Journal of the American Heart Association

ORIGINAL RESEARCH

Right Atrial Pressure During Exercise Predicts Survival in Patients With Pulmonary Hypertension

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BACKGROUND: We investigated changes in right atrial pressure (RAP) during exercise and their prognostic significance in patients assessed for pulmonary hypertension (PH).

METHODS AND RESULTS: Consecutive right heart catheterization data, including RAP recorded during supine, stepwise cycle exercise in 270 patients evaluated for PH, were analyzed retrospectively and compared among groups of patients with PH (mean pulmonary artery pressure [mPAP] ≥25 mm Hg), exercise-induced PH (exPH; resting mPAP <25 mm Hg, exercise mPAP >30 mm Hg, and mPAP/cardiac output >3 Wood Units (WU)), and without PH (noPH). We investigated RAP changes during exercise and survival over a median (quartiles) observation period of 3.7 (2.8–5.6) years. In 152 patients with PH, 58 with exPH, and 60 with noPH, median (quartiles) resting RAP was 8 (6–11), 6 (4–8), and 6 (4–8) mm Hg (P<0.005 for noPH and exPH versus PH). Corresponding peak changes (95% CI) in RAP during exercise were 5 (4–6), 3 (2–4), and –1 (–2 to 0) mm Hg (noPH versus PH P<0.001, noPH versus exPH P=0.027). RAP increase during exercise correlated with mPAP/cardiac output increase (r=0.528, P<0.001). The risk of death or lung transplantation was higher in patients with exercise-induced RAP increase (hazard ratio, 4.24; 95% CI, 1.69–10.64; P=0.002) compared with patients with unaltered or decreasing RAP during exercise.

CONCLUSIONS: In patients evaluated for PH, RAP during exercise should not be assumed as constant. RAP increase during exercise, as observed in exPH and PH, reflects hemodynamic impairment and poor prognosis. Therefore, our data suggest that changes in RAP during exercise right heart catheterization are clinically important indexes of the cardiovascular function.

Key Words: exercise ■ hemodynamics ■ mortality ■ pulmonary arterial hypertension ■ right heart catheterization

In the absence of obstruction of the vena cava, central venous pressure and right atrial pressure (RAP) are identical and reflect right ventricular preload. The gold standard to assess RAP is an invasive measurement via a central venous line. Normal RAP at rest is between 1 and 7 mm Hg.[1] An elevated resting RAP is associated with a poor prognosis in a broad spectrum of cardiovascular disorders, including chronic heart failure and precapillary pulmonary hypertension (PH).[2-5] Little is known about the course of the RAP during exercise in healthy subjects and patients with PH. In a systematic review of the literature, Kovacs et al assembled the course of the mean pulmonary artery pressure (mPAP), cardiac output (CO), and pulmonary artery wedge pressure assessed during right heart catheterization (RHC). They included 47 publications describing 72 populations comprising 1187 subjects (≈1/5 women, 1/3 during exercise).[6] However, this extensive review of the literature did not identify data on RAP during exercise. The RAP at rest is not only a prognostic factor, but is also of importance for estimating systolic pulmonary artery pressure (PAP) with

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For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- In patients with precapillary pulmonary hypertension: right atrial pressure (RAP) during exercise is not constant, RAP increase during exercise reflects hemodynamic impairment, and RAP increase during exercise is associated with higher mortality.

What Are the Clinical Implications?

- RAP increase during exercise is a marker of poor prognosis.
- As RAP cannot be assumed to be constant during exercise, right ventricular/right atrial gradient rather than systolic pulmonary artery pressure estimations should be reported during stress echocardiography.

Nonstandard Abbreviations and Acronyms

6MWD	6-minute walk distance
CO	cardiac output
exPH	exercise-induced pulmonary hypertension
PAH	pulmonary arterial hypertension
mPAP	mean pulmonary artery pressure
noPH	without pulmonary hypertension
PAP	pulmonary artery pressure
PH	pulmonary hypertension
RAP	right atrial pressure
RHC	right heart catheterization

echocardiography as transtricuspid pressure gradient+RAP.[7,8] Although the gold standard to assess RAP is invasive, echocardiographers all over the world estimate the RAP noninvasively by the size and collapsibility of the inferior vena cava.[9] However, the precision of this method is suboptimal, and it is difficult to use during exercise. Thus, systolic PAP estimated during exercise-echocardiography is usually calculated by assuming a constant RAP estimated at rest. As the course of the RAP during exercise in patients with suspected PH is not known, it is also not known whether the assumption of a constant RAP during exercise is justified.

In light of these uncertainties, the aims of the present retrospective study were as follows: First, the aim was to comprehensively analyze changes of the RAP during supine exercise RHC in patients diagnosed with PH, patients with exercise-induced PH, and patients without PH. Second, the aim was to investigate the prognostic significance of RAP at rest and during exercise.

METHODS

Study Design and Subjects

All patients undergoing supine incremental stepwise cycle exercise RHC as part of the workup of suspected PH in the PH center of the University Hospital Zürich between 2008 and 2016 were eligible. The data of this study are available from the corresponding author on reasonable request. Patients were excluded if they had only resting RHC, had repeated RHC, or did not consent to have their data used. Patients were grouped into resting PH (PH; mPAP ≥25 mmHg), patients with exercise-induced PH (exPH; exercise mPAP >30 mmHg and mPAP/CO >3 Wood Units, no resting PH),[10] and patients without PH (noPH; PH was ruled out). Patients with PH were diagnosed and classified according to current guidelines,[11] with an extensive diagnostic workup, including medical history, clinical assessment, blood analysis, pulmonary function tests, ventilation/perfusion lung scan, pulmonary computed tomography, and/or digital subtraction angiography, and grouped into pulmonary arterial hypertension (PAH), PH attributable to left heart or lung disease, chronic thromboembolic PH, or multifactorial. Of all included patients, demographics, classification, specific medication, New York Heart Association functional class, the 6-minute walk distance (6MWD) within 2 weeks of the RHC, and venous and arterial blood test results were retrieved. Follow-up data from regular visits every 3 to 6 months were analyzed until death or lung transplantation (defined as event) or until January 31, 2018, in censored patients.

