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Pulmonary Artery Wedge Pressure and Left Ventricular End-Diastolic pressure during exercise in patients with dyspnea.

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Abbreviations list:

CO: cardiac output

$_{ED}$: end-diastole

EDP: end-diastolic pressure

H2FPEF: heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure

HFpEF: heart failure with preserved ejection fraction

LA: left atrium

LV: left ventricle

$_{M}$: mean

PAP: pulmonary artery pressure

PAWP: pulmonary artery wedge pressure

ABSTRACT

Background. Pulmonary Artery Wedge Pressure (PAWP) during exercise, as a surrogate for Left Ventricular (LV) End-Diastolic Pressure (EDP), is used to diagnose heart failure with preserved ejection fraction (HFpEF). However, LVEDP is the gold-standard to assess LV filling, end-diastolic PAWP ($PAWP_{ED}$) is supposed to coincide with LVEDP, and mean PAWP throughout the cardiac cycle ($PAWP_M$) better reflects the hemodynamic load imposed on the pulmonary circulation.

Objective. To determine precision and accuracy of PAWP estimates for LVEDP during exercise, as well as the rate of agreement between these measures.

Methods. Forty-six individuals underwent simultaneous right and left heart catheterization, at rest and during exercise, to confirm/exclude HFpEF. We evaluated: linear regression between LVEDP and PAWP, Bland-Altman graphs, and the rate of concordance of dichotomized LVEDP and PAWP ≥ or < diagnostic thresholds for HFpEF.

Results. At peak exercise, $PAWP_M$ and LVEDP, as well as $PAWP_{ED}$ and LVEDP, were fairly correlated ($R^2 > 0.69$, $p < 0.01$), with minimal bias (+2 and 0 mmHg respectively) but large limits of agreement (±11 mmHg). Eighty-nine percent of individuals had concordant PAWP and LVEDP ≥ or <25 mmHg (Cohen's kappa=0.64). Individuals with either LVEDP or $PAWP_M$ ≥25 mmHg showed a $PAWP_M$ increase relative to cardiac output changes ($PAWP_M$/CO slope)>2 mmHg/L/min.

Conclusions. During exercise, PAWP is accurate but not precise for the estimation of LVEDP. Despite a good rate of concordance, these two measures might occasionally disagree.

Keywords: heart failure, cardiac catheterization, exercise, LVEDP, PAWP

BACKGROUND

Heart failure with preserved ejection fraction (HFpEF) can be considered a clinical syndrome of cardiovascular ageing, ensuing from a combination of increased left ventricular diastolic stiffness and increased stressed blood volume (or dysfunctional preload) [1,3]. Symptoms may occur despite euvolemia at physical examination, normal natriuretic peptides, as well as with normal filling pressures at rest, either estimated through echocardiography, or directly measured by cardiac catheterization [4-6]. To overcome this diagnostic challenge, invasive exercise hemodynamic testing has been suggested to unmask HFpEF, allowing to detect a steep increase in pulmonary artery wedge pressure (PAWP), with peak PAWP values ≥ 25 mmHg as the hallmark of the disease [5-7]. All this reasoning is based upon the assumption that PAWP approximates left ventricular (LV) end-diastolic pressure (EDP). However, LVEDP reflects LV diastolic stiffness more directly than PAWP, without the interposition of the left atrium (LA) and of the pulmonary circulation, while PAWP reflects the hemodynamic load imposed by the left heart on the pulmonary vascular bed and on the right heart [8]. Thus, it might be supposed that, during exercise, PAWP and LVEDP may disagree, potentially questioning the diagnosis of HFpEF in a number of individuals, especially when absolute cut-off values are employed, taking into account the methodological heterogeneity in PAWP measurement during exercise hemodynamics across centers, as well as the absence of an undisputed gold-standard reference [9]. Additionally, the accuracy and precision of PAWP as a surrogate of LVEDP has been reported in resting condition only, both for end-diastolic PAWP ($PAWP_{ED}$) and for PAWP averaged over the cardiac cycle, i.e. mean PAWP ($PAWP_{M}$) [10-14]. Thus, the primary aim of our study was to compare LVEDP and PAWP during exercise in a cohort of consecutive patients referred for exercise cardiac catheterization, in order to assess the validity of the latter as an estimate of the former. Anticipating that PAWP and LVEDP may occasionally disagree, we also exploratively aimed to verify whether additional hemodynamic parameters (i.e. flow-normalized PAWP trajectories) may reinforce the diagnosis of HFpEF in patients with either PAWP or LVEDP equal or above the arbitrary pathological threshold of 25 mmHg.

METHODS

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2020_04_21_03). We included consecutive patients with exertional breathlessness referred for elective cardiac catheterization in stable clinical conditions to confirm or exclude the diagnosis of HFpEF, who signed an informed consent for the use of their data for research purposes. Additionally, they needed to have been instrumented with both a Swan-Ganz catheter in the pulmonary artery and a pig-tail catheter in the left ventricle, and to have completed a symptom-limited step-incremental exercise test in the supine position. Finally, they needed to have readable LVEDP at peak exercise. We excluded patients who had not performed a left heart catheterization, those with reduced LV ejection fraction (< 50%), restrictive or hypertrophic or infiltrative cardiomyopathy, congenital heart disease, constrictive pericarditis, myocardial ischemia, as well as those with a clinical and hemodynamic diagnosis of pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension [15], more than moderate respiratory disorders, more than mild primary valvular regurgitation, any valvular stenosis; unstable patients (non-elective hospitalization, rapid worsening of symptoms, hemodynamic compromise), as well as individuals not able to perform a physical exercise on a supine cycle ergometer.

