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Prognostic Value of Exercise as Compared to Resting Pulmonary Hypertension in Patients with Normal or Mildly Elevated Pulmonary Arterial Pressure

To the Editor:

There is increasing evidence for the prognostic relevance of pulmonary hypertension during exercise (1–5); it is unclear, however, if this prediction goes beyond the predictive power of resting pulmonary hypertension. In this study, we aimed to assess the association between pulmonary hypertension during exercise and mortality in patients with normal or mildly elevated pulmonary arterial pressures at rest and focused on the additive prognostic information of exercise- as compared with resting hemodynamics. Some of the results of these studies have been previously reported in the form of an abstract (6).

In this single-center retrospective study, we included patients undergoing right heart catheterization (RHC) at rest and during supine ergometer exercise. Patients were referred to our clinic owing to suspected pulmonary hypertension based on their history, symptoms and investigations performed before their admission. The indication for resting RHC followed international guidelines and was based on the clinical judgment of physicians in our outpatient clinic (7). Patients who turned out to have resting mean pulmonary arterial pressure (mPAP) <25 mm Hg at RHC underwent exercise-RHC to assess pulmonary hypertension during exercise and to gain additional information regarding mechanisms of dyspnea and exercise limitation. Patients had a minimum observation time of six months. The study was approved by the local ethics committee (EK 32–352 ex 19–20). Patients undergoing exercise RHC from 2005 to August 2011 were retrospectively entered in our registry. Starting with August 2011, patients were prospectively recruited and signed informed consent. Resting- and exercise RHC was performed in all patients as previously described, pressure/cardiac output (CO) slopes were calculated as $(Pressure_{peak} - Pressure_{base})/(CO_{peak} - CO_{base})$ (8). To identify continuous exercise hemodynamic parameters predicting overall survival, we performed multivariate Cox regression analysis, adjusted for sex and age. Significant predictors were dichotomized using the approach proposed by Crowley and colleagues (9). In a second step, prognostically relevant exercise hemodynamic variables were analyzed adjusting for the presence of relevant cardiopulmonary comorbidities, smoking status, World Health Organization functional class (WHO-FC), N-terminal pro brain natriuretic peptide (NT-proBNP), 6-minute-walk distance (6MWD), peak oxygen uptake ($peak\dot{V}O_2$) and pulmonary resting hemodynamics including mPAP, pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), CO, and pulmonary vascular resistance (PVR). Models including exercise hemodynamic variables were compared with the model without these exercise hemodynamic variables using log-likelihoods. Data are presented as mean ± SD for parametric and as median (interquartile range [IQR]) for nonparametric continuous variables. Categorical data are shown as absolute and relative frequencies. Statistical software R (4.1.1) was used for data analysis (used package: survival). Between 2005 and 2017, we included 207 patients (age: 64 yr [IQR, 54–72], 69% female, body mass index: 26.6 kg/m^2 [22.8–30.1], NT-proBNP: 184pg/ml [81–493], 6MWD: 398 ± 105 m, $Peak\dot{V}O_2$: 74.4 ± 22.3% predicted, $Watt_{max}$ 75 [50–100], mPAP: 18 mm Hg [IQR, 15–21)], PAWP: 8 mm Hg [IQR, 6–10], PVR: 2.12 WU [IQR, 1.46–2.73], CO: 4.8 L/min [3.9–5.8], median follow-up time: 4.3 years [IQR, 2.0–8.5], mortality events: 40 [19%]). Ten patients had a prevalent pulmonary vascular disease based on previous RHC and were treated with at least one pulmonary arterial hypertension (PAH) drug. Eight other connective tissue disease patients received bosentan for digital ulcers. The other patients received no PAH drugs. Cardiopulmonary comorbidities were present in 147 (71%) patients.

