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# Diagnostic Performance of Passive Leg-Raise and Low-Workload Exercise to Diagnose Heart Failure With Preserved Ejection Fraction

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## ABSTRACT

**Background:** Provocative tests during right heart catheterization (RHC) can unmask occult heart failure with preserved ejection fraction (HFpEF). We sought to explore the performance of pulmonary artery wedge pressure (PAWP) during both passive leg raise (PLR) and supine low-workload exercise ($_{\text{EX1}}$; ie, the first step of a step-incremental exercise) to diagnose or exclude HFpEF.

**Methods:** In this 2-center international cohort study, we sought to evaluate the diagnostic performance of $\text{PAWP}_{\text{PLR}}$ and $\text{PAWP}_{\text{EX1}}$ in consecutive patients with unexplained dyspnea and PAWP at rest $\leq$ 15 mmHg who underwent a symptom-limited exercise supine RHC.

**Results:** We included 166 patients; more than 50% had an intermediate HFpEF probability; 75% eventually classified as HFpEF after exercise RHC. The area under the curve was 0.67 (0.58−0.76) for $\text{PAWP}_{\text{PLR}}$ and 0.85 (0.79-0.92) for $\text{PAWP}_{\text{EX1}}$. Only $\text{PAWP}_{\text{PLR}} < 4$ mmHg certainly excluded HFpEF, with higher $\text{PAWP}_{\text{PLR}}$ thresholds (eg, $< 11$ mmHg) being associated with lower sensitivity (80%) and low negative predictive value (34%). $\text{PAWP}_{\text{PLR}} \geq 21$ and $\geq 19$ mmHg identified HFpEF with a specificity of 100% and 98%, and a positive predictive value of 100% and 96%, respectively. During a low-workload exercise, $\text{PAWP}_{\text{EX1}} < 9$ mmHg ruled out HFpEF with 100% sensitivity and negative predictive value. $\text{PAWP}_{\text{EX1}} > 25$ mmHg was 100% specific for HFpEF, while $\text{PAWP}_{\text{EX1}}$ values between 21 and 25 showed acceptable specificity (90%−95%) and positive predictive value (95%−96%).

**Conclusions:** PLR and low-workload supine exercise may reduce the hemodynamic zone of uncertainty for the diagnosis of HFpEF. Both may be useful for the ruling-in of this syndrome, although they are less efficacious for ruling-out HFpEF. (*J Cardiac Fail 2025;31:1675−1683*)

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**Key Words:** HFpEF, right heart catheterization, pulmonary hypertension, exercise, diagnostic scores, passive leg raise.

## Background

Occult heart failure with preserved ejection fraction (HFpEF) is a highly prevalent condition characterized by a transient increase in left-heart filling pressure under stress conditions.[1] Accordingly, provocative tests in the catheterization laboratory represent essential diagnostic tools for HFpEF.[2] However, performing right-heart catheterization (RHC) during incremental, symptom-limited exercise not only has interpretation challenges but also requires significant time, specialized equipment, patients' cooperation, and skilled operators, and it is not universally available.[3] Thus, acute fluid load and passive leg raise (PLR) have been suggested as alternative and simpler provocative maneuvers able to enhance the diagnosis of HFpEF.[4–7] Pulmonary artery wedge pressure (PAWP) thresholds after passive leg raise (PLR) ($PAWP_{PLR}$) to rule-out and rule-in HFpEF have been proposed, though thresholds were derived and validated in relatively small cohorts.[5] Additionally, recent trials sought to incorporate low-workload exercise rather than maximal, symptom-limited effort, as an easier tool for investigating cardiovascular reserve and diagnosing occult HFpEF, even though the diagnostic performance of such an approach has not been extensively validated.

Thus, the aim of this study was to further evaluate, in a large 2-center cohort, the diagnostic performance of $PAWP_{PLR}$ to diagnose or exclude HFpEF and to assess whether low-workload exercise ($_{EX1}$) PAWP ($PAWP_{EX1}$) could retain diagnostic information similar to that of peak-exercise PAWP, thereby obviating the need of maximal, symptom-limited efforts.

## Methods

This study was approved by the ethics committees of the 2 centers (protocol n 2022 09_27_01, approved on September 27, 2022; Pro00087395 approved on May 16, 2019).

### *Inclusion and Exclusion Criteria*

We included consecutive patients who underwent supine RHC at rest and during exercise for diagnostic work-ups for or follow-up of unexplained dyspnea or suspected pulmonary hypertension between 2017 and 2022.