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication to cardiac catheterization, were abstracted from clinical charts. Echocardiography was performed by experienced cardiologists following current recommendations [16]. Images were stored in digital format for quantitative analysis, which were performed by trained personnel, blinded to clinical and hemodynamic data. The pre-test probability of HFpEF was assessed through the H_2FPEF score [17]. The H_2FPEF score is a continuous score with higher values associated with higher probability of HFpEF. For practical reasons, we considered HFpEF “likely” in those patients with a H_2FPEF score > 4 (probability >70%), HFpEF “possible” in those with a H_2FPEF score 2-4 (probability 40-70%) and HFpEF “unlikely” in those with a H_2FPEF score < 2 (probability < 40%) [4].

Right heart catheterization

Patients were studied on chronic medications, in the fasting state, without sedation, in supine position. They wore a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA) to directly measure oxygen consumption. A 7-F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace as well as by an oxygen saturation > 94% sampled at the tip of the catheter. A 5-F pig-tail catheter was placed in the LV through a 6-F right radial artery sheath. The transducers were zeroed at the midthoracic line, halfway between the anterior sternum and the bed surface using a laser caliper. Hemodynamic measurements were performed at rest, after one minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test. The increment in workload was personalized in order to obtain at least three steps of exercise before exhaustion [4]. Two milliliters of blood were sampled at the same time from the tip of the Swan-Ganz catheter and from the radial artery, in order to calculate cardiac output (CO) by the direct Fick method.

Pressures were measured both at end-expiration, and averaged over several (at least 5) respiratory cycles. Additionally, PAWP was measured:

- at end-diastole ($PAWP_{ED}$): at mid-A for patients in sinus rhythm, at mid-C – when visible – or at pre-V for patients in atrial fibrillation;
- averaging PAWP throughout the cardiac cycle (mean PAWP or $PAWP_M$).

V waves were measured on the PAWP waveform, and their amplitude was calculated as the difference between the zenith of the V wave and the mean PAWP value. A linear regression was applied to multiple pairs of PAWP and CO points, in order to calculate the PAWP/CO slope [4,6]. The speed sweep was adapted to better visualize LVEDP despite increasing heart rate during exercise.

Hemodynamic data reflect the agreement of two expert independent readers blinded to patients' data, who visually reviewed all pressure traces offline.

HFpEF was defined by either an end-expiratory $PAWP_M$ or LVEDP > 15 mmHg at rest and/or ≥ 25 mmHg at peak exercise. In case of disagreement between these two variables at peak exercise, an end-expiratory PAWP/CO slope > 2 mmHg/L/min was considered as an additional hemodynamic parameter indicative of HFpEF [4,9,14].

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) when normally distributed and as median and [first, Q_1, – third, Q_3 quartile] otherwise. Categorical data are showed as absolute number [percentage]. The agreement and the relationship between LVEDP and PAWP at different conditions was tested by Bland-Altman analysis and linear regression analysis, respectively; whilst the reliability of agreement was assessed using the Cohen's kappa.

RESULTS

General characteristics

Out of 96 exercise cardiac catheterization performed between 06/2019 and 03/2021, 50 patients presented with exclusion criteria (secondary forms of HFpEF, pulmonary vascular diseases, more than mild primary valvular regurgitation, congenital heart disease). Forty-six patients fulfilled inclusion criteria and were analyzed.

General clinical characteristics of the study cohort are reported in **Table 1**. Mean age was 71 years, 67% of individuals were females, mean body mass index was 27 Kg/m^2. Cardiovascular risk factors were well represented (79% with arterial hypertension, 22% obese, 15% with diabetes mellitus or impaired glucose tolerance, 15% with stable coronary artery disease). The majority of patients was in sinus rhythm at the time of cardiac catheterization. Median brain natriuretic peptide was 106 ng/L, median LA volume index was 34 mL/m^2, mean E/E' was 10 and systolic PAP was estimated at 36 mmHg. The pre-test probability of HFpEF, calculated based on the H_2FPEF score, was low in 13%, intermediate in 48% and high in 39% of individuals (**Central Illustration**).

Rest and exercise hemodynamics

Rest and exercise end-expiratory hemodynamic data of the whole cohort are reported in **Table 2**.

From rest to peak exercise, end-expiratory $PAWP_M$ passed in median from 14 [9-18] to 33 [26-41] mmHg, $PAWP_{ED}$ from 14 [9-17] to 31 [25-38] mmHg, LVEDP from 15 [10-20] to 30 [25-36] mmHg. Respiratory-averaged $PAWP_M$ passed in median from 10 [6-15] to 26 [22-34] mmHg, $PAWP_{ED}$ from 10 [7-14] to 25 [20-30] mmHg, LVEDP from 13 [8-17] to 26 [21-30] mmHg. CO increased from 4.6 [3.6-5.9] L/min at rest to 8.8 [7.1-11.2] L/min at peak. Twenty-six percent of patients had a PAWP V wave amplitude at peak exercise greater than 5 mmHg.

