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Influence of specific drug therapy on cardiopulmonary exercise testing parameters in patients with pulmonary hypertension

M. Schwaiblmair, C. Faul, W. von Scheidt, T. M. Berghaus

Internal Medicine I, Department of Cardiology/Pneumology, Klinikum Augsburg, Germany

Abstract

Background: The objective of the study was to quantify the cardiopulmonary exercise testing (CPET) parameters in patients with pulmonary arterial hypertension after beginning of a specific pharmacotherapy (calcium channel blocker, endothelin receptor antagonist, prostanoid and/or phosphodiesterase inhibitor).
Methods: 49 patients with a mean pulmonary arterial pressure of 45 mmHg underwent 3-monthly CPET during a follow-up of 24 months.
Results: After 3 months, peak oxygen uptake (14.0 ± 1.0 versus 15.7 ± 1.1 ml/min/kg) and oxygen pulse (8.4 ± 0.5 versus 9.4 ±0.6 ml/min/beat) significantly ($p<0.001$) improved. In the long-term follow-up we objectified significant differences ($p < 0.05$) in anaerobic threshold (8.3 ± 0.9 versus 10.7 ± 0.9 ml/min/kg) and oxygen pulse (7.4 ± 0.5 versus 8.4 ± 0.6 ml/min/beat). Ventilatory efficiency remained unchanged during follow-up.
Conclusions: Ventilatory efficiency remains unchanged by the implementation of specific pharmacotherapy in contrast to significantly improved power capacity, oxygen uptake, anaerobic threshold and oxygen pulse.

Key words: exercise test, hypertension, pulmonary, pharmacotherapy, pulmonary gas exchange

Abbreviations

$AaDO_2$: alveolar-arterial oxygen difference
AT: anaerobic threshold
CI: cardiac index
CO: cardiac output
CPET: cardiopulmonary exercise testing
CTEPH: chronic thromboembolic pulmonary hypertension
O_2 pulse: oxygen pulse
PAH: pulmonary arterial hypertension
PAP: pulmonary arterial pressure
PCWP: pressure in wedge position
PH: pulmonary hypertension
PVR: pulmonary vascular resistance
RA: right atrium pressure
RHC: right heart catheterization
SO_2: oxygen saturation
VCO_2: carbon dioxide output
Vd/Vt: functional dead space ventilation
Ve: minute ventilation
VO_2: peak oxygen uptake

Introduction

Exercise capacity is one of the most important prognostic indicators in pulmonary arte-

rial hypertension (PAH) and the success of new therapies has therefore been assessed not only by survival but also by improvement of cardiovascular impairment and functional capacity (1). Because of a wide observed variation in the NYHA/WHO functional class, efforts to identify more reliable functional parameters might help to standardize PAH clinical care and research (2). In all randomized, placebo-controlled trials of medical treatments for PAH, exercise-related measurements were used as primary end points, the most common measurement being the 6-min walk test (3).

Although the 6-min walk test is simple and inexpensive, its reliability can vary substantially. "Ceiling" effects have been noted and a clinically relevant change in patients with PAH has not been defined (1). The next step is to augment the implementation of a more objective, reliable and valid measure of functional status in this patient population. On this basis there appears to be an evidence-based rationale for the use of cardiopulmonary exercise testing (CPET) in patients with PAH in clinical settings. In general, CPET is considered the standard criterion for determining the maximal aerobic capacity (4) and may provide a more sensitive assessment than does the 6-minute walk test (5). Arena et al. has recently summarized the evidence that shows the potential clinical and research value of CPET in patients with PAH (6). Both peak oxygen consumption and measures of pulmonary gas exchange efficiency are highly reflective of disease severity, favourably respond to several pharmacological interventions, and may provide valuable prognostic insights (7).