We excluded patients with overt HFpEF hemodynamics at rest (ie, PAWP > 15 mmHg),[2] as well as those with missing values for rest, PLR or peak-exercise PAWP. Furthermore, we excluded patients with left ventricular ejection fractions < 50%, hypertrophic cardiomyopathy, infiltrative diseases, pericardial constriction, more than moderate primary valvular heart regurgitation, more than mild valvular heart stenosis, and uncorrected congenital heart disease. HFpEF was defined primarily as the presence of peak exercise PAWP ≥ 25 mmHg and/or a PAWP/CO slope > 2 mmHg/L/min.[8] Also, analyses were performed considering the other 2 exercise hemodynamic HFpEF definitions, ie, either exercise PAWP ≥ 25 mmHg alone or PAWP/CO slope > 2 mmHg/L/min alone.

### *Data Collection*

Clinical and echocardiographic data were collected during the 15 days before RHC, when there was no change in clinical status, symptoms or treatment. Echocardiography was performed by experienced cardiologists according to the current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[9] We calculated the pretest probability of HFpEF by using both the $H_2$FPEF score (heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure)[10] and the HFA-PEFF score (Heart Failure Association Pretest assessment, Echocardiography and natriuretic peptide score, Functional testing in case of uncertainty, Final etiology),[11] categorizing patients according to specific established thresholds. HFpEF was considered likely, in the presence of an HFA-PEFF score > 4 or an $H_2$FPEF score > 5; possible, if the HFA-PEFF score was 2–4 or the $H_2$FPEF score was 2–5; and unlikely when scores were < 2.

### *Right-Heart Catheterization*

RHC was performed in the supine position and in a nonfasting state. A fluid-filled pulmonary artery catheter was inserted into the internal jugular vein. The transducers were zeroed at midchest, halfway between the anterior sternum and the bed surface. Pressure values were averaged over several heartbeats and measured at end-expiration, on the basis of the agreement of 2 readers who visually reviewed all pressure traces. CO was calculated by the direct Fick method or by thermodilution. Hemodynamic measurements were performed at rest, during a passive leg-raise maneuver and during the last minute of each step of a symptom-limited, maximal exercise test.[8,12,13] During the passive leg-raise maneuver, the patients' legs were passively raised by the staff at an angle of ~ 50 degrees and placed in the binders of the bicycle, instructing the patient to avoid a Valsalva maneuver.[5] PAWP was continuously recorded for up to 3 minutes and was measured after 30 seconds–2 minutes during the passive leg raise to obtain $\text{PAWP}_{\text{PLR}}$.[5] A step-incremental exercise protocol was then performed, with steps lasting about 3 minutes and with measurements taken during the last minute of each step. Patients started pedaling at a low workload (eg, 0–25 W), which was individually chosen on the basis of the estimated physical fitness of the patient. Further increments in workload were similarly personalized based on estimated fitness, in analogy to what it is generally performed for cardiopulmonary exercise tests.[8]

### Statistics

Continuous variables are shown as median and interquartile range (IQR). Categorical variables are reported as absolute and relative frequencies. No imputations were made for missing data. The following analyses were performed primarily for HFpEF, defined as peak exercise PAWP $\geq$ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min. Supplementary analysis was then performed separately, also for HFpEF, defined as either PAWP $\geq$ 25 mmHg or PAWP/CO slope > 2 mmHg/L/min. A receiver operating curve (ROC) analysis was implemented to evaluate the global diagnostic performance of $\text{PAWP}_{\text{PLR}}$ or $\text{PAWP}_{\text{EX1}}$ as estimated by the area under the curve (AUC) with a relative 95% confidence interval (95% CI). Later, we evaluated the threshold diagnostic performance (sensitivity [SE], specificity [SP], positive predictive value [PPV], and negative predictive value [NPV]) for various cutoffs, including the values of 11 and 19 mmHg that have been previously proposed for $\text{PAWP}_{\text{PLR}}$ to exclude or confirm HFpEF, respectively.[5] For threshold diagnostic performance, we estimated the relative confidence interval by using a bootstrap approach. Specifically, we extracted 5000 samples with replacement from the original data. For each bootstrap sample, we calculated the threshold diagnostic performance and from the ordered distribution, we identified the values corresponding to 2.5% and 97.5% as the lower and upper limits of the 95% CI. All analyses were carried out using SAS 9.4.

## Results

### General Characteristics

Of 243 patients who underwent an exercise RHC, 68 were excluded because they presented with rest PAWP > 15 mmHg, and only 9 were excluded due to missing data. Finally, 166 were included in the analysis (e-Fig. 1). Their clinical characteristics are reported in Table 1. They were predominantly women (65%) with a median age of 67 (58–74) years and body mass indexes of 26.6 (23.5–31.0) kg/m$^2$. Median NTproBNP levels were 67 (30–168) pg/mL. The median LV ejection fraction was 63% (58%–66%), the median left atrial volume index was 28 (23–36) mL/m$^2$, and the median septal E/e' was 8.5 (6.9–10.8). The median $H_2$FPEF score in the whole cohort was 3 (1.5—4), and the median HFA-PEFF score was 4.[3–4] The majority of patients with HFpEF had intermediate probabilities of HFpEF, according to both the $H_2$FPEF score (59%) and the HFA-PEFF algorithm (83%), and a nonnegligible proportion of HFpEF presented with low pretest probabilities according to their $H_2$FPEF scores (32%).

