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Pulmonary arterial wedge pressure increase during exercise in patients diagnosed with pulmonary arterial or chronic thromboembolic pulmonary hypertension

Short title/running head: PAWP in PVD

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List of abbreviations

CO	cardiac output
CTEPH	chronic thromboembolic pulmonary hypertension
HFpEF	heart failure with preserved ejection fraction
mPAP	mean pulmonary artery pressure
PH	pulmonary hypertension
PAWP	pulmonary artery wedge pressure
PAP	pulmonary artery pressure
PAH	pulmonary arterial hypertension
PVR	pulmonary vascular resistance
RHC	right heart catheter

Abstract

Background: The course of pulmonary arterial wedge pressure (PAWP) during exercise in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH), further abbreviated as pulmonary vascular disease (PVD) is still unknown. The aim of the study was to describe the PAWP during exercise in patients with PVD.

Methods: In this cross-sectional study, right heart catheter (RHC) data including PAWP, recorded during semi-supine, stepwise cycle exercise in patients with PVD were analysed retrospectively. We investigated PAWP-changes during exercise until end-exercise.

Results: In 121 patients (49 female, 66 CTEPH, 55 PAH, 61.5 ± 16.5 years) resting PAWP was 10.2 ± 4.1 mmHg. Corresponding peak changes in PAWP during exercise were +2.9 mmHg (95% CI: 2.1 to 3.7 mmHg, p<0.001). Patients ≥50 years had a significantly higher increase in PAWP during exercise compared with <50 years (p<0.001). The PAWP/CO-slopes were 3.9 WU for all patients, and 1.6 WU for patients <50 years and 4.5 WU ≥ 50years.

Conclusion: In patients with PVD, PAWP increased slightly but significantly with the onset of exercise compared to resting values. The increase in PAWP during exercise was age-dependent, with patients ≥50 years showing a rapid PAWP increase even with minimal exercise. PAWP/CO slopes >2 WU are common in patients with PVD ≥50 years without exceeding the PAWP of 25 mmHg during exercise.

Trial registration:

The trial was registered at clinical trials.gov (NCT02249806).

INTRODUCTION

Right heart catheterization is currently the gold standard in diagnosing pulmonary hypertension (PH). To differentiate pre- and post-capillary PH, pulmonary artery wedge pressure (PAWP) is measured. A resting PAWP >15 mmHg is indicative of post-capillary disease [1]. An increase >18 mmHg during fluid challenge and >25 mmHg during exercise is considered pathological as this demasks occult post-capillary PH [1].

In a systematic review that included 24 studies and 237 healthy subjects, Kovacs et al. compiled pulmonary hemodynamics, including pulmonary artery pressure (PAP), cardiac output (CO), and PAWP during rest and exercise. In this study, PAWP did not exceed values >15 mmHg during exercise in patients <50 years of age. However, the older the individual (>50 years), the higher was the PAWP during exercise, which was often above 20 mmHg [2].

In the current guidelines for diagnosis and treatment of PH, normal values for PAWP at rest are defined as ≤15 mmHg, while a PAWP >25 mmHg and PAWP/CO slope >2 WU during exercise are considered to indicate left heart disease [1].

Patients with pre-capillary PH, namely patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic PH (CTEPH), further abbreviated as pulmonary vascular disease (PVD), have per definition a normal resting PAWP ≤15mmHg. However, there might be inconsistencies according to the classification if considering exercise hemodynamics as well. Nonetheless, PAWP and PAWP/CO slope during exercise have not been assessed systematically in these groups of patients. Therefore, the aim of the present study was to describe and analyze the changes in PAWP as well as PAWP/CO during exercise RHC in patients diagnosed with PVD, either classified as PAH Group 1 or CTEPH Group 4.

METHODS

Study design and subjects

All patients who underwent semi-supine incremental stepwise cycle exercise RHC in the PH-centre of the University Hospital Zurich between 11/2016 and 07/2022 as part of the work-up of suspected PH, were eligible. Patients were excluded if they had only resting-RHC e.g. due to initial severe decompensated right heart failure, had repeated RHC or did not consent to the use of their data for research purposes. Patients with PVD were included if they were diagnosed with PAH or CTEPH (WHO Group 1 or 4) and met hemodynamic criteria for pre-capillary PH at rest according to current PH guidelines with mean pulmonary artery pressure (mPAP) ≥20 mmHg, PAWP ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 WU) [1]. All RHC were diagnostic catheters in therapy naive patients. Patients with postcapillary PH (resting PAWP >15mmHg), exercise-induced post-capillary PH, defined by an increase of PAWP >25 mmHg and patients with PH due to lung disease (COPD > GOLD stage I, FVC <70%, parenchymal lung disease or emphysema) were excluded from the analysis.

Ethics

All patients gave written informed consent to RHC and further use of their data for scientific analysis. The study complies with the Declaration of Helsinki and was approved by the local ethical authorities (KEK 2019-00470).