Linear regression analysis and Bland-Altman plot of end-expiratory rest and peak exercise LVEDP vs PAWP (both $PAWP_{ED}$ and $PAWP_M$) are reported in the **Central Illustration**. Mean bias for end-expiratory $PAWP_{ED}$ vs LVEDP at peak exercise was minimal (+0.11 mmHg) but with large confidence intervals (±10.76 mmHg). At peak exercise, end-expiratory $PAWP_M$ overestimated LVEDP by 2 mmHg, again with large confidence intervals (±11.35 mmHg). Linear regression analysis and Bland-Altman plot of respiratory-averaged LVEDP vs PAWP are reported in **Figure 1** (rest), and **Figure 2** (peak exercise).

Concordance between LVEDP and PAWP

At rest, 46% of individuals had either an end-expiratory $PAWP_M$ or a LVEDP > 15 mmHg, and 57% had a $PAWP_M$ and/or a LVEDP > 15 mmHg at rest (**Central Illustration**). The rate of concordance of these two so-dichotomized measures at rest was 78%, with moderate agreement (Cohen's K = 0.56).

During exercise, 80% and 83% of individuals had either an end-expiratory $PAWP_M$ or LVEDP ≥ 25 mmHg. Eighty-seven percent of cases had an end-expiratory $PAWP_M$ and/or LVEDP ≥ 25 mmHg (**Central Illustration**). The two so-dichotomized measures were concordant in 89% of cases with substantial agreement (Cohen's K = 0.64). In particular, 3 patients had an end-expiratory $PAWP_M$ ≥ 25 mmHg but a LVEDP < 25 mmHg, and 2 patients had a LVEDP ≥ 25 mmHg but a $PAWP_M$ < 25 mmHg. All these 5 patients, with discordant $PAWP_M$ and LVEDP, had a $PAWP_M$/CO slope > 2 mmHg/L/min.

DISCUSSION

To the best of our knowledge, this is the first study comparing PAWP and LVEDP measurements obtained during exercise. Thus, obtaining LVEDP during supine exercise is feasible in patients with exertional breathlessness and/or suspicion of HFpEF. We could show a good accuracy (minimal average bias) but a relevant imprecision (large confidence intervals) of PAWP estimates for LVEDP. This result was consistent in several scenarios: i) both at rest and at peak exercise; ii) both when these variables were measured at end-expiration (as it is commonly done in many US centers [5,6]) and when they were averaged over the respiratory cycle (as it is recommended by the European Respiratory Society when large respiratory swings are present, including during physical exercise [18]). The imprecision of PAWP estimates for LVEDP could have contributed to a small but not negligible discordance of these two variables (in 11% of patients) when both were arbitrarily dichotomized at ≥ 25 mmHg at end-expiration at peak exercise to diagnose HFpEF. However, our preliminary results suggest that the incorporation of additional measures (i.e.

PAWP/CO slope) could overcome such modest discordance: all patients with either PAWP or LVEDP above diagnostic cut-off for LVEDP also had a PAWP/CO slope > 2 mmHg/L/min.

LVEDP represents the operational pressure of the LV at end-diastole. Accordingly, it is generally viewed as a suitable marker of diastolic stiffness, albeit simplifying the gold-standard pressure-volume LV curve to one pressure point [19]. However, this measure is generally felt to be more "invasive" and riskier than PAWP. LVEDP has been rarely employed during exercise for the diagnosis of HFpEF, with lower evidence on pathological LVEDP thresholds to diagnose this disease [5]. Nonetheless, LVEDP measurement might be attractive, since obtaining a reliable PAWP tracing might not be always possible in all patients [14]. Despite this, a left heart catheterization alone may carry less information than a right heart catheterization: this latter incorporates pressures and flows of the pulmonary circulation; $PAWP_{ED}$ (mid-A or mid-C) is believed to be a good surrogate of LVEDP; and $PAWP_M$ provides additional information over LVEDP on left heart filling pressures [8]. Indeed, the LA may not be a passive bystander in HFpEF: LA "myopathy", either due to intrinsically reduced LA compliance or to an upward shift of the LA compliance curve, might frequently manifest with tall (systolic) V waves in the PAWP position, increasing $PAWP_M$ well beyond $PAWP_{ED}$ and LVEDP [20,21]. Accordingly, V wave amplitude > 5 mmHg at peak exercise was present in one quarter of our patients' population, likely contributing to elevate $PAWP_M$ in median slightly above $PAWP_{ED}$ and LVEDP, irrespectively of the respiratory phase. To take into account the role of the left atrium in the clinical manifestations of HFpEF [20,21], it seems thus reasonable to prefer end-expiratory $PAWP_M$ over $PAWP_{ED}$ (and LVEDP) for diagnostic purposes.

In analogy to our results obtained during supine exercise, clinical studies comparing PAWP and LVEDP in resting conditions have overall shown a moderate to good accuracy (minimal bias) but a large imprecision (wide limits of agreement) of PAWP estimates for LVEDP [10-14].

Halpern SD et al. [10] reported data from 3926 patients (85% with a PAWP > 15 mmHg) with an indication to LV ventriculography or coronary angiography, who were studied during 10 years by 10 physicians, without pressure trace re-reading. PAWP was recorded at rest as a mean pressure ($PAWP_M$), while LVEDP was taken following the A wave “in some patients”. They found that, at end-expiration, $PAWP_M$ slightly underestimated LVEDP by 2.9 mmHg.