Ethics

All patients gave written informed consent to RHC and to have their data registered for scientific analysis. The study complies with the Declaration of Helsinki and was approved by the local ethical authorities (Business Administration System for Ethics Committees [BASEC] 2016-01594).

Exercise RHC

Exercise RHC was performed on a supine cycle ergometer (TheraVital Ergometer; MedicaGMbH, Ravensburg, Germany) with a stepwise incremental protocol (increase by 10 W every 3 minutes) as previously described.[12] A balloon-tipped, triple-lumen, fluid-filled 7.5 Fr Swan Ganz catheter (Baxter/Edwards, Deerfield, IL) was placed via a jugular vein according to standard procedures. Transducers were

set at the midthoracic level and zeroed to atmospheric pressure.[10,13] Pressure tracings of continuously and simultaneously assessed PAP and RAP on the hemodynamic monitor system (Dräger SA, Liebefeld, Switzerland) were averaged over several respiratory cycles after at least 15 minutes of rest and in the last 30 seconds of every exercise step.[10,12,14,15] The pulmonary artery wedge pressure, CO measured by thermodilution, and arterial blood oxygenation and mixed venous blood oxygenation were assessed at rest and in the last minute of every exercise step. Cardiac index was calculated as CO/body surface area. Pulmonary vascular resistance was calculated as pulmonary vascular resistance=(mPAP-pulmonary artery wedge pressure)/CO.

Data Presentation and Statistical Analysis

Data are presented as median (quartiles) according to nonnormality assessed by Shapiro-Wilk test for most variables and grouped by the 3 main hemodynamic categories (noPH, exPH, and PH). Continuous variables were compared by Mann-Whitney, Wilcoxon, or Kruskal-Wallis test, as appropriate. To assess the association of changes in RAP during exercise with survival, in a first step, Kaplan-Meier analysis with presence or absence of an exercise-induced increase in RAP as dichotomous predictor was performed. In a second step, the effect of changes in RAP on survival while adjusting for several potential explanatory variables was explored, using Cox proportional hazard regression of changes in RAP with baseline RAP, changes in heart rate with exercise, the hemodynamic diagnostic group, and age as explanatory variables.[16] In further exploratory analyses, univariable and multivariable stepwise backward Cox regression models were fitted with clinical, resting, and exercise hemodynamic variables as predictors. Univariate and stepwise backward multivariate regression was used to correlate changes of the RAP with exercise with characteristics and key hemodynamic parameters. SPSS 25, Microsoft Excel, Graph-Pad, and Sigma plot were used. $P<0.05$ was considered significant.

RESULTS

Study Population and Hemodynamics During Exercise

Of 326 patients undergoing RHC during the study period, 270 patient data sets were included in the present analysis. A total of 12 patients did not have exercise RHC, 15 underwent a different exercise protocol, 17 did not give informed consent for further data analysis, and 12 were RHC follow-ups of patients already included in the analysis (Figure 1, study flow). Patient characteristics are shown in Table 1. The median observation time was 3.7 (2.8–5.6) years. Most patients were in New York Heart Association class II or III, with a median 6MWD of 468 (359–530) m. The median peak workload achieved was 40 (30–50) W in noPH, 30 (20–40) W in exPH, and 20 (20–30) W in PH, with significant differences between groups (Table 2). Patterns of main hemodynamic responses are illustrated in Figure 2. Although the RAP decreased or remained unchanged in patients with noPH, it increased during exercise in patients with PH and exPH, with the highest RAP at end exercise reached in patients with PH (Table 2, Figure 2).

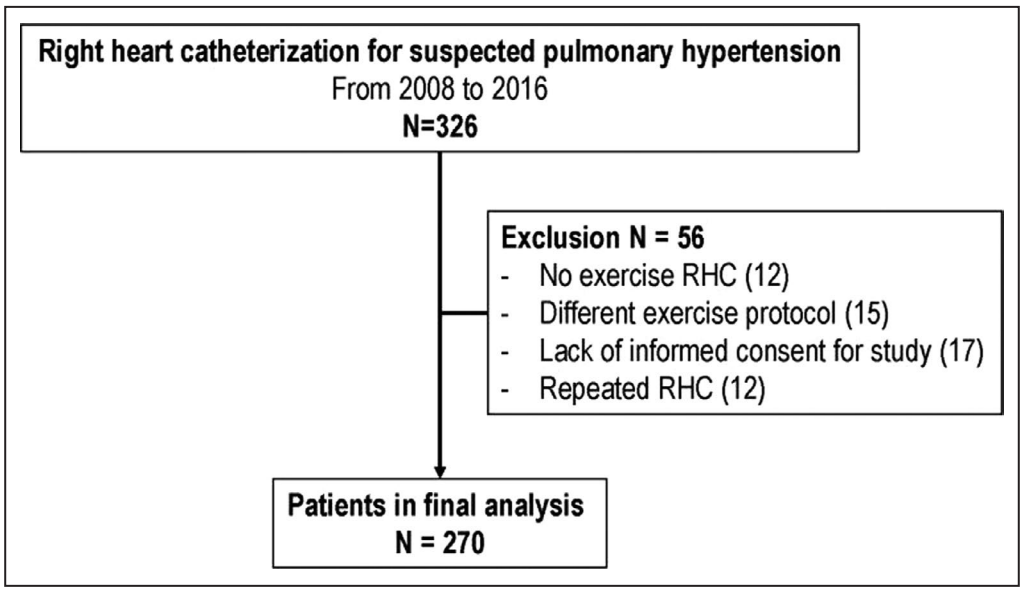

Figure 1. Patient flow.
RHC indicates right heart catheterizaton.