Exercise right heart catheterization

In this cross-sectional study, exercise RHC was performed on a semi-supine cycle ergometer (TheraVital Ergometer, MedicaGMbH, Ravensburg) with a stepwise incremental protocol (increase by 10 or 20 Watts every 3 minutes) as previously described [3]. A balloon-tipped, triple-lumen, fluid-filled 8 Fr Swan Ganz catheter (Edwards Lifescience Swan-Ganz CCombo V) was placed via a jugular vein according to standard procedures. Transducers were set at the midthoracic level and zeroed to atmospheric pressure [4,5]. PAWP pressure curves were assessed on the hemodynamic monitor system (Dräger SA, Liebefeld, Switzerland) and averaged over several respiratory cycles after at least 15 minutes of rest and during the last 30 seconds of each exercise step [3,4,6,7]. The mPAP, PAWP and cardiac output (CO), measured by continuous thermodilution, as well as arterial and mixed venous blood oxygenation (SpO_2 and SmO_2) were measured at rest and during the last minute of each exercise step. PVR was calculated as PVR=(mPAP-PAWP)/CO). PAWP/CO slope and mPAP/CO slope were calculated by $(PAWP_{Wmax} - PAWP_{rest\ semi\ supine}) / (CO_{Wmax} - CO_{rest\ semi\ supine})$ and $(mPAP_{Wmax} - mPAP_{rest\ semi\ supine}) / (CO_{Wmax} - CO_{rest\ semi\ supine})$, for individual paired slopes for each patient and in addition as overall means. For the intra-individual paired slopes, the mean value of the corresponding data was then calculated.

Data presentation and statistical analysis

To compare the PAWP at different work levels as repeated measures data during exercise, work levels in supine, semi-supine position, as well as 10 W, 20 W, up to 60 W and individual end-exercise were chosen. Data were summarized as means ± standard deviation. A linear mixed model was fitted to the data with PAWP at different work levels. Group and intervention-group interaction as fixed effects and subject as random intercept, thus controlling for confounding factors. We tested if intervention-group interaction could be removed from the model. Linear contrasts were defined according to the model and tested for mean differences between chosen work levels.

Due to the known age dependency in PAWP values, data were stratified for age ≥50 years and <50 years and overall results were adjusted for age to reduce confounding [2]. In a subgroup analysis we stratified by PH-class. We simulated the distribution of the data's residuals and the random effects with Q-Q-plots and Kentucky Anscombe plots. By visual inspection of these plots, we assumed homogeneity and normality of the residuals and the random effects that complies model assumptions.

In all analyses, a 95% confidence interval that excluded the null hypothesis was considered evidence for statistically significance. Analyses were performed using R-Studio software Version 4.1.0.

RESULTS

Participants

From September 2016 to June 2022, 341 exercise catheter data sets were identified from our data base. Of those, 101 were classified as either PH Group 2, 3 or 5 and therefore excluded from the analysis. Another 30 patients were excluded due to exercise induced post-capillary PH with a PAWP >25 mmHg at end-exercise.

A total of 121 patients (49 female, 66 CTEPH, 55 PAH, 61.5 ± 16.5 years) with PVDwere included in the analysis (see table 1). The study flow-chart is shown in figure 1.

PAWP during exercise in patients with pulmonary vascular disease

In 121 patients with PVD, mean ± SD PAWP in supine position was 10.2 ± 4.1 mmHg. At end-exercise, PAWP increased up to 13.1 ± 4.2 mmHg according to a mean change of 2.9 mmHg (95% CI: 2.1 to 3.7 mmHg, p<0.001) (see figure 2, table 2 and 4). When changing patients' position from supine to semi-supine exercise position, a non-significant reduction of PAWP was observed. At a minimal load of 10 W, there was a significant increase in PAWP by 1.6 mmHg (95% CI: 0.6 to 2.5 mmHg, p<0.001). After 10 W, none of the single increments (e.g., 10 W to 20 W, 20 W to 30 W, until end-exercise) was associated with a further significant increase in PAWP. Comparing the increase of PAWP from each step up to end-exercise, only the increase from 10 W to end-exercise resulted in a significant increase in PAWP corresponding to a mean change of +1.6 mmHg (95% CI: 0.6 to 2.5 mmHg, p<0.001).

Patients with** pulmonary vascular disease**<50 years:

In 24 patients <50 years, the supine PAWP of 10.6±2.8 mmHg decreased non-significantly by -1.3 mmHg with changing patients' position to semi-supine, and increased significantly during exercise by 2.5 mmHg (95%CI: 1.1 to 4.0 mmHg, p<0.001) to a mean PAWP of 11.8 ± 2.9 mmHg at end-exercise (see table 4).

From semi-supine to 30 W, there was a significant increase in PAWP by 2.0 mmHg (95% CI: 0.4 to 3.6 mmHg, p=0.006). None of the single increments (e.g., from 0 W to 10 W, from 10 W to 20 W, up to end-exercise) increase in PAWP were significant. Comparing the increase of PAWP from increments to end-exercise, only in 10 W to end-exercise, a significant increase in PAWP according to a mean change of +2.1 mmHg (95% CI: 0.4 to 3.8 mmHg, p=0.004) was observed.

≥50 years:

In 97 patients ≥50 years the supine PAWP of 10.8 ± 3.6 mmHg was unchanged by changing patients' position to semi-supine but significantly increased during exercise by 3.4 mmHg (95% CI: 2.4 to 4.3 mmHg, p<0.001) (see table 4). At a minimal load of 10 W, there was a significant increase in PAWP by 1.8 mmHg (95% CI: 0.7 to 2.9 mmHg, p<0.001). After 10 W, none of the single increments (e.g. from 10 W to 20 W, from 20 W to 30 W, up to end-exercise) increase in PAWP were significant. Comparing the increase of PAWP from increments to end-exercise, only in 10 W to end-exercise, a significant increase in PAWP corresponding to a mean change of +1.4 mmHg (95% CI: 0.3 to 2.5 mmHg, p=0.002) was observed.