In contrast, presently there is limited experience with the use of CPET in multicenter trials (8, 9). In patients with PAH it is well established that peak oxygen uptake (VO2) is decreased and that the Ve/VCO2 slope is increased compared with normal controls and that both parameters improve with prostaglandin treatment (5, 10 - 12). Now, we sought to determine the physiologic basis of clinical improvement in PAH, hypothesizing that one of the key mechanisms of improvement are improved blood flow and/or improved cardiac function.

Materials and methods

Subjects

In this observational study we included patients who were referred to our pulmonary hypertension (PH) centre to confirm and to classify PH as defined by the Proceedings of the 4th World Symposium on Pulmonary Hypertension (13). All patients underwent right heart catheterization (RHC) to establish the diagnosis and a progressively increasing, symptom-limited CPET with gas exchange measurements was performed. Patients with severe concomitant extracardiac diseases limiting exercise performance were excluded.

All patients were followed at the PH centre of the Klinikum Augsburg, University of Munich. CPET were repeated every 3 months according to the ERS/ESC guidelines (14). None of the patients were involved in an exercise re-conditioning program. The minimum follow-up period was 24 months.

All procedures adhered to the commonly accepted ethical guidelines, the protocol was initially reviewed and approved by an Ethics Committee and written informed consent was obtained from every patient.

Cardiopulmonary exercise testing

CPET was performed using a standardized protocol (15, 16). Work rate was continuously increased by 5 – 15 watts/min to a maximum tolerated level on an electromagnetically braked cycle ergometer (ViaSprint 150 p, Ergoline, Germany). Patients were encouraged to exercise until symptoms were intolerable.

Blood gas analysis was analyzed at rest and during maximal exercise. Heart rate was monitored continuously, and non-invasive blood pressure was taken every 2 minutes.

The maximum work rate was recorded. Oxygen uptake (VO_2), minute ventilation (Ve), and carbon dioxide output (VCO_2) were measured breath by breath wearing an adult facemask (Vmax spectra 229 D, Sensor Medics, CA, USA). Peak VO2, oxygen pulse (O2 pulse), alveolar-arterial oxygen difference ($AaDO_2$) and functional dead space ventilation (Vd/Vt) were calculated as described by Wasserman et al. (15). The anaerobic threshold (AT) was chosen as the VO_2 at which the Ve/VO_2 increased while the Ve/VCO_2 decreased or remained constant. Peak VO_2 was defined as the value of averaged data during the final 15 seconds of exercise. The Ve/VCO_2 slope was determined as the linear regression slope of Ve and VCO_2 from the start of exercise until the RC point (the time at which ventilation is stimulated by CO_2 output and end-tidal CO_2 tension begins to decrease) (15, 16).

Right heart catheterization

All patients underwent right heart catheterization (RHC). Patients received no medications on the morning of the procedure, resulting in a discontinuation of treatment with medication of about 12 h. A True Size Thermodilution Catheter ("S" Tip Catheter, Edwards Lifesciences, Irvine, CA, USA) was inserted via the right femoral vein. Hemodynamic measurements were performed in supine position and included heart rate, pressure in wedge-position (PCWP), pulmonary arterial pressure (PAP) and right atrium pressure (RA). Oxygen saturation (SO2) was measured in mixed venous blood samples (ABL 725, Radiometer, Copenhagen, Denmark). Cardiac output (CO) was obtained using the thermodilution method (Com-2, Cardiac Output Computer, Edwards Lifesciences, Irvine, CA, USA). Cardiac index (CI) and pulmonary vascular resistance (PVR) were calculated using standard formulas [PVR = (mPAP – PCWP) / CO].

Statistical analysis

The data were presented as the mean ± standard error of mean (SEM). A statistical software package (SPSS, version 12.0 for Windows; SPSS; Chicago, IL) was used for analysis. All results were tested for two-sided significance. The measured variables were compared using the Student t-test for paired probes. Simple linear regression analysis was used to examine Ve versus VCO_2 slope.

In general, p-values < 0.05 were considered to be statistically significant.