**Table 1** Clinical characteristics, hemodynamics and HFpEF definitions of the included population

| | All patients (N = 166) |
|---|---|
| Anthropometrics and Demographics | |
| Age, years | 67.0 [58.0–74.0] |
| Female gender, N (%) | 108 (65%) |
| Body mass index, kg/m$^2$ | 26.6 [23.5–31.0] |
| Comorbidities | |
| Arterial hypertension, N (%) | 114 (69%) |
| Diabetes, N (%) | 28 (17%) |
| Atrial Fibrillation, N (%) | |
| Paroxysmal, N (%) | 19 (12%) |
| Persistent, N (%) | 15 (9%) |
| Blood Tests | |
| Hemoglobin, g/dL (N = 165) | 13.3 [12.0–14.4] |
| Creatinine, mg/dL *(N = 162)* | 0.92 [0.80–1.12] |
| NTproBNP, pg/mL *(N = 134)* | 67.0 [30.0–168.0] |
| Echocardiography | |
| LV diastolic diameter, mm *(N = 138)* | 45.0 [41.0–49.0] |
| Septal wall thickness, mm *(N = 137)* | 10.0 [9.0–11.0] |
| Posterior wall thickness, mm *(N = 138)* | 9.0 [8.0–10.0] |
| LV ejection fraction, % | 63.0 [58.0–66.0] |
| LA volume index, mL/m2 | 28.0 [23.0–36.0] |
| Septal E/e' *(N=138)* | 8.5 [7.0–10.8] |
| Estimated RV systolic pressure, mmHg *(N = 100)* | 32.0 [25.0–40.0] |
| HFpEF pre-test probability scores | |
| $H_2$FPEF score | 3.0 [1.5–4.0] |
| HFA-PEFF score | 4.0 [3.0–4.0] |
| Hemodynamics | |
| PAWP at rest, mmHg | 10.0 [7.0–12.0] |
| PAWP passive leg raise, mmHg | 13.0 [11.0–17.0] |
| PAWP at low workload exercise, mmHg | 21.0 [17.0–25.0] |
| PAWP at peak, mmHg | 25.0 [18.0–30.0] |
| CO at peak, L/min | 8.7 [7.2–10.9] |
| PAWP/CO slope, mmHg/L/min | 2.9 [1.7–4.8] |
| HFpEF Definition | |
| Peak PAWP $\geq$ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min, N (%) | 125 (75%) |
| Peak PAWP$\geq$25 mmHg, N (%) | 91 (55%) |
| PAWP/CO slope > 2 mmHg/L/min, N (%) | 119 (72%) |

Continuous variables are expressed as median (1st; 3rd quartile/interquartile range). Categorical variables are reported as absolute numbers (N and %).

CO, cardiac output; HFA-PEFF, heart failure association-pretest assessment-echocardiography and natriuretic peptides-functional testing in case of uncertainty-etiological workup; HFpEF, heart failure with preserved ejection fraction; $H_2$FPEF, heavy-hypertensive-atrial fibrillation-pulmonary hypertension-elder-filling pressure; LA, left atrium; LV, left ventricle; NTproBNP, N-terminal pro-brain natriuretic peptide; PAWP, pulmonary artery wedge pressure.

### Hemodynamics

Hemodynamic characteristics are reported in Table 1. On average, patients were characterized by normal cardiovascular hemodynamics at rest, with a median resting PAWP of 10 (7–12) mmHg. After the PLR maneuver, PAWP