Of the examined pulmonary exercise hemodynamic parameters mPAP/CO-slope, PAWP/CO-slope, trans-pulmonary gradient (TPG)/CO-slope and CO_{peak} turned out as age- and sex independent predictors of mortality (Table 1). The best cut-offs were 7.5 mm Hg/L/min for mPAP/CO-slope (hazard ratio [HR], 3.24; 95% confidence interval [CI], 1.49–7.04; $P = 0.003$; reference group: <7.5 mm Hg/L/min), 6.0 mm Hg/L/min for PAWP/CO-slope (HR, 4.43; 95% CI, 1.96–10.00; $P < 0.001$; reference group: <6 mm Hg/L/min), 3.9 mm Hg/L/min for TPG/CO-slope (HR, 2.56; 95% CI, 1.24–5.30, $P = 0.013$; reference group: <3.9 mm Hg/L/min) and 8.5 L/min for CO_{peak} (HR, 4.41; 95% CI, 2.01–9.68; $P < 0.001$; reference group: ⩾8.5 L/min) (Figure 1). In multivariate models, additionally adjusting for cardiopulmonary comorbidities, smoking status, WHO-FC, and resting hemodynamics, all four parameters remained significant independent predictors of mortality (Table 2: Models 2–3). After additionally adjusting for NT-proBNP, this remained true for CO_{peak} (Table 2: Model 4). Of note, after adjusting for 6MWD or $peak\dot{V}O_2$, the addition of exercise- to resting hemodynamics did not result in an improvement of the prognostic model (Table 2: Models 5–6). Based on the data of the Austrian National Institute of Statistics, the most frequent causes of death were: cardiovascular ($N = 11$ [28%]) respiratory ($N = 8$ [20%]), and cancer ($N = 8$ [20%]). All three slopes and CO_{peak} remained significant predictors of survival after using competing risk analysis adjusting cancer related events.

Patients with a mPAP/CO-slope ⩾7.5 mm Hg/L/min were older (73 yr [68–77] vs. 60 yr [50–69], $P < 0.001$), had more cardiopulmonary comorbidities (one or more comorbidities in 46/49 [94%] vs. 95/148 [64%], $P < 0.001$), higher NT-proBNP (470 pg/ml [243–1416] vs. 144 pg/ml [66–344], $P < 0.001$) and shorter 6MWD (314 ± 85 m vs. 426 ± 99 m, $P < 0.001$) as compared with subjects with mPAP/CO-slope <7.5 mm Hg/L/min. In addition, in high-slope versus low-slope patients significantly more patients had resting PVR ⩾3 WU (32% vs. 12%; $P < 0.001$), peak work-load was significantly lower (50 W [25–50] vs. 75 W [50–100]; $P < 0.001$) and

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Table 1. Prognostic Models Predicting All-Cause Mortality by Exercise Hemodynamics

			Resting Parameters				
			mPAP	**PAWP**	**RAP**	**CO**	**PVR**
Model 1: resting parameter adjusted for age and sex	Resting parameters	HR (95% CI)	1.10 (1.00–1.21)	0.96 (0.90–1.02)	1.01 (0.95–1.07)	1.00 (0.99–1.00)	1.42 (0.98–2.05)
		P value	**0.045**	0.156	0.880	0.299	0.063
Model 1 + MPAP/CO slope	Model comparison:	*P* value	0.021	0.008	0.005	0.008	0.006
	mPAP/CO-Slope:	HR (95% CI)	1.05 (1.01–1.09)	1.01 (1.01–1.09)	1.05 (1.01–1.10)	1.06 (1.02–1.10)	1.06 (1.02–1.10)
		P value	**0.009**	**0.013**	**0.026**	**0.033**	**0.003**
Model 1 + PAWP/CO slope	Model comparison:	*P* value	0.061	0.029	0.023	0.027	0.014
	PAWP/CO-Slope:	HR (95% CI)	1.07 (1.01–1.13)	1.07 (1.00–1.14)	1.07 (0.99–1.15)	1.08 (1.02–1.15)	1.09 (1.02–1.15)
		P value	**0.024**	**0.047**	**0.072**	**0.005**	**0.006**
Model 1 + TPG/CO slope	Model comparison:	*P* value	0.031	0.011	0.006	0.014	0.031
	TPG/CO-Slope:	HR (95% CI)	1.11 (1.01–1.21)	1.11 (1.03–1.21)	1.11 (1.01–1.21)	1.13 (1.04–1.23)	1.11 (1.02–1.22)
		P value	**0.022**	**0.011**	**0.022**	**0.003**	**0.016**
Model 1 + CO_{peak}	Model comparison:	*P* value	0.001	<0.001	<0.001	<0.001	0.002
	CO_{peak}:	HR (95% CI)	0.82 (0.72–0.93)	0.82 (0.72–0.93)	0.82 (0.72–0.94)	0.71 (0.60–0.84)	0.82 (0.71–0.93)
		P value	**0.002**	**0.003**	**0.003**	**<0.001**	**0.003**