Patients ≥50 years had a statistically significant higher PAWP of 1.9 mmHg (96%CI: 0.6 to 3.2 mmHg, p=0.006) during the entire course of exercise and the increase in PAWP was significantly higher corresponding to a mean change of 2.2 mmHg (95% CI: 1.1 to 2.6 mmHg, p<0.001) compared with patients <50 years. Figure 3 shows a graphical comparison of the PAWP during exercise in patients <50 years vs. ≥50 years.

PAWP/CO-Slope in patients with pulmonary vascular disease aged < and ≥50 years

The PAWP/CO slope calculated on intra-individual paired data was 3.88 WU overall PVD -patients, 1.60 WU for patients <50 years and 4.47 WU for patients ≥50 years (95% CI: -0.1 to 5.7 WU, p=0.053) (see figure 4, Panel B), while none of the patients exceeded an absolute value of PAWP >25 mmHg during exercise according to inclusion criteria.

To demonstrate discrepancies between calculation approaches, the slopes were also calculated as overall means, resulting in 1.61 WU in all PVD -patients, 1.14 WU in patients <50 years and 1.76 WU in patients ≥50 years (see figure 4, A) when not intra-individual datasets were used for slope calculations.

PAWP during exercise in patients with CTEPH vs. PAH

Of 121 patients with PVD, 66 were diagnosed with CTEPH and 55 with PAH.

There was no statistically significant difference in PAWP during exercise between patients with CTEPH and PAH, neither in total PAWP differences nor in PAWP increase during exercise (see figure 5 and tables 6, 7 in the appendix).

DISCUSSION

The current analyses of exercise RHC data on PAWP during exercise in 121 patients with PVD diagnosed with PAH/CTEPH fills a gap of knowledge and demonstrated that the PAWP slightly (but not significantly) decreased by changing position from supine to semi-supine and rapidly and significantly increased from the onset of exercise with a levelling of towards the end-exercise. By stratifying by age, we found significant higher increases in PAWP during exercise in patients ≥50 years but no significant differences between PAH and CTEPH.

Across all patients, there was a significant increase of PAWP during exercise already at a minimal load of 10 W (semi-supine to 10 W, $p<0.001$). In younger individuals (<50 years), a significant increase in PAWP compared to resting values was found at 30 W exercise. None of the further exercise increments caused an increase of PAWP between adjacent levels of the workload. Therefore, we hypothesize that, exercise testing up to exhaustion would not be required to assess the PAWP increase in patients with PVD. A major PAWP increase can be reached at loads between 10 W and 30 W, which could improve patients' wellbeing and safety during exercise testing and shorten the overall duration of the examination. Kovacs et al. (2012) previously described the plateauing of the PAWP during exercise in healthy subjects [2]. Since, all patients with left heart failure were excluded for this analysis, there were expected similarities between the plateauing of the PAWP in the presently investigated patients with PVD and healthy individuals.

While there is robust evidence on pulmonary hemodynamics during exercise in healthy and in patients with heart failure, data is scarce in patients with PVD. Changes in resting PAWP by changing patient´s position e.g., decrease from supine to semi-supine have been described previously (2022) [8]. Singh et al. (2019) investigated dynamic right ventricular-pulmonary arterial uncoupling in 9 patients with pre-capillary PH and 11 patients with exercise PH and compared the results with 20 controls during exercise [9]. The authors concluded that the right ventricular – pulmonary arterial uncoupling during exercise blunts stroke volume and therefore cardiac output. Their findings of end-exercise PAWP (13±3 mmHg) were in line with our findings. Jain et al. (2019) assessed the hemodynamics of 27 patients with pre-capillary PH and compared those with 23 controls during exercise to identify reliable markers of early disease especially pulmonary capacitance [10]. The authors reported an end-exercise PAWP of 14.7±6.6 in patients pre-capillary PH and 10.8±4.7 in the control group. To our knowledge, this is the first paper focusing on the course PAWP during exercise (not only end-exercise) in patients with PVD.

Age stratification

In patients ≥50 years, we observed significant higher increases in PAWP during exercise (p<0.001) compared with patients <50 years. This is in agreement with the recent literature on healthy participants. A systematic review by Kovacs et al. (2012) that identified 24 studies on pulmonary vascular resistance during exercise in healthy participants, and a clinical trial by Wolsk et al. (2017) describe higher increases in PAWP in participants >50 years during exercise compared with those <50 years and concluded that even if the PAWP at rest seems to be independent from age, there is an age dependency during exercise.[2,11] The left ventricle gets stiffer with increasing age, resulting in higher PAWP-increases during exercise which can be improved by regular exercise training [12].

Comparing the increase in PAWP between age groups (figure 3), patients ≥50 years have an early increase in PAWP at a minimal load (0 W to 10 W, p<0.001) up to 14.2 ± 3.7 mmHg while patients <50 years show a slower increase in PAWP during exercise (0 W to 30 W, p<0.001) up to 11.8 ± 2.9 mmHg.