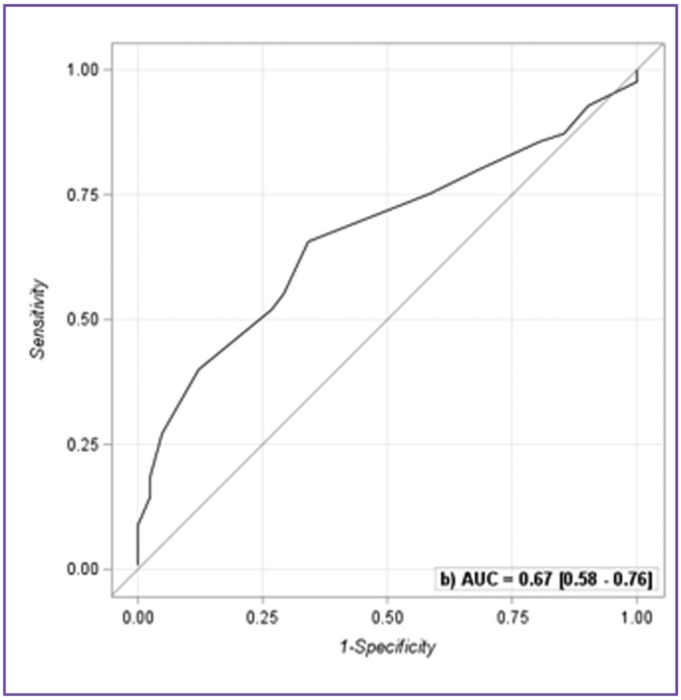

**Fig. 1.** Receiver operating characteristics curve analysis of $PAWP_{PLR}$ to diagnose HFpEF. HFpEF was defined as peak PAWP ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min. PAWP, pulmonary artery wedge pressure

increased to a median of 13 (11–17) mmHg. PAWP at peak exercise was 25 (18–30) mmHg, and the median PAWP/CO slope was 2.9 (1.7–4.8) mmHg/L/min.

Of the whole cohort, 75% (125 of 166 patients) were defined as having HFpEF according to the presence of peak PAWP ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min (Table 1). On the other hand, 55% (91 of 166 patients) had peak PAWPs ≥ 25 mmHg, while 72% (119 of 166 patients) had PAWP/CO slopes > 2 mmHg/L/min.

### *Diagnostic Performance of $PAWP_{PLR}$*

As reported in Fig. 1, the AUC of the $PAWP_{PLR}$ to identify HFpEF was 0.67 (0.58–0.75). In Table 2, the diagnostic performance measures (with the relative 95% CI) of $PAWP_{PLR}$ are reported for potential cutoffs varying from 4 mmHg–21 mmHg. The cutoff, with a sensitivity of 100% to safely rule out HFpEF, was < 4 mmHg. However, no patient was below this value, limiting its clinical utility. We observed a sensitivity equal to 95% (91%–98%) for a $PAWP_{PLR}$ cutoff of < 7 mmHg; only 5% of patients were below this value. When considering the < 11 mmHg $PAWP_{PLR}$ cutoff, we observed a low sensitivity of 80 (73%–86%); 23% of patients were below this value. And we saw a negative predictive value of 34 (22%–48%).

Moreover, a $PAWP_{PLR}$ cutoff of ≥ 21 mmHg, with a specificity of 100%, was found as a candidate to safely rule-in HFpEF, although only 11 patients (7%) were above this value. Considering a cutoff point of ≥ 19 mmHg, the number of patients above this cutoff point was 24 (14%). The specificity of the 19 mmHg $PAWP_{PLR}$ cutoff was 98%, but confidence intervals varied from 93%–100%; its positive predictive value was 96 (86%–100%). The specificity of $PAWP_{PLR}$ ≥ 17 mmHg to rule-in HFpEF was 88 (78%–98%), and the positive predictive value was 91 (84%–98%). Moving to lower values, specificity rapidly declined, with large confidence intervals: 83% (71%–93%) and 73% (59%–85%) for 16 and 15 mmHg, respectively. Their corresponding positive predictive

**Table 2** Diagnostic performance of pulmonary artery wedge pressure during the passive leg raise maneuver ($PAWP_{PLR}$)

| Cutoff | N (%) | SE | SP | PPV | NPV |
|---|---|---|---|---|---|
| 4 | 0 (0%) | 100 [100–100] | nc | 75 [75–75] | nc |
| 5 | 2 (1%) | 98 [96–100] | 0 [0–0] | 75 [75–75] | 0 [0–0] |
| 6 | 3 (2%) | 98 [94–100] | 0 [0–0] | 75 [74–75] | 0 [0–0] |
| 7 | 8 (5 %) | 95 [91–98] | 5 [0–12] | 75 [74–77] | 25 [0–60] |
| 8 | 13 (8%) | 93 [88–97] | 10 [2–20] | 76 [74–78] | 30 [8–56] |
| 9 | 22 (13%) | 87 [82–93] | 15 [5–27] | 76 [73–78] | 27 [11–45] |
| 10 | 26 (16%) | 86 [79–91] | 20 [10–32] | 76 [74–80] | 30 [15–48] |
| 11 | 38 (23%) | 80 [73–86] | 32 [20–46] | 78 [74–82] | 34 [22–48] |
| 12 | 48 (29%) | 75 [67–82] | 41 [27–56] | 80 [75–84] | 35 [25–47] |
| 13 | 70 (42%) | 66 [57–74] | 66 [51–80] | 86 [80–91] | 39 [31–47] |
| 14 | 85 (51%) | 55 [46–64] | 71 [56–83] | 85 [79–91] | 34 [28–41] |
| 15 | 90 (54%) | 52 [43–61] | 73 [59–85] | 86 [79–92] | 33 [28–39] |
| 16 | 104 (63%) | 44 [35–52] | 83 [71–93] | 89 [82–95] | 33 [28–37] |
| 17 | 111 (67%) | 40 [31–48] | 88 [78–98] | 91 [84–98] | 32 [29–36] |
| 18 | 130 (78%) | 27 [19–35] | 95 [88–100] | 95 [86–100] | 30 [27–33] |
| 19 | 142 (86%) | 18 [12–26] | 98 [93–100] | 96 [86–100] | 28 [26–30] |
| 20 | 147 (88%) | 14 [8–21] | 98 [93–100] | 95 [83–100] | 27 [26–29] |
| 21 | 155 (93%) | 9 [4–14] | 100 [100–100] | 100 [100–100] | 26 [25–28] |