Results

Baseline characteristics

The study included 49 consecutive patients between January 2005 and December 2008 [Table 1]. There were 26 women and 23 men with a mean age of 57.5 ± 2.6 years and a body mass index of 25.9 ± 0.7 kg/m^2. According to the ESC/ERS guidelines (14), we diagnosed 35 patients as PAH and 14 as inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Five patients were treated with calcium channel blockers, five with inhaled prostanoids, fourty-one with endothelin receptor antagonists and 38 patients with phosphodiesterase type-5 inhibitors. In the follow-up of 24 months, a combination therapy was necessary in 68% of the patients according to the ESC/ERS guidelines (14) and 7 were lost because of death (n=3) or lung transplantation (n=3) or moving house (n=1).

Hemodynamics

At rest, mPAP was elevated (45.0 ± 2.1 mm Hg) with a PVR of 789 dynes * s *cm-5 and with a normal PCWP of 8.2 ± 0.6 mmHg. The mRAP was elevated with 7.3 ± 0.8 mm Hg [Table 1].

Table 1: Clinical characteristics, hemodynamics and cardiopulmonary exercise parameters in patients with pulmonary hypertension (n = 49)

Characteristics	
Age, yrs	67.5 ± 2.6
Female / male, n	26 / 23
BMI, kg/qm	25.9 ± 0.7
Hemodynamics	
mPAP, mmHg	45.0 ± 2.1
CI, L*min-1*m-2	2.29 ± 0.17
PVR, dynes * s * cm-5	788.7 ± 63.2
mRAP, mmHg	7.3 ± 0.8
PCPW, mmHg	8.2 ± 0.6
SVO2, %	58.1 ± 1.4
Cardiopulmonary exercise testing	
W, watts - %	55.8 ± 4.8 - 44.7 ± 3.5
VO2, ml/min - %	991 ± 61 - 56.2 ± 3.1
VO2, ml/min/kg	14.0 ± 1.0
AT, ml/min/kg	9.2 ± 0.6
O2 pulse, ml/min/beat	8.4 ± 0.5
Ve, L/min	56.4 ± 2.5
Ve/VO2	44.5 ± 1.7
Ve/VCO2	49.2 ± 1.6
AaDO2, mmHg	52.1 ± 2.2
Vd/Vt, %	36.9 ± 2.0
a-et CO2, mm Hg	6.3 ± 0.7
Ve/VCO2 slope	50.2 ± 2.8

Data expressed as mean ± SEM
BMI = body mass index; mPAP = mean pulmonary artery pressure; CI = cardiac index; PVR = pulmonary vascular resistance; mRAP = mean right atrial pressure; PCPW = pulmonary capillary wedge pressure; SVO2 = mixed venous oxygen saturation; W = work capacity; VO2 = peak oxygen uptake; AT = anaerobic threshold; O2 pulse = oxygen pulse; Ve = peak minute ventilation; Ve/VO2 = oxygen equivalent at anaerobic threshold; Ve/VCO2 = carbon dioxide equivalent at anaerobic threshold; AaDO2 = alveolar-arterial oxygen difference at peak exercise; Vd/Vt = functional dead space ventilation at peak exercise; a-et CO2 = arterial-endexpiratory carbon dioxide difference at peak exercise; Ve-VCo2 slope: slope of minute ventilation versus carbon dioxide output

Cardiopulmonary exercise test

The patients showed a reduction in work capacity of 44.7 ± 3.5 % with a diminished aerobic capacity of 56.2 ± 3.1 % (14.0 ± 1.0 ml/min/kg), a reduced O2 pulse of 8.4 ± 0.6 ml/min/beat and elevated ventilatory equivalents for oxygen (44.5 ± 1.7) and for carbon dioxide (49.2 ± 1.6) at the AT (9.1 ± 0.6 ml/min/kg). Furthermore, we observed elevated AaDO2 (52.1 ± 2.2 mmHg) and Vd/Vt of 36.9 ± 1.9 % during peak exercise with an

elevated a-etCO2 – difference of 6.3 ± 0.7 mmHg. Ve/VCO2 slope amounted to 49.7 ± 2.7 [Table 1].