Ryan JJ et al. [11] studied 61 patients at rest (59% with PAH), and compared $PAWP_M$ (both end-expiratory and respiratory-averaged) and LVEDP measured at the C-point or at the point of upslope of the R wave at ECG. They found a slight overestimation (by 0.9 mmHg) of $PAWP_M$ vs LVEDP when these variables were both measured at end-expiration, and an underestimation (by 4.4 mmHg) when the variables were averaged over several respiratory cycles.

Bitar et al. [12] reported computer-generated values of hemodynamics measurements of 101 patients (58% with PH, three quarter of whom were post-capillary). They found that digitalized, respiratory-averaged $PAWP_M$ underestimated LVEDP by 2.9 mmHg.

Oliveira et al. [13] studied 105 patients (79% with PAWP < 15 mmHg) and found that, at end-expiration, $PAWP_{ED}$ had a good accuracy (mean bias +0.3 mmHg) to estimate LVEDP, this latter measured at the C-point.

Dickinson et al. [14] studied a quite heterogeneous cohort of patients, 57% of whom presented with post-capillary PH. Automated, respiratory-averaged $PAWP_M$ slightly underestimated LVEDP measured at the Z point by 0.8 mmHg. However, when separating the population based on the presence of sinus rhythm or of atrial fibrillation (this latter as a marker of left atrial dysfunction), they found that respiratory-averaged $PAWP_M$ overestimated LVEDP in atrial fibrillation (by 5 mmHg) and underestimated LVEDP in sinus rhythm (by 3 mmHg).

Thus, results coming from literature are quite heterogeneous, both in terms of sample size, patients’ population being investigated, methodology and timing of pressure measurement over the respiratory and cardiac cycle, as well as results obtained. Indeed, some investigators found a small but potentially relevant underestimation (by 2-4 mmHg) either of respiratory averaged $PAWP_M$ or end-expiratory $PAWP_M$, one study highlighted an overestimation of LVEDP by PAWP in patients with atrial fibrillation (as a marker of left atrial dysfunction/myopathy), while others showed the absence of a relevant bias of PAWP (especially $PAWP_{ED}$) estimates for LVEDP. However, all the studies are homogeneous in pointing to a relevant imprecision (large confidence intervals) of PAWP estimates for LVEDP in resting condition, indicating that these two measures may not coincide in an individual patient [10-14]. Even though PAWP and LVEDP are supposed to have a similar meaning (and accordingly they are quite fairly correlated with minimal albeit potentially relevant bias), intra-individual differences might be expected, either due to intrinsic limitation of pressure measurements with fluid-filled catheters, measurement errors (as for any physiological measurement), or to the fact that PAWP and LVEDP are measured in different sites of the cardiovascular system or in different time frames of the cardiac cycle. Our results, obtained during physical exercise in a quite homogeneous patients' cohort investigated with exertional dyspnea and/or suspicion of HFpEF, are overall in agreement with these previous reports obtained in resting conditions, by showing large imprecision (wide limits of agreement) and a minimal bias of PAWP (especially of $PAWP_M$), anyhow measured, in comparison with LVEDP.

Notably, a minimal bias, together with the large limits of agreement, may be clinically relevant in those individuals with left heart filling pressure values close to the thresholds adopted to discriminate pre-capillary from post-capillary PH, as well as to diagnose or exclude HFpEF during exercise. This is why provocative testing in the cath lab are increasingly integrated with a pre-test probability assessment of HFpEF, in order to obtain a consistent and definitive diagnosis when resting hemodynamics lay in a “grey zone” [22,23]: the dynamic, multipoint evaluation during provocative maneuvers may minimize and overcome the impact of aleatory fluctuations in hemodynamics at rest as well as error measurements. In line with this reasoning, the rate of concordance between end-expiratory $PAWP_M$ and LVEDP was slightly higher during exercise than at rest, indirectly highlighting the importance of provocative maneuvers to unmask HFpEF. Despite this, 5 individuals (11%) reached either the end-expiratory LVEDP or the $PAWP_M$ threshold ≥ 25 mmHg at peak exercise. Interestingly, all of them presented also with a $PAWP_M$/CO slope > 2 mmHg as an additional criterion supporting the diagnosis of HFpEF. Even though this is a marginal and exploratory result on a limited sample size, we may suggest that incorporation of the PAWP/CO slope in the definition of HFpEF (e.g. end-expiratory PAWP ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min) might help supporting the hemodynamic diagnosis of this condition, possibly overcoming the limitations of a solitary PAWP measurement at peak exercise [4,16,24].

Limitations

This study was conducted on a relatively small number of highly selected patients, mainly at intermediate or high pre-test probability of HFpEF based on the H_2FPEF score (48% and 39% of our cohort, respectively), and the majority of them were eventually found to have HFpEF based on exercise hemodynamic results. On a clinical perspective, it represents the cohort of patients in whom LVEDP measurement might be expected to be most informative for diagnostic purposes. However, these results may deserve validation in cohorts of patients without HFpEF, or with additional confounding factors (pre-capillary PH, severe respiratory disorders or severe obesity). Nonetheless, we expect that obtaining LVEDP measures during exercise in patients with a small LV (such as patients with pulmonary vascular diseases) could be more challenging because of a higher likelihood of the pig-tail catheter to mechanically trigger ventricular ectopic beats.