The diagnosis of heart failure with preserved ejection fraction (HFpEF) was codified as peak pulmonary artery wedge pressure (PAWP) ≥ 25 mmHg and/or PAWP/cardiac output slope > 2 mmHg/L/min. The number, as well as the percentage, of patients with $PAWP_{PLR}$ below the cutoff is reported. Confidence intervals for sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) are calculated by the bootstrap approach.

CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; PAWP, pulmonary artery wedge pressure; PLR, passive leg raise; PPV, positive predictive value; SE, sensitivity; SP, specificity.

values were 89% (82%–95%) and 86% (79%–92%), respectively.

Additional analysis testing the diagnostic power of $PAWP_{PLR}$ vs the other 2 hemodynamic definitions of HFpEF (either peak PAWP $\geq$ 25 mmHg or PAWP/CO slope $>$ 2 mmHg/L/min) are shown in e-Fig. 2 (AUC), e-Table 1 and e-Table 2 (diagnostic performance measures with the relative 95% CI).

## Diagnostic Performance of $PAWP_{EX1}$

Low-workload exercise ($_{EX1}$) in the whole population corresponded to 25 [20–25] Watts. Thirty-six patients (22%) stopped exercising due to exhaustion at $_{EX1}$, corresponding to 25 [15–25] Watts. The remaining 129 patients (78%) continued further steps up to peak exercise, which occurred at 50 [40–75] Watts. $PAWP_{EX1}$ corresponded to 21.0 (17.0–25.0) mmHg. ROC analysis showed that the AUC of the $PAWP_{EX1}$ against the invasive definition of HFpEF in our population was 0.85 (0.78 to 0.91) (Fig. 2). In Table 3 the diagnostic performance measures (with the relative 95% CIs) of $PAWP_{EX1}$ are reported for potential cutoffs, varying from 9 mmHg–26 mmHg.

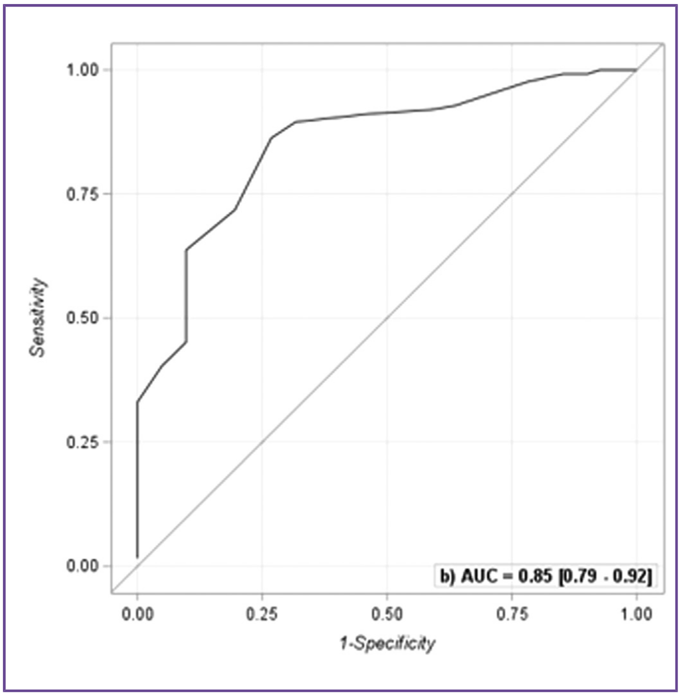

Fig. 2. Receiver operating characteristics curve analysis of $PAWP_{EX1}$ to diagnose HFpEF. HFpEF was defined as peak PAWP $\geq$ 25 mmHg and/or PAWP/CO slope $>$ 2 mmHg/L/min. $_{EX1}$, low-workload exercise; PAWP, pulmonary artery wedge pressure.