PAWP/CO Slopes

The PAWP/CO slopes were 3.88 WU for all patients, 1.60 WU for patients <50years and 4.47 WU ≥50years (see figure 4, B). In the 2022 ESC/ERS guidelines, PAWP >25 mmHg during exercise and PAWP/CO slopes >2 WU were introduced as cut offs to identify patients with post-capillary PH during exercise [1]. While patients exceeding a PAWP >25 mmHg were excluded from the study, the older patients (≥50 years, mPAP 36.8 ± 11.8, PAWP 10.2 ± 4.1 mmHg, PVR 5.0 ± 3.1 WU) would be classified as post-capillary during exercise according to the current guidelines despite having pre-capillary PH at rest and being classified as WHO-class 1 and 4. The 2022 published systematic review by Zeder and colleagues screened and compiled the recent literature for PAWP/CO slope in healthy and identified evidence for the suggestion of a 2 WU threshold for classification and prognostic relevance [13]. The common way to calculate the slopes of individual patients is to build the ratio of two differences: PAWP/CO slope=(PAWPmax–PAWPrest)/(COmax–COrest) as described by Zeder et al.

Building the ratio of the two mean differences in our cohort (meanPAWPmax-meanPAWPrest)/(meanCOmax-meanCOrest) would lead to PAWP/CO slopes of 1.61 WU (vs. 3.88 WU for mean of individual slopes) for all patients, 1.14 WU (vs. 1.6 WU) for patients <50years and 1.76 WU (vs. 4.47 WU) ≥50years (see figure 4, A) and would therefore be prone to relevant underestimation of all three slopes (all <2 WU). Meta-analysis of published data usually base their calculation on the published means and standard deviation of the study-level data as individual data is not available. Therefore, we believe that the values published in the meta-analysis by Zeder et al. might underestimate the individual slopes of older individuals [13].

Following the ERS/ESC definition and classification of PH our strictly selected cohort is clearly classified as pre-capillary PH. Interestingly, even in these patients with low resting and exercise PAWP (all <25 mmHg during exercise), some patients clearly exceeded the PAWP/CO slope >2 WU threshold, especially patients ≥50 years.

Esfandiari et al. (2019) performed a systematic review on hemodynamics during exercise in healthy and compared age >40 years and <40 years. They reported that healthy participants <40 years increase their CO progressively during exercise, while those >40 years were not able to further increase their CO from moderate to maximum exercise [14]. In our study, patients ≥50 years showed limited increase of CO during exercise while the PAWP rose, resulting in high PAWP/CO slopes. With these results, an age dependent rather than an absolute cut-off value of 2 WU should be considered for the identification of post-capillary PH during exercise. Controversially, in the Kovacs et al. review (2012), participants >50 years were able to increase CO during exercise which would not negatively influence PAWP/CO slopes, but the exercise intensity (e.g. submaximal or maximal) is unclear. Therefore, the authors themselves refer to interpret these results with caution [2].

The importance of the PAWP/CO slope in heart failure especially with preserved ejection fraction (HFpEF) is well known. Eisman et al. (2018) analysed data of 175 participants, 30 controls, 32 patients with HFpEF with resting PAWP >15 mmHg and 110 patients with dyspnea on exertion with resting PAWP <15 mmHg. The authors concluded that PAWP/CO slopes >2 WU are very common in the exercise dyspnea group and therefore may refine early HFpEF diagnosis [15]. This "early stage" HFpEF population therefore reveals similarities to our ≥50 years cohort, but their end-exercise mean PAWP was 25 ± 8 mmHg whereas our ≥50 years cohort had an end-exercise PAWP of 14.2 ± 3.7 mmHg. Therefore, a PAWP/CO slope >2 WU and a total increase of PAWP >25 mmHg seems to be sufficient to diagnose HFpEF and post-capillary PH, but it may not be directly transferable to PVD, especially in patients >50 years.

Limitations

The main findings are mainly driven by patients ≥50 years, which is due to the large sample size in this age group (119 vs. 24). The hemodynamic of patients included was generally slightly milder compared with the latest Swiss PH registry data, which revealed an mPAP of 41±11 mmHg along with a PVR of 7±4 WU for the years 2016-19 [16]. This was most probably because we chose to study patients with relatively mild disease who were able to perform exercise RHC.

Conclusion

In patients with PVD, the increase in PAWP during exercise appears to be dependent on age. In particular, in patients ≥50 years of age, PAWP increases early during exercise and at minimal exercise. Maximum values of PAWP increase were reached at 10-30 Watts and within the first minutes of exercise.

PAWP/CO slopes >2 WU are common in patients with PVD ≥50 years without exceeding the PAWP of 25 mmHg during exercise. The threshold for defining post-capillary PH during exercise may need-to be age-adjusted for patients with PVD > 50 years.

Tables

Table 1 Patients' characteristics

Number of participants	121
Chronic thromboembolic pulmonary hypertension	66
Pulmonary arterial hyptertension	55
Idiopathic	26

Heritable	1	
Connective tissue disaease	19	
HIV	2	
Portal Hypertension	3	
Congenital heart disease	2	
Schistosomiasis	2	
Female; male	59; 62	
Age [years]	62 ± 17	
Weight [kg]	76 ± 19	
Height [cm]	168 ± 11	
BMI [kg/m^2]	26 ± 5	
SpO_2 at rest [%]	94 ± 3.8	
Right heart catheterization data:	rest	end-exercise
Mean pulmonary artery pressure [mmHg]	36.8±11.8	61.0±18.4
Pulmonary artery wedge pressure [mmHg]	10.2±4.1	13.1±4.2
Cardiac output [l/min]	5.3±1.4	7.1±2.2
Pulmonary vascular resistance [WU]	5.0±3.1	6.8±3.8
mPAP/COslope [WU]	NA	13.4±15.1
PAWP/COslope [WU]	NA	3.88±6.2

Data are presented as means ± standard deviations or absolute numbers. BMI, body mass index, SpO2, oxygen saturation by pulse oximetry.