Definition of abbreviations: CI = confidence interval; CO = cardiac output; HR = hazard ratio; mPAP = mean pulmonary arterial pressure; NT-proBNP = N terminal pro brain natriuretic peptide; PAWP = pulmonary artery wedge pressure; peak$\dot{V}O_2$ = peak oxygen uptake; PVR = pulmonary vascular resistance; RAP = right atrial pressure; WHO-FC = World Health Organization functional class; 6MWD = 6-minute-walk distance.

Model 1 adjusting for age and sex. Hazard ratios (95% CI) and *P* values are given for different resting hemodynamics separately (mPAP, PAWP, RAP, CO, and PVR). Parameters of exercise hemodynamics (mPAP/CO slope, PAWP/CO slope, TPG/CO slope, peak CO) are added individually to the model. Here, HR (95% CI) as well as the *P* values for the exercise hemodynamics are given. The models including exercise hemodynamics are compared to the initial model without exercise hemodynamics. In the line "model comparison" the *P* value for this comparison is given.

In model 1, all analyzed parameters of exercise hemodynamics are significant predictors of prognosis and are superior to the model including only resting hemodynamics.

Bold values are statistically significant.

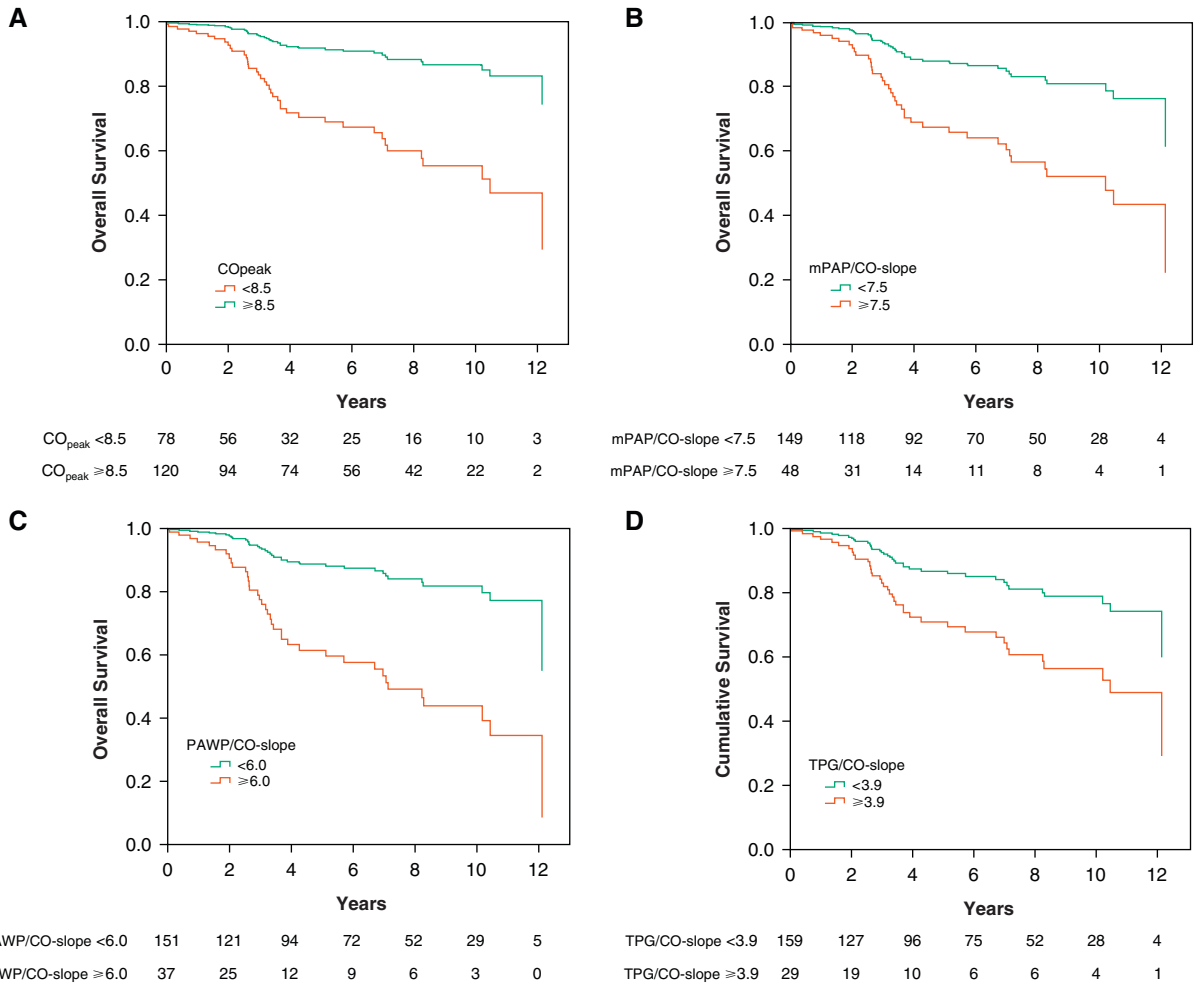

Figure 1. Multivariate COX Regression for (*A*) CO_{peak} ($P < 0.001$), (*B*) mPAP/CO-slope ($P = 0.036$), (*C*) PAWP/CO-slope ($P < 0.001$), and (*D*) TPG/CO-slope ($P = 0.011$) accounting for age and sex. CO = cardiac output; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; TPG = transpulmonary gradient.

mPAP was higher both at rest (21 mm Hg [IQR, 18–23] vs. 17 mm Hg [IQR, 14–21]; $P < 0.001$) and at peak exercise (45 ± 9 mm Hg vs. 39 ± 10 mm Hg; $P < 0.001$).