Additionally, we arbitrarily defined as “pathological” an end-expiratory LVEDP at peak ≥ 25 mmHg, in the absence of validated reference values for this variable. However, PAWP, whose diagnostic and prognostic role in HFpEF is nowadays undisputed [25], resulted to be quite fairly correlated with LVEDP. Thus, the adopting an end-expiratory cut-off value at peak ≥ 25 mmHg might be reasonable for both variables.

CONCLUSIONS

PAWP and LVEDP are fairly correlated both at rest and during exercise in a population with exertional breathlessness and suspicion of HFpEF. While $PAWP_{ED}$ had no relevant bias as compared with LVEDP, $PAWP_{M}$ slightly overestimated LVEDP, likely due to concomitant left atrial dysfunction, increasing $PAWP_{M}$ values over end-diastolic values. This adequate accuracy of exercise PAWP vs LVEDP (minimal or no bias), is counterbalanced by relevant imprecision. However, the rate of agreement of these variables, dichotomized based on currently adopted PAWP cut-offs to diagnose HFpEF, increases from rest to exercise. In particular, when arbitrarily assuming an end-expiratory cut-off value to diagnose HFpEF of ≥ 25 mmHg for both end-expiratory $PAWP_{M}$ and end-expiratory LVEDP, these two measures might only occasionally disagree, questioning or preventing the diagnosis of HFpEF in a minority of patients. Incorporation of flow-corrected PAWP measures in the definition of HFpEF ($PAWP_{M} \geq 25$ mmHg and/or $PAWP_{M}$/CO slope > 2 mmHg/L/min) might maximize the diagnostic yield of exercise right heart catheterization especially in those patients with peak PAWP just below 25 mmHg, without the need to recur to a simultaneous left heart catheterization.

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FIGURES TITLES AND LEGENDS

Central Illustration. Accuracy and precision of end-expiratory $PAWP_{ED}$ and $PAWP_M$ estimates for LVEDP, as well as the rate of agreement of PAWP and LVEDP for the diagnosis of HFpEF at rest and during exercise in our population. The pre-test probability of HFpEF in our cohort was intermediate-high based on the H_2FPEF score. Exemplificative pressure traces recordings (LV pressure, red; PAWP, blue) are shown both at rest and during exercise. Linear regression analysis and Bland-Altman plot of end-expiratory LVEDP vs PAWP values are shown both at rest and at peak exercise. Venn diagrams show the agreement of dichotomized PAWP and LVEDP values above the diagnostic threshold to diagnose HFpEF, both at rest and at peak exercise. Agreement between PAWP and LVEDP was higher during exercise than at rest. Despite substantial agreement at peak exercise, 5 individuals had either PAWP or LVEDP above the diagnostic threshold for HFpEF. All of them presented with a PAWP/CO slope > 2 mmHg/L/min, suggesting that incorporation of flow-corrected PAWP in the definition of HFpEF (PAWP ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min) may maximize the diagnostic yield of exercise right heart catheterization.

Abbreviations. CO, cardiac output; ED, end-diastolic; HFpEF, heart failure with preserved ejection fraction; LVEDP, left ventricular end-diastolic pressure; M, mean; PAWP, pulmonary artery wedge pressure.

Figure 1. Linear regression analysis and Bland-Altman plot of respiratory-averaged LVEDP vs PAWP values at rest. PAWP values are reported both at end-diastole (mid-A wave for patients in sinus rhythm; mid-C or pre-V wave for patients in atrial fibrillation), panels A and B, and averaged over the cardiac cycle (mean PAWP), panels C and D

Abbreviations. LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary artery wedge pressure.

Figure 2. Linear regression analysis and Bland-Altman plot of respiratory-averaged LVEDP vs PAWP values at peak exercise. PAWP values are reported both at end-diastole (mid-A wave for patients in sinus rhythm; mid-C or pre-V wave for patients in atrial fibrillation), panels A and B and averaged over the cardiac cycle (mean PAWP), panels C and D

Abbreviations. LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary artery wedge pressure.

TABLES

Table 1. General characteristics of the study population

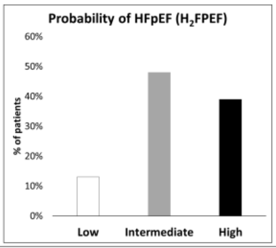
Demographics and anthropometrics	
Age, years	71±9
Female sex, n (%)	31 (67)
BMI, Kg/m^2	27±6
Comorbidities and CV risk factors	
Obesity, n (%)	10 (22)
Arterial hypertension, n (%)	36 (79)
Diabetes mellitus or impaired glucose tolerance, n (%)	7 (15)
Coronary artery disease, n (%)	7 (15)
Sinus rhythm, n (%)	42 (91)
Paroxysmal or persistent atrial fibrillation, n (%)	9 (20)
Permanent atrial fibrillation, n (%)	4 (9)
COPD, n (%)	10 (22)
Blood tests	
Creatinine, mg/dL	0.9±0.2
Hemoglobin, g/dL	13.1±1.6
BNP, ng/L	106 [51-240]
Echocardiography	
Interventricular septum thickness, mm	10.4±1.3
Posterior wall thickness, mm	9.4±1.3
LV mass index, g/m^2	85 [73-103]
LV EDV, mL	85 [77-103]
LV EF, %	64±6
LA volume index, mL/m^2	34 [26-49]
E/E’ avg	10±4
Estimated sPAP, mmHg	36±8
HFpEF probability	
H2FPEF score	4±2
Low, n (%)	6 (13)
Intermediate, n (%)	22 (48)
High, n (%)	18 (39)

Abbreviations. BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; EDV, end-diastolic volume; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; sPAP, systolic pulmonary artery pressure. Data are expressed as mean±SD, median [Q_1-Q_3] or N (%).