Table 2 Pulmonary artery wedge pressure during exercise

Pulmonary arterial wedge pressure [mmHg] during exercise			
	All (N=121)	≥50years (N=97)	<50years(N=24)
Endpoint	***mean±SD***	***mean±SD***	***mean±SD***
$Baseline_{supine}$	10.2±4.1	10.8±3.6	10.6±2.8
$Baseline_{semi-supine}$	10.0±1.1	10.9±3.6	9.3±2.8
10W	11.5±3.6	12.7±3.4	9.7±2.5
20W	12.4±3.8	13.5±3.3	11.0±2.7
30W	12.8±3.5	14.0±3.2	11.2±2.6
40W	12.8±3.6	13.9±3.2	11.6±2.7

50W	13.2±3.1	14.3±2.9	11.6±2.4
60W	13.2±3.1	14.1±2.9	12.2±2.4
W_{max}	13.1±4.2	14.2±3.7	11.8±2.9

Data are presented as means ± standard deviations. PAWP; pulmonary artery wedge pressure, N; number of participants, W_{max}; end-exercise.

Table 3 Changes in pulmonary artery wedge pressure during exercise in all patients

Pulmonary arterial wedge pressure [mmHg] during exercise – All patients (N=121)			
Contrast	**mean difference**	**95% confidence interval**	**p-value**
$Baseline_{supine}$ vs. $Baseline_{semi-supine}$	-0.2	-1.0 to 0.6	0.999
$Baseline_{supine}$ vs. W_{max}	2.9	2.1 to 3.7	**<0.001**
$Baseline_{semi-supine}$ vs. 10W	1.6	0.6 to 2.5	**<0.001**
$Baseline_{semi-supine}$ vs. W_{max}	3.1	2.3 to 4.0	**<0.001**
10W vs. W_{max}	1.6	0.6 to 2.5	**<0.001**
20W vs. W_{max}	0.8	-0.1 to 1.7	0.146
30W vs. W_{max}	0.3	-0.6 to 1.3	0.973
40W vs. W_{max}	0.3	-0.7 to 1.2	0.991
50W vs. W_{max}	0.0	-1.2 to 1.1	1.000
60W vs. W_{max}	-0.1	-1.2 to 1.1	1.000

Data are presented as mean differences and 95% confidence intervals. PAWP; pulmonary artery wedge pressure, N; number of participants, W_{max}; end-exercise.

Table 4 Changes in pulmonary artery wedge pressure during exercise in patients stratified by age - <50 years and ≥50 years.

PAWP [mmHg] during exercise – <50 years and ≥50 years (N=97)			
Contrast	**mean difference**	**95% confidence interval**	**p-value**
<50 years (N=24)			
$Baseline_{supine}$ vs. $Baseline_{semi-supine}$	-1.3	-2.8 to 0.2	0.117
$Baseline_{supine}$ vs. W_{max}	1.2	-0.3 to 2.7	0.213

$Baseline_{semi-supine}$ vs. W_{max}	2.5	1.1 to 4.0	**<0.001**
$Baseline_{semi-supine}$ vs. 30W	2.0	0.4 to 3.6	**0.006**
10W vs. W_{max}	2.1	0.4 to 3.8	**0.004**
20W vs. W_{max}	0.8	-0.7 to 2.4	0.754
30W vs. W_{max}	0.6	-1.1 to 2.2	0.976
40W vs. W_{max}	0.2	-1.4 to 1.8	1.000
50W vs. W_{max}	0.2	-1.7 to 2.1	1.000
60W vs. W_{max}	-0.4	-2.3 to 1.4	1.000
≥50 years (N=97)			
$Baseline_{supine}$ vs. $Baseline_{semi-supine}$	0.1	-0.9 to 1.1	1.000
$Baseline_{supine}$ vs. W_{max}	3.4	2.4 to 4.3	**<0.001**
$Baseline_{semi-supine}$ vs. W_{max}	3.3	2.3 to 4.2	**<0.001**
$Baseline_{semi-supine}$ vs. 10W	1.8	0.7 to 2.9	**<0.001**
10W vs. W_{max}	1.4	0.3 to 2.5	**0.002**
20W vs. W_{max}	0.7	-0.3 to 1.8	0.397
30W vs. W_{max}	0.2	-0.9 to 1.4	0.999
40W vs. W_{max}	0.3	-0.8 to 1.4	0.996
50W vs. W_{max}	-0.2	-1.5 to 1.2	1.000
60W vs. W_{max}	0.0	-1.3 to 1.4	1.000

Data are presented as mean differences and 95% confidence intervals. PAWP; pulmonary artery wedge pressure, N; number of participants, W_{max}; end-exercise.

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Figure Legends

Figure 1: Figure 1 shows the patients flow chart.

Figure 2: Figure 2 shows the pulmonary artery wedge pressure (PAWP) during incremental exercise in 121 included patients with PVD. Data are presented as means with standard deviations. Semi-supine to 10 Watt, 10 Watt to end-exercise as well as semi-supine to end-exercise showed significant increases in PAWP as indicated by the p-values. After 10 Watt,

none of the single increments were associated with a further significant PAWP-increase between steps.