In this study, we confirm the prognostic relevance of pulmonary hypertension during exercise in patients with normal or mildly elevated pulmonary arterial pressure. We show for the first time that mPAP/CO-slope, PAWP/CO-slope, TPG/CO-slope, and CO_{peak} are not only age- and sex-independent predictors of mortality but also independent of cardiopulmonary comorbidities, smoking status, WHO-FC, and resting hemodynamics, thus providing additional prognostic information.

Based on recent studies, pressure/CO-slopes emerge as valuable prognostic parameters for patients with normal or mildly elevated pulmonary arterial pressures (10–12) and mPAP/CO-slope <3 mm Hg/L/min may even serve as cut-off for normal exercise hemodynamics (2, 3). In our study, we do not only confirm the prognostic relevance of Pressure/CO slopes (mPAP/CO-, TPG/CO-, and PAWP/CO slope), but extend our knowledge by showing that in patients with normal or mildly elevated resting mPAP, these slopes are independent predictors of mortality even after adjustment for continuous pulmonary resting hemodynamic parameters. This suggests that both pre- and post-capillary causes of pulmonary pressure elevation during exercise may contribute to mortality risk.

Previous studies have found a broad range of predictive mPAP/CO-slopes and PAWP/CO-slopes (2, 4, 13). This may be explained by the fact that optimal prognostic cut-offs are highly dependent on the analyzed patients and other circumstances including body position during exercise. The finding that in addition to pressure/CO-slopes CO_{peak} was a significant predictor of prognosis supports previous results of Chaouat and colleagues, who identified cardiac index during exercise as independent prognosticator (1), although their finding was derived from a set of 55 patients with severe PAH, while our patients had no more than mild pulmonary hypertension. Of note, in our study, there was a strong negative nonlinear correlation between the mPAP/CO slope and CO_{peak} ($r_s = -0.803$, $P < 0.001$), suggesting that a steep mPAP increase might limit CO_{peak} during exercise.