Time course of cardiopulmonary exercise parameters in patients with pulmonary hypertension after 3 and 24 months of specific drug therapy, respectively

After a 3 month specific drug therapy we observed highly significant improvements in power capacity (44.7 ± 3.5 versus 51.1 ± 3.8 % of predicted, p < 0.001), VO2 (14.0 ± 1.0 versus 15.7 ± 1.1 ml/min/kg, p < 0.001), AT (9.2 ± 0.6 versus 10.7 ± 0.8 ml/min/kg, p = 0.006) and O2 pulse (8.4 ± 0.5 versus 9.4 ± 0.6 ml/min/beat, p < 0.001). Furthermore we demonstrated a significant reduction in Ve/VO2 (44.5 ± 1.7 versus 41.7 ± 1.7, p = 0.019). No significant differences existed in Ve/VCO2, AaDO2, Vd/Vt and Ve/VCO2 slope [Table 2].

In the long-term follow-up, we could objectify significant differences in AT (8.3 ± 0.9 versus 10.7 ± 0.9 ml/min/kg, p = 0.001) [Figure 1] and O2 pulse (7.4 ± 0.5 versus 8.4 ± 0.6 ml/min/beat, p = 0.016) [Figure 2]. Furthermore, we observed stable CPET parameters during the following 2 years in power capacity, VO2, Ve/VO2, Ve/VCO2, AaDO2, Vd/Vt and Ve/VCO2 slope [Table 3].

Table 2: Cardiopulmonary exercise parameters in patients with pulmonary hypertension after 3 months of specific drug therapy (n = 49)

	Specific drug therapy		Significance
	before	after 3 months	
W, watts	55.8 ± 4.8	63.5 ± 5.6	p < 0.001
W, %	44.7 ± 3.5	51.1 ± 3.8	p < 0.001
VO2, ml/min	991 ± 61	1110 ± 76	p < 0.001
VO2, %	56.2 ± 3.1	63.2 ± 3.7	p < 0.001
VO2, ml/min/kg	14.0 ± 1.0	15.7 ± 1.1	p < 0.001
AT, ml/min/kg	9.2 ± 0.6	10.7 ± 0.8	p = 0.006
O2 pulse, ml/min/beat	8.4 ± 0.5	9.4 ± 0.6	p = 0.001
Ve, L/min	56.4 ± 2.5	61.6 ± 2.9	p = 0.002
Ve/VO2	44.5 ± 1.7	41.7 ± 1.7	p = 0.019
Ve/VCO2	49.2 ± 1.6	47.8 ± 1.9	ns
AaDO2, mmHg	52.1 ± 2.2	52.9 ± 2.3	ns
Vd/Vt, %	36.9 ± 1.9	36.1 ± 2.0	ns
a-et CO2, mm Hg	6.3 ± 0.7	5.8 ± 0.7	ns
Ve/VCO2 slope	50.2 ± 2.8	47.4 ± 2.6	ns

Data expressed as mean ± SEM

W = work capacity; VO2 = peak oxygen uptake; AT = anaerobic threshold; O2 pulse = oxygen pulse; Ve = peak minute ventilation; Ve/VO2 = oxygen equivalent at anaerobic threshold; Ve/VCO2 = carbon dioxide equivalent at anaerobic threshold; AaDO2 = alveolar-arterial oxygen difference at peak exercise; Vd/Vt = functional dead space ventilation at peak exercise; a-et CO2 = arterial-endexpiratory carbon dioxide difference at peak exercise; Ve-VCo2 slope: slope of minute ventilation versus carbon dioxide output