Figure 3: Figure 3 shows the pulmonary artery wedge pressure (PAWP) during stepwise incremental exercise in patients with PVDstratified by age <50 years (panel A.) and ≥50years (panel B.). Data in A. and B. are presented as means with standard deviations according to corresponding 95% confidence intervals between patients <50 years (dotted line) and ≥50 years (line). Panel A: Semi-supine to 30 W as well as semi-supine to end-exercise there were significant increases in PAWP corresponding to the presented p-values. After 30 W, to end-exercise, none of the increments were associated with a significant increase in PAWP. Panel B: Semi-supine to 10 W, semi-supine to end-exercise and from 30 W upon end-exercise there were significant increases in PAWP corresponding to the presented p-values. After 10 W, none of the increments were associated with a significant increase in PAWP. Panel C shows a comparison of the pulmonary artery wedge pressure during incremental exercise between age groups. The p-value refers to the significant higher increase in PAWP during exercise in patients ≥50years compared with <50 years.

Figure 4: Figure 4 shows the pulmonary artery wedge pressure / cardiac output slope stratified by age <50 years (red circles) and ≥50 years (blue triangles) during exercise from 0 Watt semi-supine up to end-exercise. The dotted line represents the 2 WU slope threshold. Panel A shows the PAWP/CO slopes calculated by dividing the overall mean differences (($meanPAWP_{Wmax}$–$meanPAWP_{rest}$)/($meanCO_{Wmax}$–$meanCO_{rest}$)) for the two age groups resulting in both slopes lower than the 2 WU threshold. Panel B shows the PAWP/CO slopes calculated as paired data for each individual patient (represented by the grey arrows), resulting in a slope clearly above the 2 WU threshold for patients ≥50years.

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None of the other authors have any conflicts of interest in context with this manuscript.

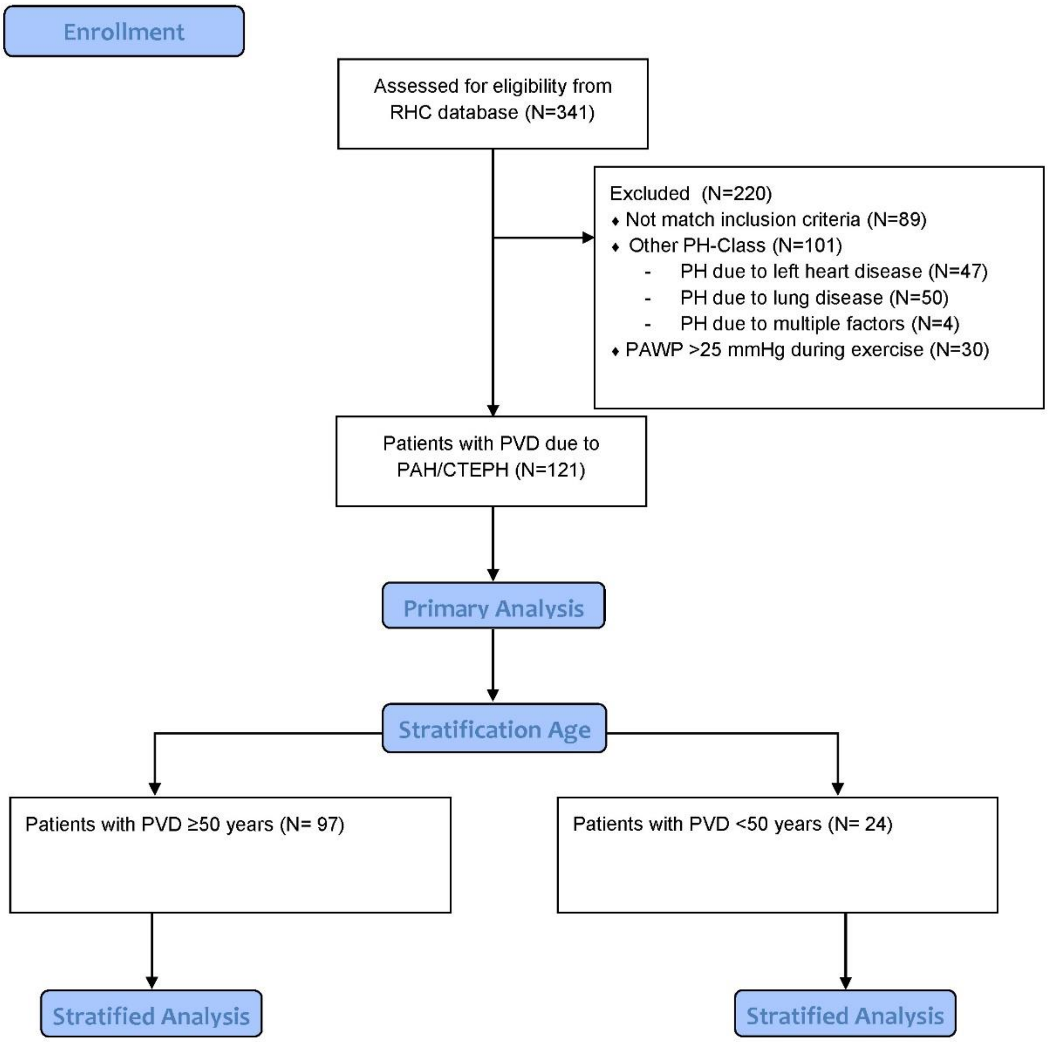
Enrollment
Assessed for eligibility from RHC database (N=341)
Excluded (N=220)
♦ Not match inclusion criteria (N=89)
♦ Other PH-Class (N=101)
- PH due to left heart disease (N=47)
- PH due to lung disease (N=50)
- PH due to multiple factors (N=4)
♦ PAWP >25 mmHg during exercise (N=30)
Patients with PVD due to PAH/CTEPH (N=121)
Primary Analysis
Stratification Age
Patients with PVD ≥50 years (N= 97)
Patients with PVD <50 years (N= 24)
Stratified Analysis
Stratified Analysis