The clinical consequences of our study need to be further explored. We do not advise the investigation of pulmonary hypertension during exercise as an additive invasive testing to patients, but our data suggest that protocols encompassing both rest

Table 2. Additional Prognostic Models Predicting All-Cause Mortality by Exercise Hemodynamics

			Resting Parameters				
			mPAP	PAWP	RAP	CO	PVR
Model 2: resting parameter adjusted for age, sex, smoking status, and comorbidities	Resting parameters	HR (95% CI)	1.12 (1.02–1.24)	0.97 (0.91–1.03)	1.01 (0.95–1.08)	1.00 (0.99–1.01)	1.40 (0.93–2.09)
		P value	**0.023**	0.329	0.727	0.401	0.106
Model 2 + MPAP/CO-slope	Model comparison:	*P* value	0.016	0.006	0.005	0.007	0.005
	mPAP/CO-Slope:	HR (95% CI)	1.06 (1.02–1.10)	1.06 (1.03–1.10)	1.07 (1.03–1.11)	1.06 (1.02–1.10)	1.07 (1.03–1.11)
		P value	**0.005**	**0.001**	**<0.001**	**0.001**	**0.001**
Model 2 + PAWP/CO slope	Model comparison:	*P* value	0.052	0.025	0.020	0.024	0.011
	PAWP/CO-Slope:	HR (95% CI)	1.07 (1.01–1.14)	1.08 (1.02–1.15)	1.08 (1.02–1.15)	1.08 (1.02–1.15)	1.10 (1.03–1.17)
		P value	**0.031**	**0.012**	**0.008**	**0.011**	**0.004**
Model 2 + TPG/CO slope	Model comparison:	*P* value	0.028	0.009	0.006	0.013	0.027
	TPG/CO-Slope:	HR (95% CI)	1.12 (1.02–1.22)	1.14 (1.05–1.24)	1.16 (1.06–1.26)	1.14 (1.04–1.24)	1.13 (1.03–1.24)
		P value	**0.012**	**0.002**	**0.001**	**0.004**	**0.010**
Model 2 + CO_{peak}	Model comparison:	*P* value	<0.001	<0.001	<0.001	<0.001	0.001
	CO_{peak}:	HR (95% CI)	0.79 (0.69–0.91)	0.78 (0.67–0.89)	0.78 (0.68–0.90)	0.73 (0.61–0.90)	0.79 (0.68–0.92)
		P value	**0.002**	**<0.001**	**<0.001**	**<0.001**	**0.002**
Model 3: resting parameter adjusted for age, sex, WHO functional class	Resting parameters	HR (95% CI)	1.12 (1.02–1.23)	0.97 (0.91–1.03)	1.02 (0.95–1.09)	1.00 (0.99–1.01)	1.41 (0.95–2.09)
		P value	**0.022**	0.330	0.659	0.348	0.087
Model 3 + MPAP/CO-slope	Model comparison:	*P* value	0.021	0.008	0.005	0.009	0.007
	mPAP/CO-Slope:	HR (95% CI)	1.05 (1.01–1.09)	1.06 (1.02–1.10)	1.06 (1.03–1.10)	1.06 (1.02–1.10)	1.06 (1.03–1.11)
		P value	**0.007**	**0.001**	**0.001**	**0.002**	**0.001**
Model 3 + PAWP/CO slope	Model comparison:	*P* value	0.063	0.029	0.024	0.030	0.015