Table 1. Baseline Characteristics

Characteristics	Overall	noPH	exPH	PH
Subjects/women (%)	270/170 (63)	60/48 (80)	58/39 (67)	152/83 (55)
Age, y	62 (51–72)	53 (43–63)	63 (54–72)	67 (53–73)
Body mass index, kg/m^2	25.4 (22.6–28.4)	24.2 (20.9–27.5)	25.6 (22.6–28.2)	25.5 (22.8–29.2)
Hemodynamic classification				
noPH	60 (22)	60 (100)		
exPH	58 (21)		58 (100)	
PH	152 (57)			152 (100)
Pulmonary arterial hypertension	79 (29)			79 (52)
Idiopathic	52 (19)			52 (34)
Connective tissue diseases	20 (7)			20 (13)
HIV	1 (0)			1 (1)
Portopulmonary	5 (2)			5 (3)
PH associated with left heart disease	24 (9)			24 (16)
PH associated with lung disease	24 (9)			24 (16)
Chronic thromboembolic PH	23 (9)			23 (15)
Multifactorial	3 (1)			3 (2)
NYHA classification	3 (2–3)	2 (2–3)	2 (2–3)	3 (2–3)
I	21 (8)	10 (17)	4 (7)	7 (5)
II	92 (34)	23 (38)	31 (53)	38 (25)
III	109 (40)	19 (32)	17 (29)	73 (48)
IV	30 (11)	2 (3)	5 (9)	23 (15)
Not classified	18 (7)	6 (10)	1 (2)	11 (7)
NT-proBNP, ng/L	231 (94–752)	95 (41–194)	180 (80–446)	436 (141–1361)
Pulse oximetry at rest, %	93 (90–95)	95 (94–96)	94 (92–95)	91 (88–94)
6-min walking distance, m	468 (359–530)	512 (450–595)	498 (418–556)	437 (339–502)

Data are given as median (quartiles) or number (percentage). exPH indicates exercise-induced PH; noPH, without PH; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and PH, pulmonary hypertension.

mPAP significantly increased in all groups during exercise: the highest increase was found in PH, followed by exPH (Table 2, Figure 2). Heart rate, stroke volume, and consequently CO and cardiac index increased with exercise in all groups, with a significantly higher increase in noPH compared with PH or exPH (Table 2). The pressure/flow relationship, as assessed by mPAP/CO, did not significantly increase in noPH but increased in exPH and even more in PH. Of interest, the RAP/CO relationship significantly decreased in noPH, whereas it significantly increased in exPH and PH (Table 2).

Transplant-Free Survival

Kaplan-Meyer analysis indicates a >4-fold risk of death or lung transplantation (hazard ratio [HR], 4.24; 95% CI, 1.69–10.64; *P*=0.002) (Figure 3) and a shorter transplant-free survival in patients with an exercise-associated increase in RAP compared with patients with unaltered or decreasing RAP during exercise (7.0 years [95% CI, 6.5–7.5 years] versus 8.3 years [95% CI, 7.8–8.9 years]; *P*=0.002, log-rank test). In Cox regression, an exercise-induced increase in RAP remained a significant predictor of transplant-free survival even when age, resting RAP, heart rate, and diagnostic group (Table 3) were included as explanatory variables with known effect on outcome in the analysis.

To evaluate the association of various clinical, resting, and exercise hemodynamic variables with transplant-free survival, various Cox regression models were fitted. They revealed that age, diagnostic group, New York Heart Association functional class, and the 6MWD were significant clinical predictors of transplant-free survival, with age and the 6MWD being the strongest significant predictors in the stepwise backward regression model (Table 4). With exception of RAP, resting hemodynamic variables were significant predictors in the univariate analysis, with heart rate and the arterial blood oxygenation remaining significant in the stepwise backward regression analysis (Table 4). Changes of hemodynamic parameters during exercise were also univariate predictors of transplant-free survival, whereas changes in arterial blood oxygenation were not statistically significant. In the stepwise backward regression

