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Effect of Supervised Training Therapy on Pulmonary Arterial Compliance and Stroke Volume in Severe Pulmonary Arterial Hypertension and Inoperable or Persistent Chronic Thromboembolic Pulmonary Hypertension

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Keywords

Pulmonary hypertension · Pulmonary arterial hypertension · Pulmonary arterial compliance · Training · Stroke volume · Right heart catheter

Abstract

Background: Pulmonary arterial compliance (PAC) is a prognostic parameter in pulmonary arterial hypertension (PAH) reflecting the elasticity of the pulmonary vessels. ***Objectives:*** The objective of this post hoc analysis of a prospective randomized controlled trial (RCT) was to assess the effect of exercise training on PAC and stroke volume (SV) in patients with PAH and persistent/inoperable chronic thromboembolic pulmonary hypertension (CTEPH). ***Method:*** From the previous RCT, 43 out of 87 patients with severe PAH ($n = 29$) and CTEPH ($n = 14$) had complete haemodynamic examinations at baseline and after 15 weeks by right heart catheterization and were analysed (53% female, 79% World Health Organization functional class III/IV, 58% combination therapy, 42% on supplemental oxygen therapy, training group $n = 24$, and control group $n = 19$). Medication remained unchanged for all patients. ***Results:*** Low-dose exercise training at 4–7 days/week significantly improved PAC (training group 0.33 ± 0.65 mL/mm Hg vs. control group −0.06 ± 1.10 mL/mm Hg; mean difference 0.39 mL/mm Hg, 95% confidence interval [CI] 0.15–0.94 mL/mm Hg; $p = 0.004$) and SV (training group 9.9 ± 13.4 mL/min vs. control group −4.2 ± 11.0 mL/min; mean difference 14.2 mL, 95% CI 6.5–21.8 mL; $p < 0.001$) in the training versus control group. Furthermore, exercise

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training significantly improved cardiac output and pulmonary vascular resistance at rest, peak oxygen consumption, and oxygen pulse. ***Conclusions:*** Our findings suggest that supervised exercise training may improve right ventricular function and PAC at the same time. Further prospective studies are needed to evaluate these findings.

Introduction

Pulmonary arterial hypertension (PAH) and inoperable or persistent chronic thromboembolic pulmonary hypertension (CTEPH) are devastating and progressive pulmonary vascular diseases that lead to right heart failure and premature death. Mortality for PAH and inoperable or persistent CTEPH remains high despite therapeutic advances in the last 2 decades [1]. To assess prognosis and to guide therapy, current guidelines recommend a combination of treatment targets including haemodynamic measurements by right heart catheter, transthoracic echocardiography at rest, biomarkers, and exercise testing [2], which were predominantly derived from large registries like Compera [3], REVEAL [4], and the French registry [5]. To further improve risk assessment, therapy-guidance and patient outcome, new prognostic markers are needed.

Pulmonary Arterial Compliance

Pulmonary arterial elasticity maintains low pulse pressure and low pulsatile afterload for the right ventricle. Pulmonary arterial compliance (PAC) is calculated as

$$PAC = \frac{SV}{PP} = \frac{\left(\frac{CO}{heart\ rate}\right)}{sPAP - dPAP}$$

which is the simplest and most practical method for estimating pulmonary arterial elasticity [6]. It plays a key role in accommodating much of the SV of the right ventricle due to passive arterial expansion and in maintaining diastolic pulmonary blood flow due to arterial recoil. PAC decreases in pulmonary hypertension (PH) [6] and correlates with PH severity [7]. The increase in pulmonary arterial stiffness is associated with accumulation of collagen and loss of elastin in the proximal pulmonary arteries [8–12]. There is even further evidence suggesting that loss of PAC may actually initiate PH [13]. Decreased PAC increases right ventricular pulsatile afterload [12,14,15], which leads to decreased CO over time and finally to right heart failure [12, 16]. It has been shown that decreased PAC is independently associated with RV failure, dilatation, and hypertrophy [17], regardless of improvements of pulmonary vascular resistance (PVR) achieved under targeted PH therapy [14, 16, 18].

The aim of this post hoc analysis was to assess, whether supervised training could also improve vascular stiffness by increasing PAC and RV function by increasing SV apart from improving PVR, CO, and cardiac index as classic predictors of outcome.

Methods

The full design and methodology of the initial randomized controlled trial (RCT) has been published previously [19]. This prospective RCT, conducted from June 2010 (first patient, first visit) to May 2015 (end of study), was a 15-week study investigating the effects of supervised exercise training in patients with severe but stable PAH and inoperable or persistent CTEPH. Patients were randomized to either training therapy or a control group. Primary end point was the change in peak VO_2. Secondary end points included changes in haemodynamics at rest and during exercise, biomarkers, and echocardiography parameters as previously described [19].