	PAWP/CO-Slope:	HR (95% CI)	1.06 (1.00–1.13)	0.98 (0.82–1.05)	1.08 (1.02–1.14)	1.07 (1.01–1.14)	1.09 (1.02–1.16)
		P value	**0.040**	**0.014**	**0.010**	**0.015**	**0.006**
Model 3 + TPG/CO slope	Model comparison:	*P* value	0.031	0.011	0.006	0.015	0.032
	TPG/CO-Slope:	HR (95% CI)	1.11 (1.02–1.21)	1.13 (1.04–1.23)	1.15 (1.06–1.26)	1.13 (1.04–1.23)	1.12 (1.02–1.23)
		P value	**0.014**	**0.003**	**0.001**	**0.005**	**0.013**
Model 3 + CO_{peak}	Model comparison:	*P* value	<0.001	<0.001	<0.001	<0.001	0.001
	CO_{peak}:	HR (95% CI)	0.80 (0.70–0.92)	0.78 (0.68–0.90)	0.78 (0.68–0.90)	0.73 (0.61–0.87)	0.79 (0.69–0.92)
		P value	**0.001**	**<0.001**	**0.001**	**0.001**	**0.002**
Model 4: resting parameter adjusted for age, sex, ln(NTproBNP)	Resting parameters	HR (95% CI)	1.13 (1.02–1.26)	0.97 (0.91–1.04)	1.03 (0.96–1.10)	1.00 (0.99–1.01)	1.28 (0.85–1.92)
		P value	**0.023**	**0.0444**	0.457	0.506	0.236
Model 4 + MPAP/CO-slope	Model comparison:	*P* value	0.0193	0.099	0.080	0.105	0.071
	mPAP/CO-Slope:	HR (95% CI)	1.03 (0.99–1.08)	1.04 (1.00–1.08)	1.04 (1.00–1.09)	1.04 (1.00–1.08)	1.04 (1.00–1.09)
		P value	0.159	0.071	0.054	0.075	**0.047**
Model 4 + PAWP/CO slope	Model comparison:	*P* value	0.410	0.269	0.271	0.257	0.148
	PAWP/CO-Slope:	HR (95% CI)	1.03 (0.96–1.10)	1.04 (0.97–1.11)	1.04 (0.97–1.11)	1.04 (0.97–1.11)	1.06 (0.98–1.14)
		P value	0.392	0.245	0.245	0.232	0.126
Model 4 + TPG/CO slope	Model comparison:	*P* value	0.123	0.054	0.026	0.066	0.080
	TPG/CO-Slope:	HR (95% CI)	1.08 (0.99–1.18)	1.10 (1.01–1.20)	1.12 (1.02–1.23)	1.09 (1.00–1.19)	1.09 (1.00–1.19)
		P value	0.093	**0.032**	**0.013**	**0.042**	0.051
Model 4 + CO_{peak}	Model comparison:	*P* value	0.012	0.006	0.012	0.006	0.019
	CO_{peak}:	HR (95% CI)	0.82 (0.70–0.96)	0.81 (0.69–0.94)	0.82 (0.70–0.96)	0.77 (0.64–0.94)	0.83 (0.70–0.97)
		P value	**0.015**	**0.008**	**0.016**	**0.008**	**0.022**
Model 5: resting parameter adjusted for age, sex, 6 MWD	Resting parameters	HR (95% CI)	1.11 (0.99–1.24)	0.95 (0.88–1.04)	0.95 (0.87–1.04)	1.00 (0.98–1.01)	1.63 (0.95–2.78)
		P value	0.078	0.280	0.241	0.534	0.073
Model 5 + MPAP/CO-slope	Model comparison:	*P* value	0.753	0.488	0.540	0.549	0.419