The optimal cutoff value of $PAWP_{EX1}$ to exclude HFpEF with certainty and with 100% sensitivity and 100% NPV was a $PAWP_{EX1} < 9$ mmHg, but only 3 patients (2% of the whole population) were below this cutoff. Sensitivity marginally decreased to 98 [94–100] %) when moving to $PAWP_{EX1} < 12$ mmHg, together with a reduction in negative predictive value up to 75 (50%–100%). On the other hand, all 42 patients with $PAWP_{EX1}$ equal to or greater than 26 mmHg were affected by HFpEF. A $PAWP_{EX1} \geq 24$ mmHg retained a specificity and positive predictive value of 90% (80%–98%) and 94% (87%–98%), respectively. Moving to lower values, a $PAWP_{EX1} \geq 21$ mmHg retained a specificity and positive predictive value of 90% (80%–98%) and 95% (91%–99%), respectively, while a $PAWP_{EX1} \geq 20$ mmHg retained a specificity and positive predictive value of 80% (68%–93%) and 92% (87%–97%), respectively.

**Table 3** Diagnostic performance of pulmonary artery wedge pressure at low-workload exercise ($PAWP_{EX1}$)

| Cutoff | N (%) | SE | SP | PPV | NPV |
|---|---|---|---|---|---|
| 9 | 3 (2%) | 100 [100–100] | 7 [2–15] | 77 [75–78] | 100 [100–100] |
| 10 | 5 (3%) | 99 [98–100] | 10 [2–20] | 77 [75–79] | 80 [33–100] |
| 11 | 7 (4%) | 99 [98–100] | 15 [5–27] | 78 [76–80] | 88 [50–100] |
| 12 | 12 (7%) | 98 [94–100] | 22 [10–34] | 79 [77–82] | 75 [50–100] |
| 13 | 20 (12%) | 94 [90–98] | 32 [17–46] | 81 [78–84] | 65 [45–84] |
| 14 | 24 (14%) | 93 [88–97] | 37 [22–51] | 82 [78–85] | 63 [44–81] |
| 15 | 27 (16%) | 92 [87–96] | 41 [27–56] | 83 [79–86] | 63 [47-80] |
| 16 | 33 (20%) | 91 [85–96] | 54 [39–68] | 86 [82–90] | 67 [53–80] |
| 17 | 41 (25%) | 90 [84–94] | 68 [54–83] | 90 [85–94] | 68 [57–81] |
| 18 | 47 (28%) | 86 [79–92] | 73 [59–85] | 91 [87–95] | 64 [53–76] |
| 19 | 61 (37%) | 77 [69–84] | 78 [66–90] | 91 [87–96] | 52 [44–62] |
| 20 | 68 (41%) | 72 [64–79] | 80 [68–93] | 92 [87–97] | 49 [41–57] |
| 21 | 82 (50%) | 64 [55–72] | 90 [80–98] | 95 [91–99] | 45 [39–52] |
| 22 | 85 (52%) | 61 [52–69] | 90 [80–98] | 95 [90–99] | 44 [38–50] |
| 23 | 94 (57%) | 54 [45–63] | 90 [80–98] | 95 [89–99] | 39 [34–45] |
| 24 | 105 (64%) | 45 [36–54] | 90 [80–98] | 94 [87–98] | 35 [31–40] |
| 25 | 113 (68%) | 40 [31–49] | 95 [88–100] | 96 [90–100] | 35 [31–38] |
| 26 | 124 (75%) | 33 [25–42] | 100 [100–100] | 100 [100–100] | 33 [31–36] |

The diagnosis of heart failure with preserved ejection fraction (HFpEF) was codified as peak PAWP $\geq$ 25 mmHg and/or PAWP/cardiac output slope $>$ 2 mmHg/L/min. The number, as well as the percentage, of patients with $PAWP_{EX1}$ below the cutoff is reported. Confidence intervals for sensitivity, specificity, positive predictive value, and negative predictive value were calculated by using the bootstrap approach.

$_{EX1}$, low workload exercise; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; PAWP, pulmonary artery wedge pressure; PPV, positive predictive value; SE, sensitivity; SP, specificity.