Post hoc Analysis and Statistical Methods

The analyses were performed by 2 statisticians (N.B. and C.F.). Data are given as mean values ± standard deviations. We performed a post hoc analysis of the study by Ehlken et al. [19] focussing on SV and PAC. SV was calculated as

$$SV = \left(\frac{CO}{heart\ rate}\right)$$

PAC was calculated according to the formula

$$PAC = \frac{SV}{PP} = \frac{\left(\frac{CO}{heart\ rate}\right)}{sPAP - dPAP}$$

To enhance interpretation of PAC, further parameters reflecting RV load were calculated. RV afterload can be described as the sum of RV pressures throughout RV ejection. Effective arterial elastance (EA) is a lumped measure of RV afterload [20] and integrates pulsatile and resistive loading of the RV. EA is calculated as

$$EA = \frac{end - systolic\ pressure}{SV} = \frac{sPAP}{SV}$$

For further interpretation of the primary research question, change of clinical parameters including 6-min walking distance (6MWD), haemodynamic parameters, parameters of cardiopulmonary exercise testing, and N-terminal pro brain natriuretic peptide (NT-proBNP) were analysed. Descriptive analyses of these parameters include mean and standard deviation of baseline measurements and difference between baseline and 15 weeks of exercise training as well as quartiles of the differences. Non-parametric Mann-Whitney U tests have been performed to assess the differences of

Table 1. Baseline characteristics

	Control	Training	*p* value
Patients, *n*	19	24	
Gender male/female, *n*	8/11	12/12	0.606
Age, years	58±14	55±15	0.506
Height, cm	171±9	170±10	0.736
Weight, kg	80±18	78±17	0.711
WHO functional class, *n* (%) baseline			
II	3 (15.8%)	4 (16.7%)	
III	14 (73.7%)	19 (79.2%)	0.519
IV	1 (5.3%)	0 (0.0%)	
Diagnosis, *n* (%)			
PAH	10 (52.6%)	19 (79.1%)	0.065
CTEPH	9 (47.4%)	5 (20.9%)	
NT-proBNP, pg/mL	1,453±1,658	1,233±2,586	0.765
Right heart catheterization			
Mean pulmonary arterial pressure, mm Hg	38.1±10.8	40.4±12.5	0.529
PVR, WU	5.76±2.62	7.36±3.26	0.090
Central venous pressure, mm Hg	6.9±4.3	7.3±3.6	0.742
Pulmonary arterial oxygen saturation, %	63.2±9.0	64.6±11.5	0.678
Pulmonary arterial wedge pressure, mm Hg	10.2±4.5	8.7±2.4	0.168
Cardiac index, L/min/m^2	2.5±0.4	2.7±0.7	0.294
PAH-targeted medication, *n* (%)			
Endothelin receptor antagonist	11 (57.9%)	17 (70.8%)	0.377
Phosphodiesterase-5 inhibitor	12 (63.25%)	18 (75.0%)	0.401
Prostanoids inhaled	4 (21.1%)	3 (12.5%)	0.451
Prostanoids oral	0 (0%)	1 (4.2%)	0.368
Calcium channel blockers	2 (10.5%)	3 (12.5%)	0.841
Imatinib	1 (5.3%)	0 (0%)	0.368
Soluble guanylate cyclase stimulator	2 (10.5%)	3 (12.5%)	0.841
Combination therapy, *n* (%)			
Monotherapy	9 (47.4%)	9 (37.5%)	
Dual therapy	8 (42.1%)	10 (41.7%)	0.939
Triple therapy	2 (10.5%)	5 (20.8%)	
Oxygen therapy, yes/no, *n*	9/10	9/15	0.515

Values are presented as mean ± standard deviation unless specified otherwise. *p* values were derived from χ^2 tests or two-sided unpaired Student's *t* tests. WHO functional class was missing for 1 patient in each group. NT-proBNP at baseline was missing for 3 patients in the control group. Pulmonary arterial oxygen saturation was missing for 1 patient in the control group and 3 patients in the training group. Cardiac index was missing for 1 patient in each group. NT-proBNP, N-terminal pro brain natriuretic peptide; PAH, pulmonary arterial hypertension; WHO, World Health Organization; PVR, pulmonary vascular resistance; WU, Wood units; CTEPH, chronic thromboembolic pulmonary hypertension.

the changes between training and control group. To correct for haemodynamic imbalances between groups, differences of changes between groups were compared by analysis of covariance with baseline mean pulmonary arterial pressure and PVR as covariates. All analyses have been performed using IBM SPSS 25 (SPSS Statistics V25, IBM Corporation, Somers, NY, USA).