Table 2. (*Continued*).

			Resting Parameters				
			mPAP	**PAWP**	**RAP**	**CO**	**PVR**
	mPAP/CO-Slope:	HR (95% CI)	1.01 (0.98–1.24)	1.02 (0.97–1.07)	1.02 (0.97–1.07)	1.02 (0.97–1.07)	1.02 (1.00–1.03)
		P value	0.748	0.466	0.522	0.534	0.391
Model 5 + PAWP/CO slope	Model comparison:	*P* value	0.934	0.636	0.476	0.601	0.392
	PAWP/CO-Slope:	HR (95% CI)	1.00 (0.93–1.08)	1.02 (0.95–1.09)	1.03 (0.96–1.10)	1.02 (0.95–1.09)	1.03 (0.96–1.11)
		P value	0.931	0.627	0.458	0.591	0.371
Model 5 + TPG/CO slope	Model comparison:	*P* value	0.575	0.407	0.798	0.605	0.690
	TPG/CO-Slope:	HR (95% CI)	1.03 (0.92–1.15)	1.05 (0.94–1.18)	1.02 (0.89–1.16)	1.03 (0.92–1.17)	1.03 (0.90–1.17)
		P value	0.564	0.386	0.795	0.596	0.682
Model 5 + CO_{peak}	Model comparison:	*P* value	0.319	0.212	0.186	0.261	0.3944
	CO_{peak}:	HR (95%CI)	0.90 (0.73–1.11)	0.88 (0.72–1.08)	0.87 (0.71–1.08)	0.87 (0.69–1.11)	0.91 (0.73–1.13)
		P value	0.331	0.230	0.202	0.276	0.400
Model 6: resting parameter adjusted for age, sex, peak$\dot{V}O_2$	Resting parameters	HR (95%CI)	1.30 (1.04–1.63)	0.94 (0.83–1.06)	0.95 (0.81–1.10)	0.98 (0.95–1.01)	2.24 (1.03–4.90)
		P value	**0.020**	0.296	0.475	0.127	0.043
Model 6 + MPAP/CO-slope	Model comparison:	*P* value	0.905	0.507	0.403	0.637	0.806
	mPAP/CO-Slope:	HR (95%CI)	1.01 (0.81–1.28)	1.07 (0.88–1.30)	1.10 (0.89–1.37)	1.06 (0.85–1.32)	1.04 (0.79–1.37)
		P value	0.904	0.483	0.368	0.623	0.801
Model 6 + PAWP/CO slope	Model comparison:	*P* value	0.942	0.890	0.943	0.774	0.866
	PAWP/CO-Slope:	HR (95%CI)	0.99 (0.80–1.23)	0.98 (0.78–1.24)	1.01 (0.78–1.30)	0.96 (0.74–1.25)	1.02 (0.80–1.31)
		P value	0.942	0.893	0.942	0.783	0.863
Model 6 + TPG/CO slope	Model comparison:	*P* value	0.761	0.166	0.214	0.175	0.926
	TPG/CO-Slope:	HR (95%CI)	1.06 (0.74–1.50)	1.28 (0.93–1.75)	1.27 (0.90–1.79)	1.32 (0.91–1.91)	1.02 (0.62–1.70)
		P value	0.760	0.132	0.177	0.144	0.926
Model 6 + CO_{peak}	Model comparison:	*P* value	0.830	0.681	0.743	0.437	0.797
	CO_{peak}:	HR (95%CI)	0.96 (0.68–1.36)	0.93 (0.67–1.30)	0.95 (0.68–1.31)	1.17 (0.79–1.72)	1.05 (0.98–1.03)
		P value	0.829	0.681	0.744	0.433	0.798

For definition of abbreviations, *see* Table 1.

We provide additional five prognostic models (models 2–6: additionally adjusted for cardiopulmonary comorbidities and smoking status (model 2), WHO-FC (model 3), natural logarithm of NT-proBNP (ln[NT-proBNP]) (model 4), 6MWD (model 5) and peak$\dot{V}O_2$ (model 6), in all of them also adjusting for age and sex. Hazard ratios (95% CI) and *P* values are given for different resting hemodynamics separately (mPAP, PAWP, RAP, CO, and PVR).

Parameters of exercise hemodynamics (mPAP/CO slope, PAWP/CO slope, TPG/CO slope, peak CO) are added individually to the models. Here, HR (95% CI) as well as the *P* values for the exercise hemodynamics are given. The models including exercise hemodynamics are compared to the initial models without exercise hemodynamics. In the line "model comparison" the *P* value for this comparison is given.

In models 2–3, all analyzed parameters of exercise hemodynamics are significant predictors of prognosis and are superior to the model including only resting hemodynamics.

In model 4, adjusting also for ln(NT-proBNP), peak CO is still a significant predictor of prognosis and is superior to the model including only resting hemodynamics.