Table 2. Hemodynamics at Rest and Stepwise Supine Cycling Exercise

Value/ Group	Rest	Peak Exercise	Median Change (Peak Exercise–Rest) (95% CI)
Work rate, W			
noPH		40 (30–50)	
exPH		30 (20–40)*	
PH		20 (20–30)†	
Systolic blood pressure, mm Hg			
noPH	123 (110–136)	150 (138–162)§	23 (20 to 29)
exPH	124 (110–138)	165 (149–181)§	34 (30 to 41)*
PH	129 (114–144)	160 (151–179)§	28 (24 to 32)
Diastolic blood pressure, mm Hg			
noPH	72 (66–79)	76 (65–87)	3 (–1 to 6)
exPH	72 (64–80)	81 (70–93)§	8 (5 to 13)*
PH	78 (70–86)	87 (84–90)§	10 (7 to 12)†
Heart rate, bpm			
noPH	71 (67–79)	111 (100–125)§	37 (33 to 42)
exPH	72 (62–79)	110 (97–124)§	39 (33 to 44)
PH	77 (68–86)†	108 (97–117)†,§	31 (27 to 33)†
Right atrial pressure, mm Hg			
noPH	6 (4–8)	5 (3–8)	-1 (–2 to 0)
exPH	6 (4–8)	9 (7–11)*,§	3 (2 to 4)*
PH	8 (6–11)†, ‡	13 (9–17)†,§,‡	5 (4 to 6)†, ‡
Mean pulmonary artery pressure, mm Hg			
noPH	16 (14–19)	25 (22–28)§	8 (6 to 9)
exPH	21 (18–23)*	37 (33–41)*,§	16 (15 to 19)*
PH	34 (29–43)†	54 (47–64)†,§,‡	19 (17 to 20)†
Pulmonary artery wedge pressure, mm Hg			
noPH	9 (5–13)	12 (8–16)	1 (0 to 4)
exPH	11 (9–13)	15 (12–18)§	4 (2 to 6)*
PH	12 (9–15)	16 (12–20)§	5 (4 to 6)†, ‡
Cardiac output, L/min			
noPH	5.3 (4.1–6.5)	7.3 (5.9–8.4)§	1.9 (1.5 to 2.3)
exPH	5.7 (4.7–6.7)	7.1 (5.8–8.4)§	1.2 (0.9 to 1.8)*
PH	5.3 (4.2–6.4)	6.5 (5.0–8.0)§	0.9 (0.7 to 1.1)†
Cardiac index, L/min per m^2			
noPH	3.0 (2.7–3.6)	4.2 (3.4–5.6)§	1.1 (0.9 to 1.3)
exPH	3.0 (2.5–3.5)	4 (3.3–4.7)§	0.7 (0.6 to 1.0)*
PH	2.9 (2.4–3.5)	3.6 (3.1–4.3)*, †, ‡	0.5 (0.4 to 0.6)†
Pulmonary vascular resistance, Wood Units			
noPH	1.2 (0.7–1.7)	1.6 (1.3–2.5)§	0.3 (0.2 to 0.5)
exPH	1.6 (1.3–2.1)*	3.0 (2.9–3.5)*,§	1.5 (1.4 to 1.6)*
PH	4.0 (2.7–6.1)†	5.4 (3.5–8)†,§,‡	1.0 (0.9 to 1.5)†
SaO_2, %			
noPH	95 (95–97)	95 (94–96)	-1 (–1 to 0)
exPH	94 (92–96)	94 (91–97)	-2 (–3 to –1)
PH	91 (88–94)	90 (84–94)§	-3 (–4 to –2)†
$SmvO_2$, %			
noPH	72 (68–78)	48 (35–61)§	-23 (–25 to –22)
exPH	70 (67–73)	41 (31–51)§	-29 (–34 to –24)
PH	66 (61–71)	37 (27–47)§	-29 (–31 to –27)†
RAP/cardiac output, Wood Units			
noPH	1.2 (0.8–1.6)	0.6 (0.3–1.1)§	-0.4 (–0.6 to –0.2)
exPH	1.0 (0.6–13.1)	1.3 (0.9–1.7)*,§	0.3 (0.1 to 0.5)*
PH	1.4 (0.9–2.2)†	2.0 (1.2–2.9)†,§,‡	0.6 (0.4 to 0.8)†
mPAP/cardiac output, Wood Units			
noPH	2.9 (2.1–3.7)	3.3 (2.4–4.2)§	0.2 (–0.3 to 0.6)
exPH	3.4 (2.8–4.0)*	4.9 (3.5–6.3)*,§	1.4 (1.3 to 2.0)*
PH	6.6 (4.6–8.8)†	8.4 (6.0–11.5)†,§,‡	1.6 (1.4 to 1.9)†

Data are given as median (quartiles) and median change (95% CI). $P<0.05$ in Kruskal-Wallis tests was followed by post hoc Mann-Whitney U tests. Bpm indicates beats per minute; exPH, exercise-induced PH; mPAP, mean pulmonary artery pressure; noPH, without PH; PH, pulmonary hypertension; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; and $SmvO_2$, mixed venous oxygen saturation.

*$P<0.05$ between noPH and exPH.

†$P<0.05$ between noPH and PH.

‡$P<0.05$ between exPH and PH.

§$P<0.001$ between rest and peak exercise.

model, only the change in RAP remained a significant predictor of transplant-free survival (HR, 1.085; 95% CI, 1.024–1.151; P=0.006; Table 4). Exercise-induced changes in RAP were significantly associated with several clinical and hemodynamic variables, and the mPAP/CO ratio was the best single predictor in stepwise backward regression analysis (Table 5).

DISCUSSION

We assessed changes of the RAP during supine cycling exercise in relation to various other hemodynamic and clinical outcomes in a large sample of patients assessed for PH. The main novel findings of our investigation are that changes in RAP during exercise were highly variable between individuals and differed between groups of patients without PH (noPH), showing an unchanged or decreasing RAP, and patients with PH at rest or during exercise (exPH or PH) in whom RAP increased with exercise (Figure 2). Most important, we found that the risk of death or lung transplantation was >4-fold elevated among patients with an RAP increase during exercise compared with the remaining patients (HR, 4.24; 95% CI, 1.69–10.4; Figure 3). Therefore, our data indicate that RAP during exercise should not be considered constant, and estimates of systolic PAP by echocardiography based on the transtricuspid pressure gradient during exercise have to account for RAP