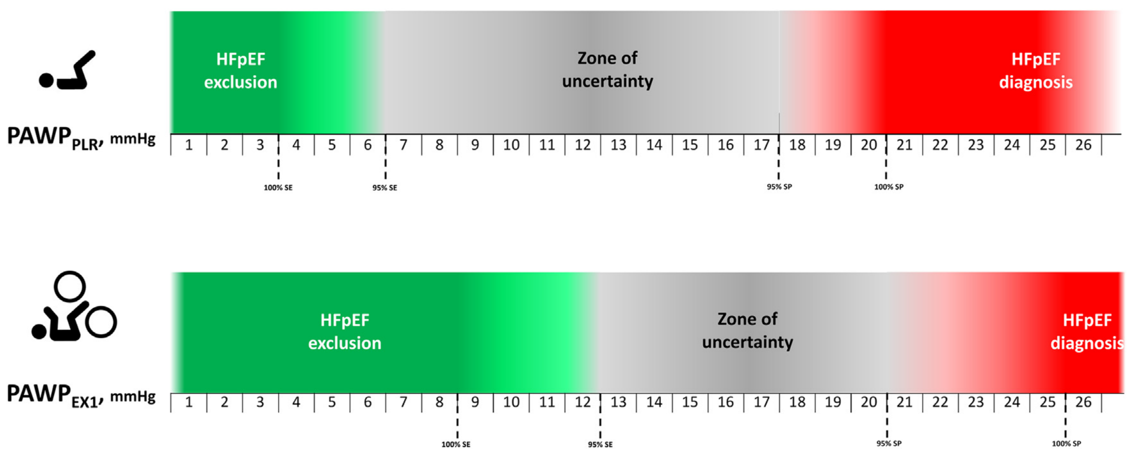

**Fig. 3.** Zone of diagnostic uncertainty of pulmonary artery wedge pressure during provocative tests. Thresholds to surely or safely exclude or rule-in HFpEF are reported. $_{EX1}$, low-workload exercise; HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure; PLR, passive leg raise; SE, sensitivity; SP, specificity.

Additional analysis testing the diagnostic power of $PAWP_{EX1}$ vs the other 2 hemodynamic definitions of HFpEF (either peak PAWP $\geq$ 25 mmHg or PAWP/CO slope > 2 mmHg/L/min) are shown in e-Fig. 3 (AUC) and e-Table 3 and e-Table 4 (diagnostic performance measures with the relative 95% confidence interval).

Additional analysis considering only the 78% of patients who continued exercising beyond $_{EX1}$ is reported in e-Table 5, showing similar cutoff values.

## Discussion

Data from this international cohort of patients with unexplained dyspnea undergoing exercise RHC showed that both PLR and low-workload exercise tests may enhance the diagnosis of HFpEF over resting hemodynamics, extending the information found in previous reports.[1,5,14] In particular, both tests resulted in more solid rule-in than rule-out HFpEF, and the diagnostic performance of low-workload exercise exceeded that of PLR. Finally, we highlighted the hemodynamic zone of uncertainty of both tests (Fig. 3) that could be of clinical interest.[15]

In recent years, provocative tests in the catheterization laboratory have been recommended with increasingly frequency so as to unmask occult HFpEF in patients with exertional dyspnea and in patients with suspicion of pulmonary hypertension and cardiovascular comorbidities.[6] PLR is a simple maneuver that provides a pure increase in cardiac preload, mimicking the hemodynamic effect of a volume infusion.[16,17] Exercise includes other triggers to filling-pressure increase, ie, sympathetic activation with venoconstriction and shift of stressed blood volume from below to above the diaphragm.[18,19] While healthy hearts allow a modest increase in left filling pressure, HFpEF is characterized by an abnormal rise in PAWP in response to increased venous return and exercise, as a consequence of LV diastolic dysfunction, LA myopathy and abnormal venous compliance and capacitance.[20]

Van de Bovenkamp et al. demonstrated that $PAWP_{PLR} \geq$ 19 mmHg had a 100% positive predictive value in identifying occult HFpEF and that $PAWP_{PLR}$ < 11 mmHg had a 100% negative predictive value to rule out HFpEF.[5] Such results were derived from 72 individuals (39 non-HFpEF and 33 occult HFpEF) evaluated in The Netherlands between 2014 and 2020 and validated in 42 individuals (24 non-HFpEF and 18 occult HFpEF) in the U.S. In our larger cohort (n = 166; n = 42 non-HFpEF and n = 124 occult HFpEF), similarly coming from the U.S. and Europe, only a $PAWP_{PLR}$ > 21 mmHg emerged as being optimally specific (100%) in identifying HFpEF, even though such a high $PAWP_{PLR}$ value was poorly represented in the population (5%), potentially limiting its clinical utility. On the other hand, a $PAWP_{PLR} \geq$ 19 mmHg retained good diagnostic performance in identifying HFpEF, with 97% specificity and 96% PPV. A $PAWP_{PLR} \geq$ 17 mmHg is probably the lower limit of clinically acceptable diagnostic performance in identifying HFpEF, with 90% specificity and 93% PPV.