Table 2. Rest and exercise hemodynamics of the study population. End-expiratory pressure measurements are reported.

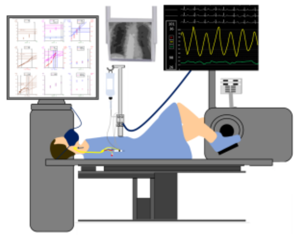
	Rest	**Peak exercise**
Workload, W		50 [40-75]
HR, bpm	69 [60-76]	110 [97-122]
HR, % of predicted		74 [66-82]
Systolic BP, mmHg	144 [136-155]	180 [160-195]
Diastolic BP, mmHg	73 [64-80]	87 [75-100]
Mean PAP, mmHg	20 [16-25]	40 [37-49]
LVEDP, mmHg	15 [10-20]	30 [25-36]
$PAWP_M$, mmHg	14 [9-18]	33 [26-41]
$PAWP_{ED}$, mmHg	14 [9-17]	31 [25-38]
$PAWP_M$ / CO slope, mmHg/L/min		2.4 [1.8-4.3]
PAWP, V wave, mmHg	15 [10-24]	38 [32-48]
Mean RAP, mmHg	6 [4-8]	16 [12-22]
CO, L/min	4.6±1.5	8.8 [7.1-11.2]
CI, L/min/m^2	2.6±0.7	5.1 [4.1-6.2]

Abbreviations. BP, blood pressure; CO, cardiac output; CI, cardiac index; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressure; $PAWP_{ED}$, end-diastolic pulmonary artery wedge pressure; $PAWP_M$, mean pulmonary artery wedge pressure; RAP, right atrial pressure. Data are expressed as mean±SD or median [Q_1-Q_3],

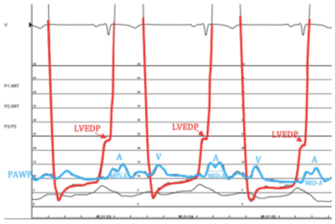


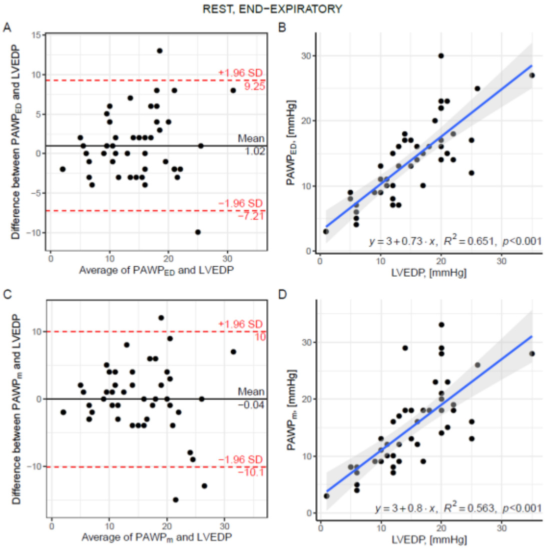
N=46 patients
with dyspnea and preserved LV EF

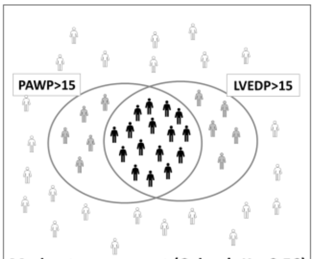
Simultaneous RHC and LHC at rest and during exercise



REST

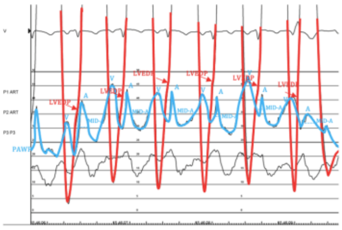


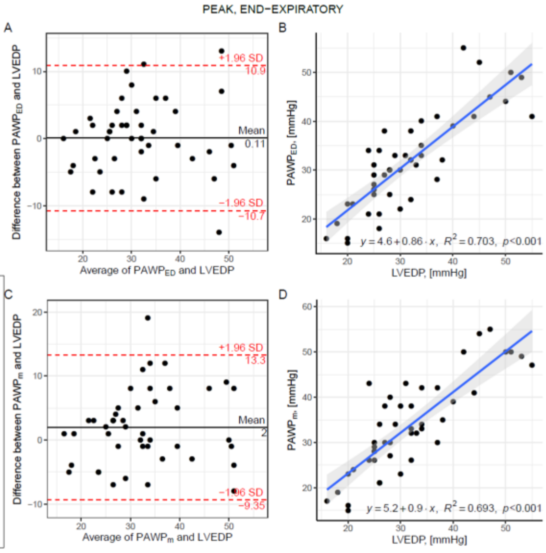


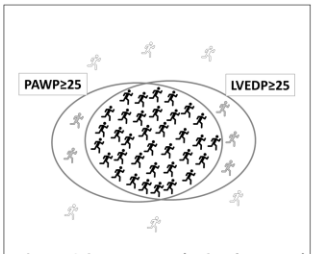


Moderate agreement (Cohen's K = 0,56)