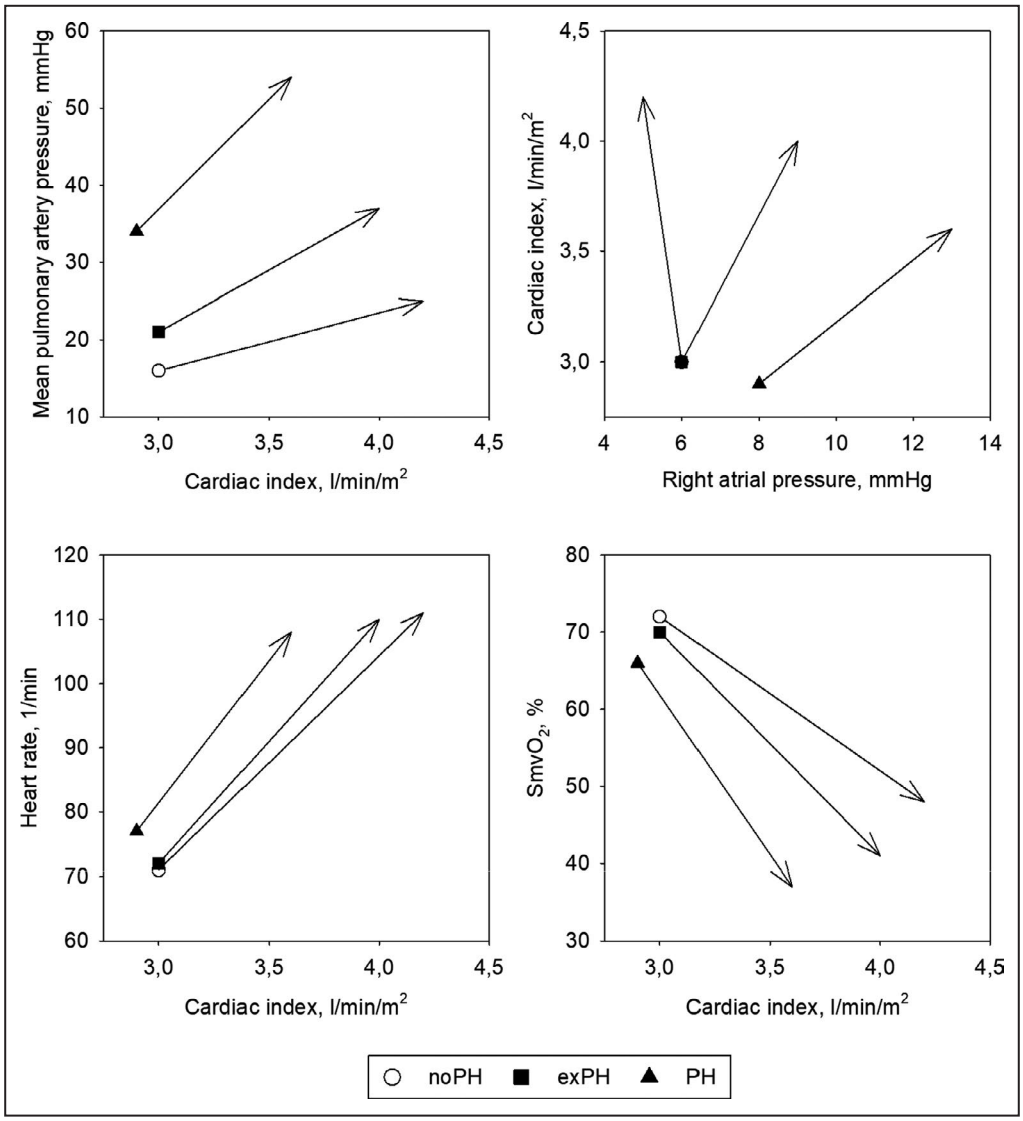

Figure 2. Patterns of hemodynamic responses recorded by right heart catheter during exercise tests. Left upper panel: mean pulmonary artery pressure (mPAP) vs cardiac index (CI); right upper panel: CI vs right atrial pressure (RAP). Left lower panel: heart rate vs CI; right lower panel: mixed venous oxygen saturation ($SmvO_2$) vs CI. The lines connect median values of variables at rest (symbols) with maximal values at end exercise (arrowheads). In patients without pulmonary hypertension (noPH), highest CI values were achieved with only minimal increase in mPAP and no increase in RAP and were associated with higher $SmvO_2$. In contrast, in patients with pulmonary hypertension (PH), there is a major increase in mPAP and in RAP but an only minor increase in CI but the highest decrease in $SmvO_2$. Values of patients with exercise-induced pulmonary hypertension (exPH) fall in between the 2 extremes. All exercise-induced within-group changes in CI, mPAP, RAP, and $SmvO_2$ are significant at $P<0.05$, with exception of the nonsignificant decrease in RAP in noPH; all between-group differences of changes in CI, mPAP, and RAP are significant at $P<0.05$, with exception of the nonsignificant difference in changes in CI between PH and exPH; PH additionally revealed significantly lower heart increase and higher decrease in SmvO2 vs noPH, but not vs exPH. Numerical values are listed in Table 2.

changes. Our data suggest that changes in RAP are included into the assessment of the hemodynamic response to exercise as they bear important physiologic and prognostic information.

Pulmonary hemodynamics during exercise have gained a lot of interest in recent years.[10] Exercise PH may uncover early-stage pulmonary vascular disease, but may also occur in left heart disease, lung disease, or a combination of these conditions.[10,17,18] It has recently been reaccepted that an increase in mPAP >30 mm Hg along with an mPAP/CO of >3 WU serve as reasonable diagnostic criteria for exPH,[18] and this definition was also used in the present cohort. Besides hemodynamics during exercise being

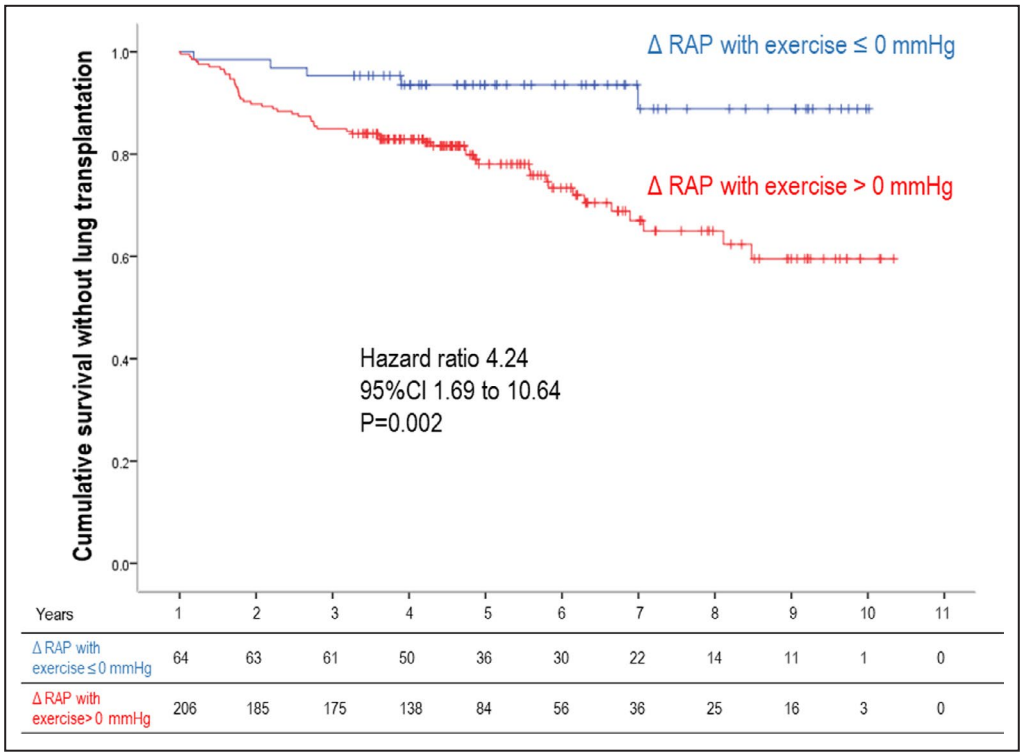

Figure 3. Kaplan-Meier analysis reveals a reduced transplant-free survival in patients with exercise-induced increase in right atrial pressure (RAP; ΔRAP with exercise >0 mm Hg, red line) compared with patients with a decrease or no change in RAP (ΔRAP with exercise ≤0 mm Hg, blue line).