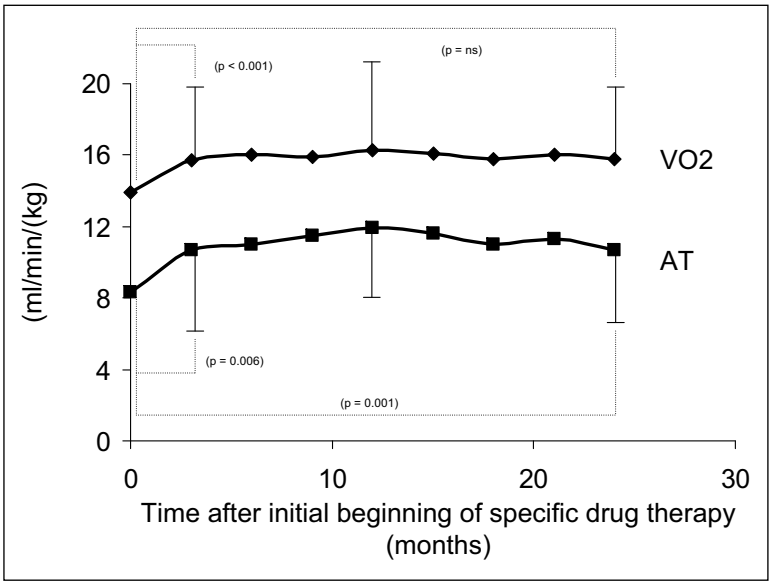

Figure 1: Time course of maximal oxygen uptake and anaerobic threshold after beginning of specific drug therapy in patients with pulmonary hypertension (n = 42, mean ± SD)

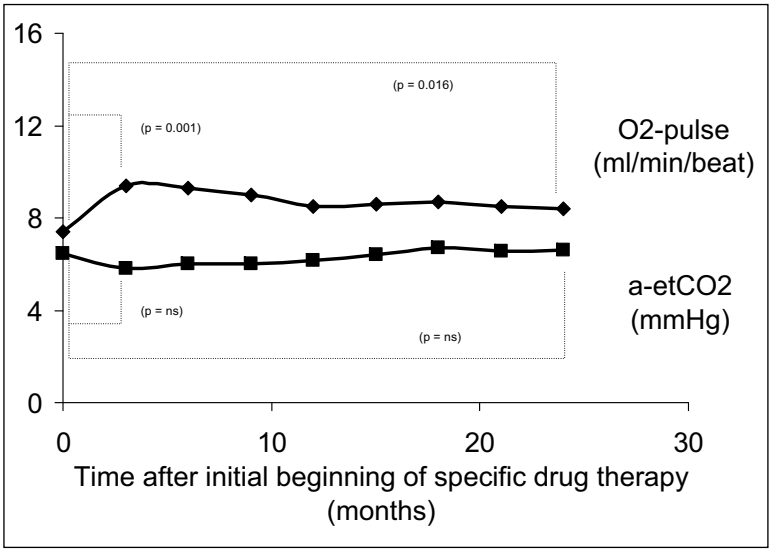

Figure 2: Time course of oxygen pulse and arterial-endexpiratory carbon dioxide difference after beginning of specific drug therapy in patients with pulmonary hypertension (n = 42, mean ± SD)

Table 3: Cardiopulmonary exercise parameters in patients with pulmonary hypertension after 24 months of specific drug therapy (n = 42)

	Specific drug therapy		Significance
	before	after 24 months	
W, watts	59.9 ± 6.6	59.2 ± 5.9	ns
W, %	51.1 ± 5.6	52.1 ± 5.1	ns
VO2, ml/min	955 ± 81	1042 ± 85	ns
VO2, %	56.9 ± 5.2	64.7 ± 5.9	ns
VO2, ml/min/kg	13.9 ± 1.5	15.8 ± 1.5	ns
AT, ml/min/kg	8.3 ± 0.9	10.7 ± 0.9	p = 0.001
O2 pulse, ml/min/beat	7.4 ± 0.5	8.4 ± 0.6	p = 0.016
Ve, L/min	53.4 ± 3.8	57.2 ± 3.9	ns
Ve/VO2	44.5 ± 2.3	42.3 ± 2.7	ns
Ve/VCO2	49.8 ± 2.0	48.9 ± 2.6	ns
AaDO2, mmHg	51.4 ± 2.9	51.1 ± 3.1	ns
Vd/Vt, %	35.2 ± 2.7	36.1 ± 2.9	ns
a-et CO2, mm Hg	6.5 ± 1.2	6.6 ± 1.2	ns
Ve/VCO2 slope	47.1 ± 3.5	46.1 ± 3.6	ns