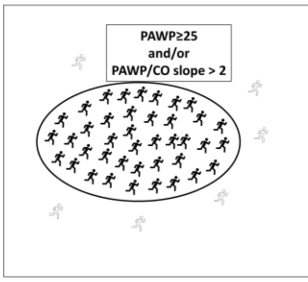
PEAK EXERCISE

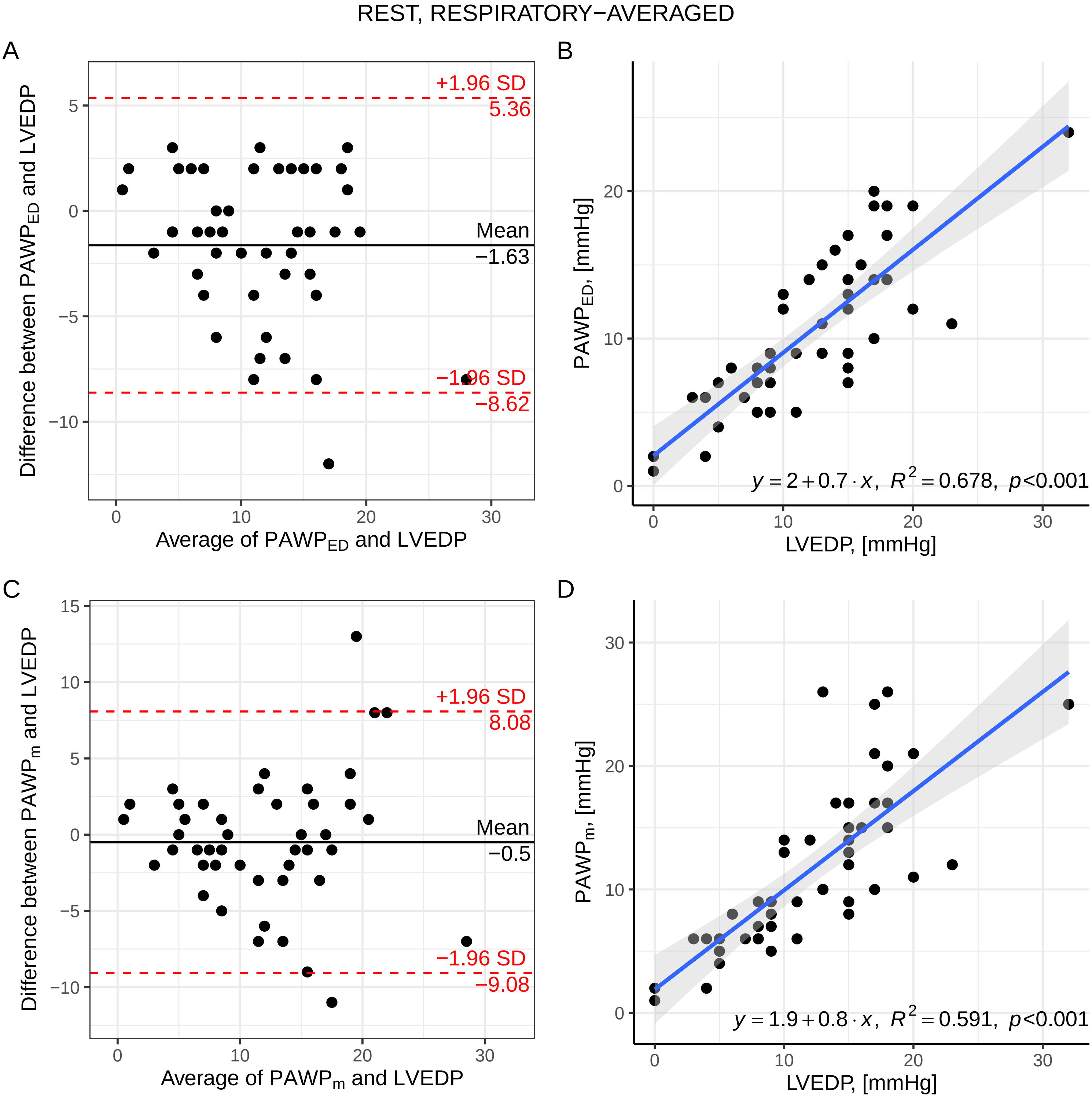


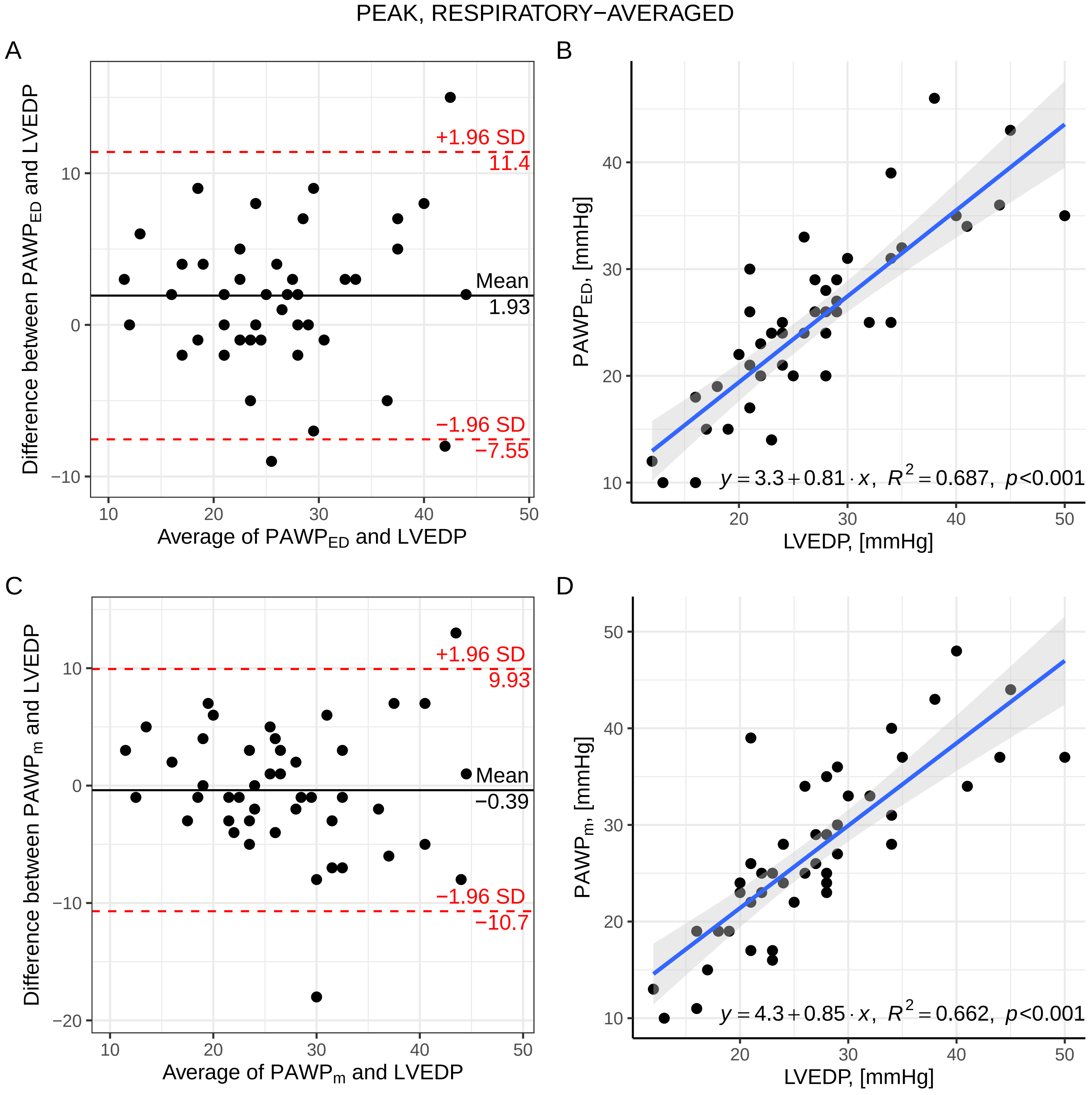




Substantial agreement (Cohen's K=0,64)




REST, RESPIRATORY−AVERAGED
A
+1.96 SD
5.36
Mean
−1.63
−1.96 SD
−8.62
Difference between PAWP$_{ED}$ and LVEDP
Average of PAWP$_{ED}$ and LVEDP
5
0
−5
−10
0
10
20
30
B
PAWP$_{ED}$, [mmHg]
LVEDP, [mmHg]
$y = 2 + 0.7 \cdot x$, $R^2 = 0.678$, p<0.001
20
10
0
0
10
20
30
C
+1.96 SD
8.08
Mean
−0.5
−1.96 SD
−9.08
Difference between PAWP$_m$ and LVEDP
Average of PAWP$_m$ and LVEDP
15
10
5
0
−5
−10
0
10
20
30
D
PAWP$_m$, [mmHg]
LVEDP, [mmHg]
$y = 1.9 + 0.8 \cdot x$, $R^2 = 0.591$, p<0.001
30
20
10
0
0
10
20
30


PEAK, RESPIRATORY−AVERAGED
A
Difference between $PAWP_{ED}$ and LVEDP
Average of $PAWP_{ED}$ and LVEDP
+1.96 SD
11.4
Mean
1.93
−1.96 SD
−7.55
10
0
−10
10
20
30
40
50
B
$PAWP_{ED}$, [mmHg]
LVEDP, [mmHg]
$y = 3.3 + 0.81 \cdot x,\ R^2 = 0.687,\ p<0.001$
10
20
30
40
20
30
40
50
C
Difference between $PAWP_m$ and LVEDP
Average of $PAWP_m$ and LVEDP
+1.96 SD
9.93
Mean
−0.39
−1.96 SD
−10.7
10
0
−10
−20
10
20
30
40
50
D
$PAWP_m$, [mmHg]
LVEDP, [mmHg]
$y = 4.3 + 0.85 \cdot x,\ R^2 = 0.662,\ p<0.001$
10
20
30
40
50
20
30
40
50