Excluding HFpEF based on $PAWP_{PLR}$ was more challenging. Only very low $PAWP_{PLR}$ values (eg, < 4 or < 7 mmHg) may eventually help to rule out HFpEF, even though the negative predictive value was extremely poor. The differences between our results and those obtained by van de Bovenkamp et al.[5] could be explained partially by their modest single-center sample size, the pretest probability of HFpEF and the different exercise hemodynamic definitions of HFpEF that were employed. Our multicenter international cohort was larger, and a nonnegligible proportion of our patients with HFpEF presented with low pretest probabilities, according to their $H_2$FPEF scores (32%), than the proportion reported in the derivation cohort by Van de Bovenkamp et al. (9%). Additionally, van de Bovenkamp and colleagues considered HFpEF only in patients with peak PAWP $\geq$ 25 mmHg, whereas we used a more inclusive definition (eg, peak PAWP $\geq$ 25 mmHg and/or PAWP/CO slope $>$ 2 mmHg/L/min). However, when reproducing the analysis made by van de Bovenkamp et al. (defining HFpEF as peak PAWP $\geq$ 25 mmHg), we obtained similarly imperfect $\text{PAWP}_{\text{PLR}}$ cutoffs to exclude HFpEF, with NPVs always lower than 80%. Collectively, these findings suggest that PLR could help to identify HFpEF in patients with exertional dyspnea, but they bear limited power to exclude the disease, in contrast to previous evidence,[5] and they have a potential hemodynamic zone of uncertainty (eg, PAWP from 4−7 to 17−21 mmHg).

Given the quite large margin of uncertainty resulting from PLR, at least submaximal exercise would be desirable to complete an invasive evaluation. Indeed, low workload exercise is less time- and resource-consuming than a maximal stress test, carries less patient discomfort, and may hold diagnostic value in the uneventful case of musculoskeletal problems leading to exercise interruption. $\text{PAWP}_{\text{EX1}}$ has been introduced as an inclusion criterion in clinical trials involving left atrial shunting devices to treat HFpEF.[21] Its diagnostic power was certainly higher than that of PLR, irrespective of the HFpEF definition adopted.

Notably, 43% of our patients with HFpEF could have been diagnosed because their $\text{PAWP}_{\text{EX1}}$ exceeded the commonly employed diagnostic threshold for HFpEF (ie, $>$ 25 mmHg). Additionally, lower thresholds (ie, those between 20 and 25 mmHg) also maintained adequate specificity (86%−92%) and positive predictive value (93%−94%). This confirms Borlaug's pioneering experience[1] and is coherent with recent reports showing that many individuals may reach diagnoses of HFpEF at low workload in the supine position.[22]

Similar to PLR, exclusion of HFpEF resulted critical also with low workload exercise. Indeed PAWP values below 9 mmHg during low workload exercise, despite being exceedingly rare in our cohort, safely excluded HFpEF; values below 12 mmHg showed potentially clinically acceptable specificity and negative predictive value. Only when relying on absolute peak PAWP values to diagnose HFpEF (ie, peak PAWP $\geq$ 25 mmHg), PAWPEX1 could safely exclude HFpEF when it was below 14 mmHg.

### *Limitations*

This work was conducted in 2 tertiary referral centers; it focused data collection on hemodynamic variables. Most patients normally evaluated with exercise RHC are symptomatic for dyspnea according to New York Heart Association classes II and III, so we did not collect information on symptom burden, although it might have been useful. Referral centers inherently carry selection bias, but our 2-center recruitment process might have mitigated this aspect, ideally providing a quite representative international cohort of patients referred to exercise RHC for exertional dyspnea. The prevalence of HFpEF in that population was quite high, which probably reflects the index of suspicion by referring cardiologists. Indeed, many patients with noncardiac dyspnea may have been judged to have too low a likelihood of HFpEF to be referred for invasive testing. Nonetheless, the high prevalence of HFpEF may have especially influenced the NPV of PAWP thresholds during PLR and $_{\text{EX1}}$. Finally, both centers performed exercise testing via supine exercise. Thresholds for upright exercise may be different.[22] Finally, cutoffs were derived from a relatively small sample of patients, so larger studies may be needed to confirm our results.

## Conclusions

Our data solidify the upper diagnostic thresholds for PAWP measured at PLR and low workload exercise (eg, 20−25 W) to rule in HFpEF in individuals complaining of exertional breathlessness. In these situations, maximal symptom-limited exercise testing may not be necessary. However, PLR and low-workload exercise showed limited ability to exclude the disease, reinforcing the hemodynamic zone of uncertainty about the diagnosis of HFpEF in individuals complaining of exertional breathlessness.

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## Bullet points about how our work applies to patients

- Our work provides updated reference values for simple tests (passive leg raises, low-workload exercises) during right-heart catheterization to unmask heart failure with preserved ejection fraction (HFpEF).
- When passive leg raises or low-workload exercises unmask HFpEF, maximal exercise could be avoided.
- Maximal exercise may be required when passive leg raises or low-workload exercises are not diagnostic, because thresholds for ruling out HFpEF are less solid.

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## Supplementary materials

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