Figure 1

Course of the pulmonary artery wedge pressure during exercise in patients with pulmonary vascular disease

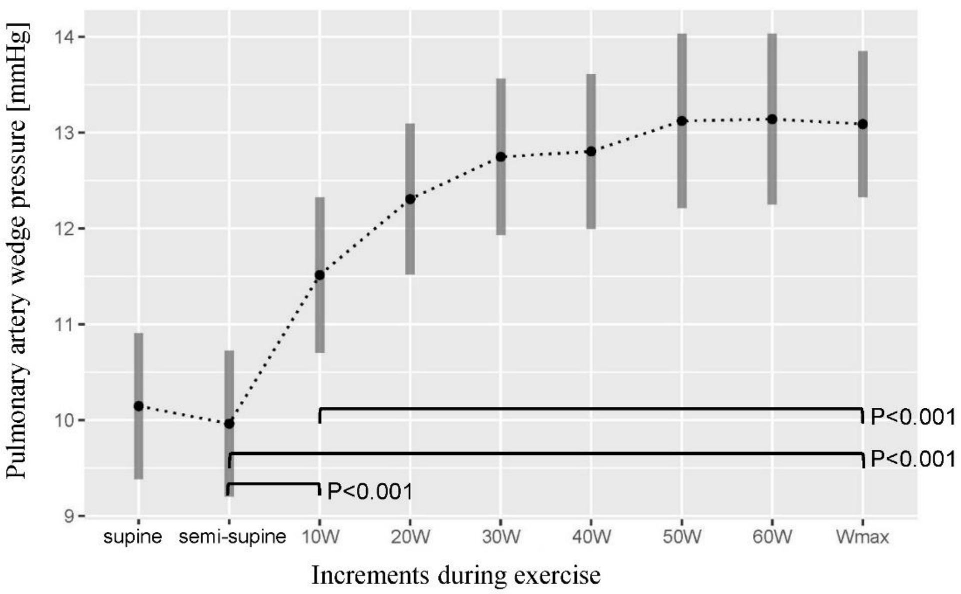

Figure 2

Course of the pulmonary artery wedge pressure during exercise in patients with pulmonary vascular disease aged <50 years vs. ≥50 years

