 42       | 0.012   | 42       | 0.012   |
|                              | 7.00 (6.82–7.18) | 26       | 22       | 0.012   | 42       | 0.012   | 42       | 0.012   |
|                              | 7.15 (6.71–7.59) | 26       | 22       | 0.012   | 42       | 0.012   | 42       | 0.012   |
|                              | CO (L/min) |                        |                        |          |                        |          |                        |          |
|                              | 9.50 (8.97–10.03) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.15 (7.56–8.71) | 20       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.15 (7.56–8.71) | 20       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.15 (7.56–8.71) | 20       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.15 (7.56–8.71) | 20       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | RAP (mmHg) |                        |                        |          |                        |          |                        |          |
|                              | 17.73 (16.32–19.14) | 25       | 25       | <0.0001 | 40       | <0.0001 | 40       | <0.0001 |
|                              | 8.18 (7.53–8.84) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.18 (7.53–8.84) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.18 (7.53–8.84) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 8.18 (7.53–8.84) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | PAWP (mmHg) |                        |                        |          |                        |          |                        |          |
|                              | 15.00 (14.16–15.84) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 7.15 (6.77–7.59) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 7.15 (6.77–7.59) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 7.15 (6.77–7.59) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |
|                              | 7.15 (6.77–7.59) | 15       | 15       | 0.009   | 20       | 0.009   | 20       | 0.009   |

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 and 16; 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 (Table S10) 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.
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.
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 ≥ 40–45%). However, many characteristics were not uniformly reported across the studies, precluding to determine whether these patients would fulfill 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 dysfunction42 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.,\textsuperscript{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 age—(in particular with lower chronotropic response),\textsuperscript{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\textsuperscript{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.,\textsuperscript{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.\textsuperscript{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,\textsuperscript{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 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,\textsuperscript{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),\textsuperscript{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.\textsuperscript{3,4} However, in an ad hoc analysis, we performed on previously published exercise haemodynamic data from 57 patients from our laboratory,\textsuperscript{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.

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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 (PICO).

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.

Table S11. Rest and exercise hemodynamics of heart failure with preserved ejection fraction and control subjects across included studies. Data are reported as median (interquartile range).

Table S12. Rest and exercise hemodynamics of control subjects in supine position as reported in individual studies.

Table S13. Rest and exercise hemodynamics of heart failure with preserved ejection fraction and control subjects across included studies. Data are reported as median (interquartile range).

Table S14. Rest and exercise hemodynamics of control subjects in upright position as reported in individual studies.

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.

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