Data expressed as mean ± SEM
W = work capacity; VO2 = peak oxygen uptake; AT = anaerobic threshold; O2 pulse = oxygen pulse; Ve = peak minute ventilation; Ve/VO2 = oxygen equivalent at anaerobic threshold; Ve/VCO2 = carbon dioxide equivalent at anaerobic threshold; AaDO2 = alveolar-arterial oxygen difference at peak exercise; Vd/Vt = functional dead space ventilation at peak exercise; a-et CO2 = arterial-endexpiratory carbon dioxide difference at peak exercise; Ve-VCo2 slope: slope of minute ventilation versus carbon dioxide output

Discussion

To our knowledge, this is one of the very few studies describing CPET data in the short- and long-term course after beginning of specific pharmocotherapy in patients with pulmonary hypertension. After a 3-month specific drug therapy we demonstrated highly significant improvements in power capacity, peak oxygen uptake, anaerobic threshold and oxygen-pulse. Astonishingly, the ventilatory efficiency parameters, such as Ve/VCO2-slope, showed no significant changes after initiation of specific drug therapy. In the long-term follow-up of 24 months only the anaerobic threshold and the oxygen-pulse significantly improved in comparison to the initial testing. In contrast, we observed stabilized values by the other CPET-parameters.

A significant finding of our study was the confirmation that the ventilatory efficiency parameters are unchanged after beginning of the specific drug therapy in contrast to the significantly improved power capacity. These results are not observed in the study of Oudiz et al., studying 14 patients after initiation of sildenafil treatment (17). The difference could be a result of a smaller and different patient group, differences in medical treatment and in observation period such of a different power capacity. On the other hand, our results with unchanged ventilatory equivalents are in agreement with previous study results. For example, Raeside et al. (18) had shown that pulmonary artery pressure measured during exercise correlates with Ve/VO2 and Ve/VCO2 but not with O2 pulse or VO2. Many randomized PAH trials could not consequently

demonstrate a significant change in mean pulmonary artery pressure after beginning of specific drug therapy. Therefore, it is the possible cause of unchanged ventilatory efficiency in our study group and the stabilized ventilatory efficiency parameters could be the expression of a persistent ventilation/perfusion mismatch because of the remodelling pulmonary vasculature.

Peak oxygen uptake (VO2) is the most frequently analyzed CPET parameter and has consistently demonstrated prognostic significance in patients with pulmonary hypertension (5, 19 - 26). During follow-up, the higher oxygen consumption is possibly determined by the improved maximal cardiac output during exercise, the increased potential for O2 extraction by the exercising muscle, and/or by a higher ventilatory capacity (26). Our study is in agreement with a study of Wax et al. (27), who showed that in 16 PAH patients undergoing CPET, peak VO2 and O2 pulse increased significantly after two years of treatment with intravenous epoprostenol.