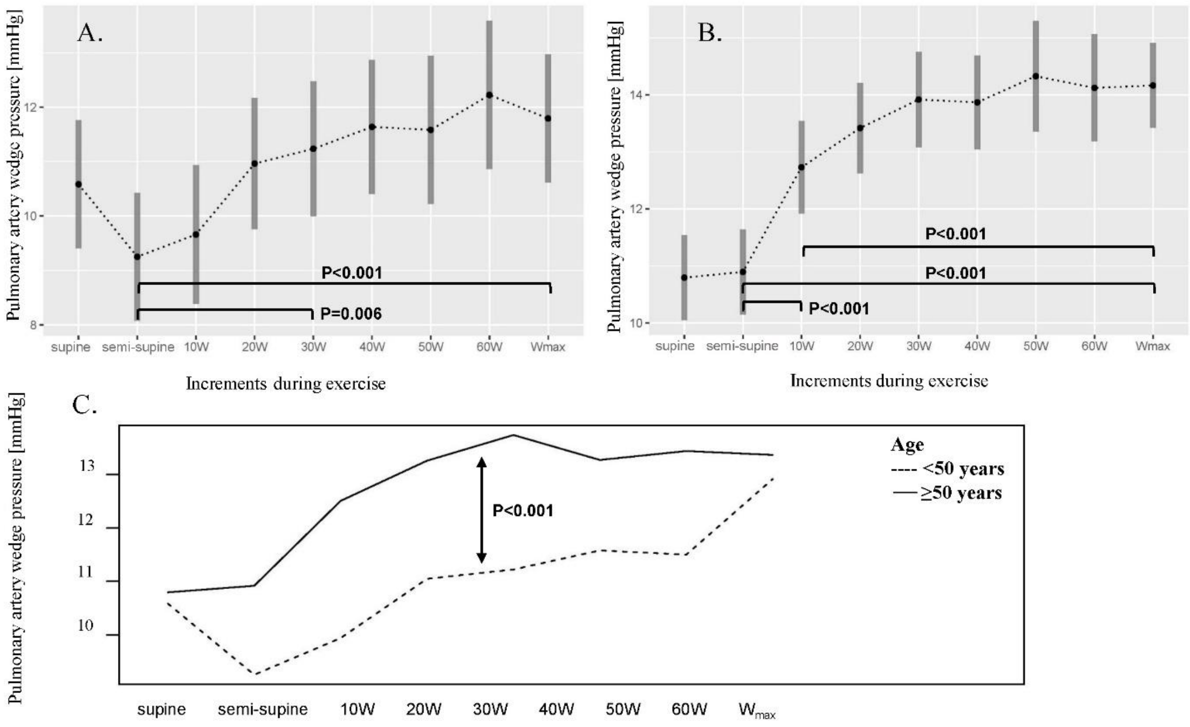

Figure 3

PAWP/CO Slope

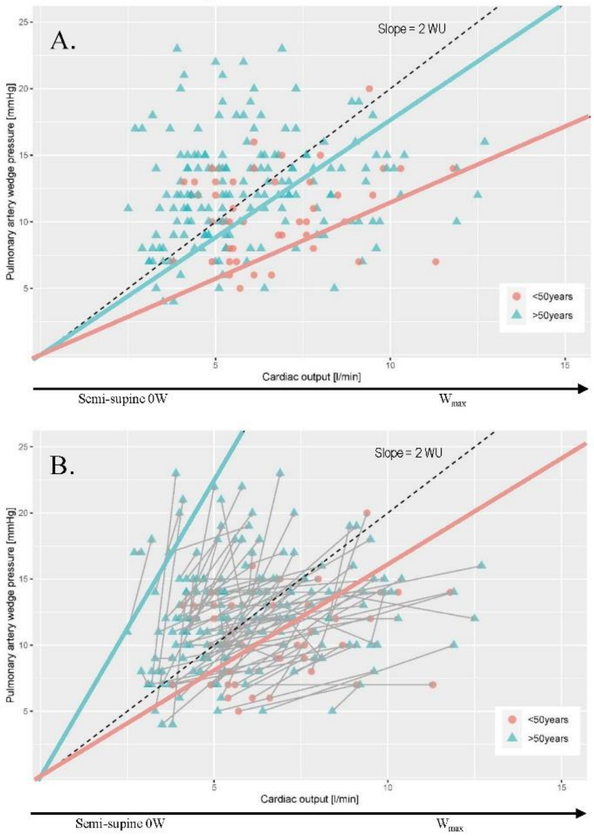

Figure 4

Supplementary data

Table 6 Contrasts of pulmonary artery wedge pressure during exercise in patients with chronic thromboembolic pulmonary hypertension.

PAWP [mmHg] during exercise – CTEPH (N=66)			
Contrast	**mean difference**	**95% confidence interval**	**p-value**
$Baseline_{supine}$ vs. $Baseline_{semi\text{-}supine}$	0.1	-1.0 to 1.7	1.000
$Baseline_{supine}$ vs. W_{max}	2.8	1.7 to 3.0	**<0.001**
$Baseline_{semi\text{-}supine}$ vs. W_{max}	2.8	1.7 to 3.9	**<0.001**
10W vs. W_{max}	1.2	-0.1 to 2.5	0.109
20W vs. W_{max}	0.5	-0.7 to 1.7	0.916
30W vs. W_{max}	0.3	-1.0 to 1.6	0.997
40W vs. W_{max}	0.3	-1.0 to 1.5	0.999
50W vs. W_{max}	-0.3	-1.8 to 1.1	0.999
60W vs. W_{max}	-0.1	-1.4 to 1.3	1.000

Data are presented as mean differences and 95% confidence intervals. PAWP; pulmonary artery wedge pressure, CTEPH; chronic thromboembolic pulmonary hypertension, N; number of participants, W_{max}; end-exercise.

Table 7 Contrasts of pulmonary artery wedge pressure during exercise in patients with pulmonary arterial hypertension.

PAWP [mmHg] during exercise – PAH (N=55)			
Contrast	**mean difference**	**95% confidence interval**	**p-value**
$Baseline_{supine}$ vs. $Baseline_{semi\text{-}supine}$	-0.5	-1.7 to 0.8	0.967
$Baseline_{supine}$ vs. W_{max}	3.1	1.8 to 4.3	**<0.001**
$Baseline_{semi\text{-}supine}$ vs. W_{max}	3.5	2.2 to 4.8	**<0.001**
10W vs. W_{max}	2.0	0.6 to 3.6	**<0.001**
20W vs. W_{max}	1.1	-0.3 to 2.5	0.916
30W vs. W_{max}	0.4	-1.1 to 1.8	0.997
40W vs. W_{max}	0.3	-1.2 to 1.8	0.999
50W vs. W_{max}	0.3	-1.6 to 2.3	0.999
60W vs. W_{max}	-0.2	-2.3 to 1.8	1.000

Data are presented as mean differences and 95% confidence intervals. PAWP; pulmonary artery wedge pressure, N; number of participants, W_{max}; end-exercise.

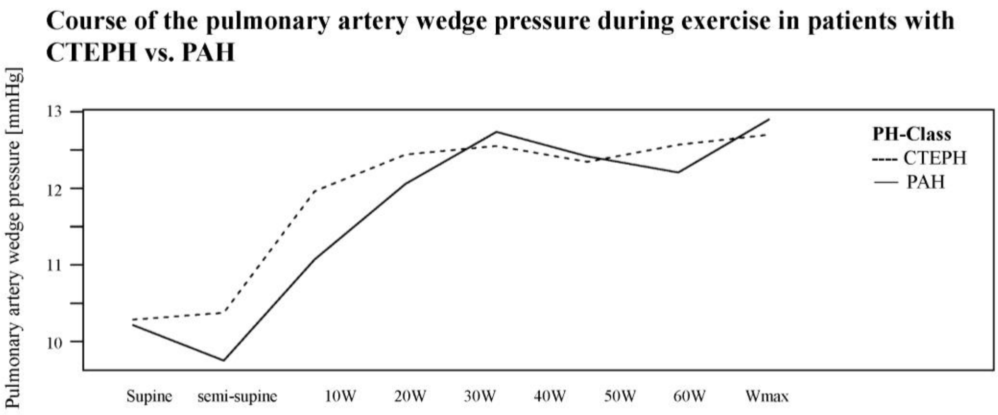

Figure 5: Figure 5 shows a comparison of the pulmonary artery wedge pressure during step-wise incremental exercise in patients with PVD stratified by chronic thromboembolic pulmonary-(CTEPH, dotted line) and pulmonary arterial hypertension (PAH, line).