Bold values are statistically significant.

and exercise testing during RHC are positioned to improve prognosis estimates. This approach may additionally contribute to the differentiation between early pulmonary vascular disease and latent left heart disease. Currently, close clinical follow-up of patients with abnormal pulmonary hypertension during exercise and their inclusion into appropriate clinical trials should be recommended.

The addition of exercise hemodynamics is not intended to replace noninvasive methods for assessing function, such as 6MWD, which itself is prognostic. Of note, after adjusting for 6MWD or peak$\dot{V}O_2$, the outcome estimates generated by analyzing specific exercise hemodynamic variables were no longer significant. Although this finding might be partly explained by the limited number of patients and events in our study, it also emphasizes the usefulness of 6MWD and cardiopulmonary exercise testing in the clinical practice. To which extent pulmonary exercise hemodynamics may serve as general prognosticators in the risk assessment for pulmonary vascular disease may therefore warrant exploration in larger multicenter studies.

Our data have been derived from a single center retrospective analysis, which is a limitation of the study. A multivariate analysis including all slopes in one model was not possible, due to high collinearity. Due to the limited small sample size patients with malignancies were not excluded from primary analysis. However, after adjusting for cancer related events, exercise hemodynamics remained significant prognosticators. As further potential limitation, CO was measured by thermodilution, potentially leading to slightly different CO values as compared with the gold-standard Fick-method. However, all measurements were performed by the same experienced team using standardized protocols that should minimalize methodologic errors.

In conclusion, in patients with normal or mildly elevated pulmonary arterial pressures, mPAP/CO, PAWP/CO, and TPG/CO-slopes, and CO_{peak} are predictors of all-cause mortality, after correction for age, sex, comorbidities, smoking status, WHO-FC, and resting hemodynamics suggesting that exercise hemodynamics provide robust and independent prognostic information. ■

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References

1. Chaouat A, Sitbon O, Mercy M, Ponçot-Mongars R, Provencher S, Guillaumot A, *et al.* Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. *Eur Respir J* 2014;44:704–713.
2. Ho JE, Zern EK, Lau ES, Wooster L, Bailey CS, Cunningham T, *et al.* Exercise pulmonary hypertension predicts clinical outcomes in patients with dyspnea on effort. *J Am Coll Cardiol* 2020;75:17–26.
3. Lewis GD, Murphy RM, Shah RV, Pappagianopoulos PP, Malhotra R, Bloch KD, *et al.* Pulmonary vascular response patterns during exercise in left ventricular systolic dysfunction predict exercise capacity and outcomes. *Circ Heart Fail* 2011;4:276–285.
4. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, *et al.* Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail* 2018;11:e004750.
5. Hasler ED, Müller-Mottet S, Furian M, Saxer S, Huber LC, Maggiorini M, *et al.* Pressure-flow during exercise catheterization predicts survival in pulmonary hypertension. *Chest* 2016;150:57–67.
6. Douschan P, Foris V, Avian A, Sassmann T, Olschewski H, Kovacs G. MPAP/CO-slope during exercise as predictor of mortality in patients at risk for pulmonary hypertension. *Eur Respir J* 2020;56:1508.
7. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;46:903–975.
8. Kovacs G, Maier R, Aberer E, Brodmann M, Scheidl S, Hesse C, *et al.* Assessment of pulmonary arterial pressure during exercise in collagen vascular disease: echocardiography vs right-sided heart catheterization. *Chest* 2010;138:270–278.
9. Crowley J, Leblanc M, Gentleman R, Salmon S. Exploratory methods in survival analysis. *Lect Notes Monogr Ser* 1995;27:55–77.
10. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, *et al.* Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J* 2015;46:728–737.
11. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, *et al.* An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017;50:1700578.
12. Zeder K, Banfi C, Steinrisser-Allex G, Maron BA, Humbert M, Lewis GD, *et al.* Diagnostic, prognostic and differential-diagnostic relevance of pulmonary hemodynamics during exercise - a systematic review. *Eur Respir J* 2022;60:2103181.
13. Stamm A, Saxer S, Lichtblau M, Hasler ED, Jordan S, Huber LC, *et al.* Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis. *Eur Respir J* 2016;48:1658–1667.

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