of importance to detect potentially latent and early pulmonary vascular diseases, especially in patients at risk, exercise hemodynamics also have a prognostic implication in patients diagnosed with PAH or distal chronic thromboembolic PH.[12,19] We recently showed that patients with scleroderma with exPH have a similarly impaired transplant-free survival as patients with scleroderma with PAH[15] and that pressure/flow ratios assessed during exercise predict transplant-free survival in patients with PAH or distal chronic thromboembolic PH.[12] Hemodynamics during exercise are also increasingly used in the noninvasive assessments of PH by echocardiography in the follow-up of patients with PH or as a screening tool for patients at risk, such as those with scleroderma, relatives of patients with PAH, or those at high altitude.[20-22] Echocardiographic assessment has been shown to correlate well with invasive hemodynamics if applied by experienced hands.[23] However, there remain many questions about the normal and abnormal response to exercise in healthy subjects or patients at risk or with manifest PH.[6,10]

Table 3. Cox Regression Analysis of Predictors of Survival Without Lung Transplantation (With Focus on RAP)

Dependent Variable=Transplant-Free Survival	Univariable Analysis				Multivariable Analysis			
	Hazard Ratio	95% CI		*P*	Hazard Ratio	95% CI		*P*
		Lower	Upper			Lower	Upper	
Δ Right atrial pressure, mm Hg	1.113	1.061	1.167	<0.001	1.066	1.006	1.129	0.030
Right atrial pressure at rest, mm Hg	1.025	0.957	1.098	0.485				
Δ Heart rate, bpm	1.324	1.158	1.514	<0.001				
Age, y	1.053	1.028	1.078	<0.001	1.039	1.015	1.066	0.002
Group (noPH, reference PH)	0.193	0.069	0.542	0.002				
Group (exPH, reference PH)	0.646	0.336	1.242	0.190				

N=270. Δ Indicates change of variables with stepwise cycling exercise (peak exercise–rest). In multivariable stepwise backward regression, dependent variables with $P<0.05$ were maintained in the model; the final remaining step is shown. Bpm indicates beats per minute; exPH, exercise-induced PH; noPH, without PH; PH, pulmonary hypertension; and RAP, right atrial pressure.

Table 4. Cox Regression Analyses of Predictors of Survival Without Lung Transplantation

Dependent Variable=Transplant-Free Survival		Univariable Analysis				Multivariable Stepwise Backward Regression Analysis			
		Hazard Ratio	95% CI		*P*	Hazard Ratio	95% CI		*P*
			Lower	Upper			Lower	Upper	
Clinical variables	Age, y	1.053	1.028	1.078	<0.001	1.042	1.015	1.070	0.002
	Sex (Men=0, Women=1)	1.681	0.995	2.841	0.052	0.589	0.332	1.044	0.070
	BMI, kg/m^2	0.938	0.890	0.989	0.014	0.926	0.874	0.981	0.009
	Group (noPH, reference PH)	0.193	0.069	0.542	0.002				
	Group (exPH, reference PH)	0.646	0.336	1.242	0.190				
	NYHA class	2.164	1.521	3.081	<0.001				
	6MWD, m	0.995	0.993	0.997	<0.001	0.996	0.993	0.993	<0.001
Hemodynamics at rest	HR, bpm	1.036	1.015	1.058	0.001	1.031	1.009	1.053	0.006
	RAP, mm Hg	1.025	0.957	1.098	0.485				
	mPAP, mm Hg	1.036	1.018	1.055	<0.001				
	CO, L/min	0.776	0.648	0.930	0.006	0.669	0.551	0.811	<0.001
	PVR, WU	1.166	1.097	1.240	<0.001				
	mPAP/CO, mm Hg/L per min	1.141	1.082	1.203	<0.001				
	SaO_2, %	0.908	0.871	0.946	<0.001	0.882	0.836	0.931	<0.001
	$SmvO_2$, %	0.908	0.880	0.938	<0.001				
Δ in Hemodynamics from rest to peak exercise	ΔHR, bpm	0.979	0.963	0.995	0.010				
	ΔRAP, mm Hg	1.113	1.061	1.167	<0.001	1.116	1.062	1.172	<0.001
	ΔmPAP, mm Hg	1.032	1.003	1.061	0.029				
	ΔCO, L/min	0.673	0.517	0.877	0.003				
	ΔPVR, WU	1.259	1.058	1.497	0.009				
	ΔmPAP/CO,WU	1.324	1.158	1.514	<0.001				
	ΔSpO_2, %	0.987	0.973	1.001	0.090				
	Δ$SmvO_2$, %	0.983	0.966	0.999	0.038				

n = 270. In multivariable stepwise backward regression, dependent variables with $P<0.05$ were maintained, and variables with $P\geq0.1$ were removed; the final step remaining is shown for each group. 6MWD indicates 6-minute walk distance; BMI, body mass index; bpm, beats per minute; CO, cardiac output; exPH, exercise-induced PH; HR, heart rate; mPAP, mean pulmonary artery pressure; no PH, without PH; NYHA, New York Heart Association; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; $SmvO_2$, mixed venous oxygen saturation; SpO_2, arterial blood oxygenation; and WU, Wood Units.