In accordance with the study results of Sun et al. (11), one of the main finding is the significantly improved anaerobic threshold in combination with an increased oxygen pulse in the long-term course by the implementation of a specific drug therapy in accordance with the study results of Sun et al. (11). Because O2 pulse equals the product of stroke volume and arterial oxygen content, an improved peak O2 pulse likely reflects an improvement in peak stroke volume paralleling disease severity. The AT, a relevant determinant of O2 delivery, is one of the measurements that provide a non-invasive estimate of the adequacy of cardiovascular function in response to an exercise stimulus. Patients with pulmonary circulatory disease have typically a reduced VO2 and a low AT, reflecting impaired O2 delivery. The AT becomes a higher fraction of peak VO2 as disease severity worsens, suggesting a decrease in cardiovascular reserve as PAH worsens. These unfavourable conditions could be partially reversed by the specific drug therapy. Our results suggest that the higher O2 pulse after 3 respectively 24 months may reflect a better pulmonary perfusion and an improved oxygen delivery to the body during exercise at least due to an improved increase in stroke volume during exercise: Alternatively, the O2 pulse may be affected by changes in O2 content, particularly in our setting where AaDO2 was increased during exercise.

Presently there is limited experience with the use of CPET in multicenter trials in PAH. In one multicenter study on beraprost in PAH patients, the 6-min walk test revealed a significant improvement after three and six months of treatment, whereas there were no significant changes in CPET variables (8). These results raised several questions and concerns about the quality of the CPET studies performed at each study center, especially as the 6-min walk test itself was used as a surrogate for CPET, based on its correlation with peak VO2. It appears that the results of CPET were largely influenced by the experience of the involved centers, whose variability was probably related to the interpretation of the CPET studies rather than to the performance of the studies. Additionally, the report by Barst et al. (8) was controlled and our study was uncontrolled and 68% of our patients were treated with a combination therapy. Alternatively, perhaps sitaxentan is not as effective as other therapeutic options.

Furthermore – in spite of comparable peak VO2-values – our study results are different to the results of the STRIDE-1 trial (8). Barst et al. (8) only found an increase of VO2 between 0.5 to 3.1 % in the verum group with a change of AT of -0.7 to 0.9% and a decrease of Ve/VCO2 of -2 to -7% after 12 weekly sitaxsentan therapy. In contrast, we observed a significant VO2 increase of 12% with an improvement of 16% and a Ve/VCO2 decrease of 3%. Interestingly, Barst et al. (8) demonstrated significantly better hemodynamics with an increase of cardiac index of 0.3 to 0.4 L/min/qm and a fall of pulmonary vascular resistance of 194 to 221 dyn/s/cm5. Barst et al. (8) noted that the reasons for the discrepancy between results obtained from CPET versus other measures that

have been validated in previous PAH trials are unclear. However, the possibility of greater technical expertise required to conduct CPET testing, intrasubject variability and the lack of validation of CPET parameters as efficacy endpoints in PAH trials may be important considerations (28).

In summary, based upon our results, we propose that indices of CPET might be helpful in the assessment of therapy efficiency of specific drugs in the treatment of pulmonary hypertension (27). If a simple non-invasive measurement, such as the oxygen pulse or anaerobic threshold, could be shown to be useful in evaluating pulmonary vascular disease, it might serve to supplement other methods currently used to monitor clinical course and treatment. In our opinion, it is necessary to include peak O2 pulse observing therapy efficiency. The increase in peak O2 pulse seen in our treated patients likely reflects an improvement in stroke volume and cardiac output at peak exercise with specific drug therapy, although an increase in arterial-mixed venous O2 difference cannot be absolutely excluded. Furthermore, after initiation of specific drug therapy for PAH, patients with chronically impaired pulmonary blood flow may not manifest significant gains in aerobic capacity until vascular remodelling and/or aerobic training allows the skeletal musculature to use the greater cardiac output afforded by the improved pulmonary blood flow. This may in part account for the delayed, but continued improved AT in our PAH cohort study.

Author contributions

Drs. Schwaiblmair and Berghaus conceived and designed the study. Dr. Schwaiblmair performed the statistical analyses and drafted the article. Drs. Schwaiblmair, Faul and Berghaus acquired the study data. All authors participated in interpreting the data and revising the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Correspondence address:
Martin Schwaiblmair, PhD
Klinikum Augsburg
University of Munich
Stenglinstr. 2
86156 Augsburg
martin.schwaiblmair@klinikum-augsburg.de