The response of the RAP to exercise is not clear to date, possibly because of the fact that most patients assessed during exercise had more or less simultaneous assessments of PAP and CO, whereas RAP was often not available with commonly used Swan-Ganz catheters that lack a separate atrial port. As we assessed a large group of 270 patients during supine cycling exercise, using RHC with a separate port to simultaneously measure RAP with all above-mentioned hemodynamic measurements, our study provides a unique data set of comprehensive hemodynamic profiles. We found that, in patients with PH, most of them with PAH, the RAP increases with even slight exercise (on average only 20 W) by a median of 5 mm Hg and irrespective of diagnostic PH group (Table 2). This increase of the RAP in PH during mild exercise was higher compared with that of patients with exPH and much higher compared with that of patients evaluated for suspected PH but in whom the diagnosis was ruled out (Figure 2). RAP even slightly decreased during exercise in patients with normal hemodynamics (noPH). The reason for that cannot be conclusively unravelled. However, it might be speculated that the RAP decrease during exercise in patients without PH is related to the stable or even decreasing pulmonary vascular resistance during exercise along with pulmonary artery distension and vessel recruitment and thus favorable ventriculoarterial coupling.[24,25] The increase in RAP during progressive exercise in patients with PH and

Table 5. Regression Analysis of Exercise-Induced Changes in RAP and Other Variables

Dependent Variable=Δ RAP During Exercise	Univariable Analysis			Stepwise Backward Regression Model		
	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Sex (men=0, women=1)	−2.135	−3.357 to −0.951	0.001			
Age, y	0.129	0.092 to 0.166	<0.001			
Group (noPH, exPH, or PH)	0.544	0.279 to 0.809	<0.001			
RAP at rest, mm Hg	0.219	0.058 to 0.380	0.008			
ΔmPAP, mm Hg	0.249	0.185 to 0.312	<0.001			
ΔPVR, WU	1.287	0.86 to 1.713	<0.001			
ΔmPAP/CO, WU	1.472	1.173 to 1.770	<0.001	1.463	1.157 to 1.769	<0.001

n = 270. R^2 of the final model was 0.257, $P < 0.001$. Δ Indicates change of parameters with stepwise cycling exercise (peak exercise–rest). CO indicates cardiac output; exPH, exercise-induced PH; mPAP, mean pulmonary artery pressure; noPH, without PH; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; and WU, Wood Units.

exPH may also reflect a reduced compliance and impairment in right heart function that required higher filling pressures to increase the CO during exercise, whereas the more compliant healthy right ventricle in individuals with noPH may have accommodated the need for a greater oxygen delivery during exercise by increasing contractility in accordance with Guytons experiments in dogs, which showed that the venous return determines the CO (Figure 2).[26,27] In addition, the greater exercise-induced decrease in mixed-venous oxygen saturation in PH compared with noPH reflects the requirement for greater oxygen extraction to compensate for the more advanced right ventricular performance impairment that prevents an adequate increase in CO (Figure 2).

The finding of a changing RAP during exercise might have the following clinical or research implications: The RAP is probably the easiest accessible invasive hemodynamic index as it can be obtained by a simple, even peripherally inserted, central venous line. In the present series of 270 exercise RHC data sets, we found that the change of the RAP with exercise is correlated with the main hemodynamic measure in exercise RHC (namely, the mPAP/CO), and both RAP and mPAP behaved differently in patients with normal and impaired pulmonary circulation (Figure 2). To which extent assessment of the exercise RAP (eg, combined with cardiopulmonary exercise testing or stress-echocardiography) would add in the diagnosis or follow-up of PH in general or where RHC is not readily available remains to be addressed by future, well-designed prospective trials.

Another implication to be considered with the present finding of a changing RAP with exercise is the assessment by echocardiography. As the RAP estimated noninvasively by echocardiography based on the collapsibility of the vena cava or jugular vein distension is not reliable during exercise, it seems wise to report the tricuspid pressure gradient only instead of additionally indicating RAP, as already suggested by experts.[23]

Of interest, we found that patients demonstrating a decrease or no change in RAP during exercise have a significantly better transplant-free survival compared with patients with an increase in RAP during exercise in whom the risk of an unfavourable outcome was >4-fold greater (Figure 3). Univariable Cox regression analyses identified various other clinical and hemodynamic predictors of transplant-free survival (Table 5). Only the age, 6MWD, heart rate, and arterial blood oxygenation at rest and the exercise-induced change in RAP were maintained in stepwise backward analyses, likely because of multiple dependencies between several variables. In previous analyses of registries and cohorts, resting RAP was associated with prognosis,[28] whereas this was not observed in the current study. Potential explanations are differences in patient groups, in particular, inclusion of patients with noPH and patients with PH in various risk classes in the current study, time point of assessment (ie, untreated baseline condition versus over the course of treatment), and differences in the statistical approach, such as stratified or continuous analyses.[29-31]

Limitations of our study are the retrospective design and that all patients were assessed during supine cycle ergometry. We do, thus, not know whether the changes in RAP and other hemodynamics would have been comparable if exercise would have been performed in another body position or on a treadmill. According to standards of RHC in clinical practice, vascular pressures were referenced to atmosphere, thus integrating intrathoracic pressure changes that vary during exercise in particular in chronic obstructive pulmonary disease with dynamic hyperinflation. This limitation applied to RAP as well as to mPAP and pulmonary artery wedge pressure but did not conceal the significant association of hemodynamics with prognosis. However, in this cohort, only a minority of

patients experienced chronic obstructive pulmonary disease. The average workload achieved in our large collective is relatively low; however, most patients experienced PH and were assessed supine, which is known to be associated with a reduced exercise capacity.[32] Our noPH group consisted of patients who were evaluated by RHC because of suspected PH. Thus, these patients were not healthy, but experienced dyspnea or were at risk of PH. However, we would assume that healthy subjects would decrease their pulmonary vascular resistance and RAP even more with exercise, although this is not known to date.

In conclusion, this analysis of RAP recorded simultaneously with standard hemodynamics during exercise RHC shows that the RAP cannot be assumed to remain constant during exercise. RAP increases in all PH groups even during mild exercise, but decreases or remains constant in dyspneic patients without PH. The exercise-induced change in RAP correlates well with other relevant exercise hemodynamic parameters, including the pressure-flow relationship (mPAP/CO), and it is an independent predictor of transplant-free survival. Therefore, the exercise-induced change in RAP should be considered in the diagnosis and management of dyspneic patients with and without PH.

ARTICLE INFORMATION

Received June 26, 2020; accepted September 30, 2020.

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Acknowledgments

All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors contributed to the production of the final manuscript with revision for important intellectual content.

Sources of Funding

This study was funded by the Swiss National Science Foundation and Zürich Lung League.

Disclosures

Dr Ulrich and Dr Bloch received grants from the Swiss National Science Foundation and the Zürich Lung League. Dr Ulrich received travel support and speakers' fees from Actelion SA, Switzerland, Bayer SA, Germany, MSD, Switzerland, and Orpha Swiss. Dr Grünig reports grants and personal fees from Actelion, Bayer AG, and MSD; grants from GSK, Novartis, and United Therapeutics; and personal fees from Actelion, MSD, SCOPE, Orpha Swiss GmbH, and Zürich Heart House. The remaining authors have no disclosures to report.

REFERENCES

1. Watts JA, Kelly FR, Bauch TD, Murgo JP, Rubal BJ. Rest and exercise hemodynamic and metabolic findings in active duty soldiers referred for cardiac catheterization to exclude heart disease: insights from past invasive cardiopulmonary exercise testing using multisensor high fidelity catheters. *Catheter Cardiovasc Interv*. 2018;91:35–46.
2. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53:582–588.
3. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med*. 2001;345:574–581.
4. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349.
5. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J*. 2010;35:1079–1087.
6. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34:888–894.
7. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogra*. 2010;23:685–713; quiz 786–788.
8. Mitchell C., Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32:1–64.
9. Beigel R, Cercek B, Arsanjani R, Siegel RJ. Echocardiography in the use of noninvasive hemodynamic monitoring. *J Crit Care*. 2014;29(184):e181–e188.
10. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grunig E, Howard L, Humbert M, et al. An official European respiratory society statement: pulmonary haemodynamics during exercise. *Euro Respir J*. 2017;50.
11. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, 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 Resp J*. 2015;46:903–975.
12. Hasler ED, Muller-Mottet S, Furian M, Saxer S, Huber LC, Maggiorini M, Speich R, Bloch KE, Ulrich S. Pressure-flow during exercise catheterization predicts survival in pulmonary hypertension. *Chest*. 2016;150:57–67.
13. Kovacs G, Avian A, Olschewski A, Olschewski H. Zero reference level for right heart catheterisation. *Eur Respir J*. 2013;42:1586–1594.
14. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings: how to handle the problems of zero leveling and respiratory swings. *Am J Respir Crit Care Med*. 2014;190:252–257.
15. Stamm A, Saxer S, Lichtblau M, Hasler ED, Jordan S, Huber LC, Bloch KE, Distler O, Ulrich S. Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis. *Eur Respir J*. 2016;48:1658–1667.
16. Bewick V, Cheek L, Ball J. Statistics review 12: survival analysis. *Crit Care*. 2004;8:389–394.
17. Lau EM, Godinas L, Sitbon O, Montani D, Savale L, Jais X, Lador F, Gunther S, Celermajer DS, Simonneau G, et al. Resting pulmonary artery pressure of 21–24 mmhg predicts abnormal exercise haemodynamics. *Eur Respir J*. 2016;47:1436–1444.
18. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jais X, Parent F, Gunther S, et al Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J*. 2015;46:728–737.
19. Chaouat A, Sitbon O, Mercy M, Poncot-Mongars R, Provencher S, Guillaumot A, Gomez E, Selton-Suty C, Malvestio P, Regent D, et al. Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. *Eur Respir J*. 2014;44:704–713.

20. Argiento P, Vanderpool RR, Mule M, Russo MG, D'Alto M, Bossone E, Chesler NC, Naeije R. Exercise stress echocardiography of the pulmonary circulation: limits of normal and sex differences. *Chest*. 2012;142:1158–1165.
21. Naeije R, Huez S, Lamotte M, Retailleau K, Neupane S, Abramowicz D, Faoro V. Pulmonary artery pressure limits exercise capacity at high altitude. *Eur Respir J*. 2010;36:1049–1055.
22. Bossone E, Naeije R. Exercise-induced pulmonary hypertension. *Heart Fail Clin*. 2012;8:485–495.
23. Claessen G, La Gerche A, Voigt JU, Dymarkowski S, Schnell F, Petit T, Willems R, Claus P, Delcroix M, Heidbuchel H. Accuracy of echocardiography to evaluate pulmonary vascular and RV function during exercise. *JACC Cardiovasc Imaging*. 2016;9:532–543.
24. Lewis GD, Bossone E, Naeije R, Grunig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013;128:1470–1479.
25. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordegraaf A, Bogaard HJ. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. *Am J Respir Crit Care Med*. 2015;191:1050–1057.
26. Henderson WR, Griesdale DE, Walley KR, Sheel AW. Clinical review: Guyton–the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. *Crit Care*. 2010;14:243.
27. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol*. 1957;189:609–615.
28. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010;122:156–163.
29. Boucly A, O'Connell C, Savale L, O'Callaghan DS, Jais X, Montani D, Humbert M, Simonneau G, Sitbon O. Tunnelled central venous line-associated infections in patients with pulmonary arterial hypertension treated with intravenous prostacyclin [in French]. *Presse Med*. 2016;45:20–28.
30. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, Olsson KM, Meyer K, Vizza CD, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J*. 2015;2017:50.
31. Kylhammar D, Kjellstrom B, Hjalmarsson C, Jansson K, Nisell M, Soderberg S, Wikstrom G, Radegran G, SveFph S. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2017;39:4175–4181.
32. Welbergen E, Clijsen LP. The influence of body position on maximal performance in cycling. *Eur J Appl Physiol Occup Physiol*. 1990;61:138–142.