Statement of Responsibility

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Population and Randomization

Forty-three out of 87 patients with severe PAH ($n = 24$) or inoperable or persistent CTEPH ($n = 19$) had complete haemodynamic examinations at baseline and after 15 weeks by right heart catheterization and were analysed per protocol. Medication remained unchanged for all patients. Twenty-four patients were analysed from the training group, and 19 from the control group. The con-

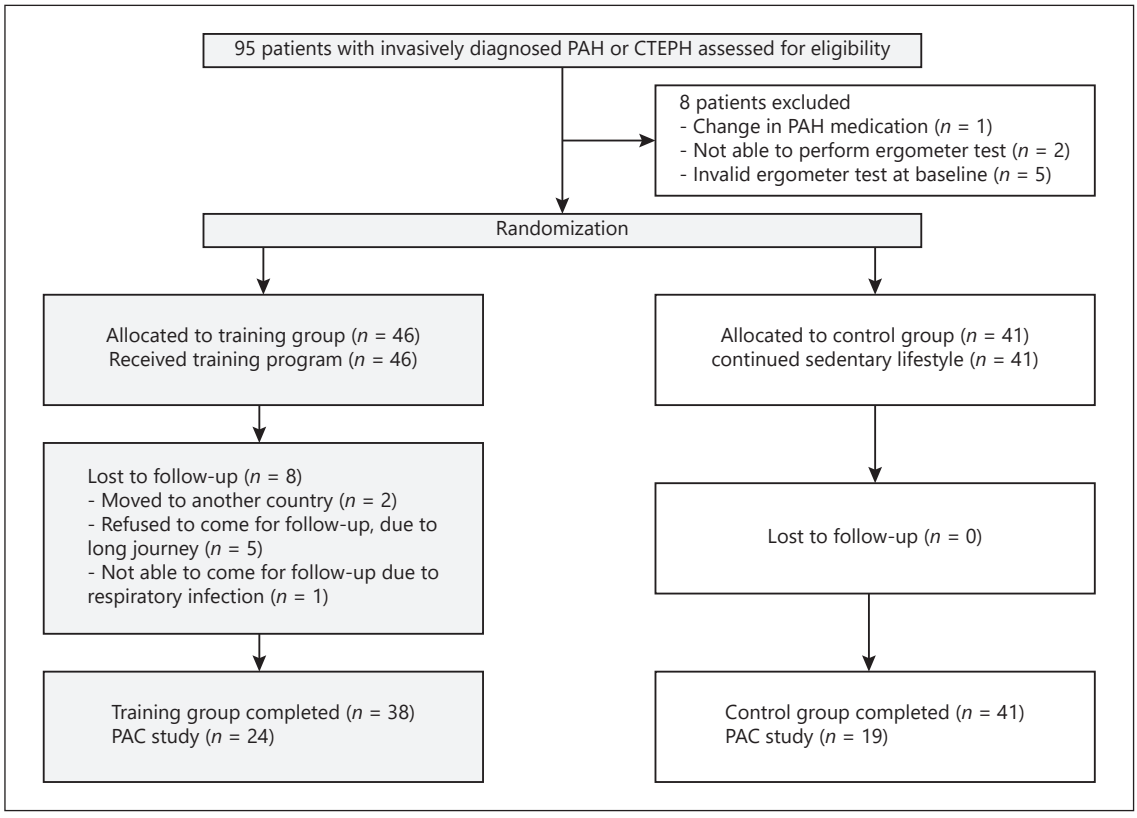

Fig. 1. Study design. The flow chart shows the number of patients for each study group, the number and reasons for exclusion, and the number of patients valid for PAC analysis. PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PAC, pulmonary arterial compliance.

trol and training groups were well balanced in their baseline characteristics, disease severity, and medication (Table 1). Mean age in the training group was 55 ± 15 years and 58 ± 14 years in the control group. Nineteen patients in the training group had PAH (79.1%) versus ten patients in the control group (52.6%). Five patients in the training group had CTEPH (20.96%) versus 9 patients in the control group (47.4%, Fig. 1).

Main Outcomes: Change in SV and PAC at Rest

Both SV (training group 9.9 ± 13.4 mL vs. −4.2 ± 11.0 mL in the control group, mean difference 14.2 mL, 95% confidence interval [CI] 6.5–21.8 mL, $p < 0.001$; Fig. 2) and PAC (training group 0.33 ± 0.65 mL/mm Hg vs. control group −0.06 ± 1.10 mL/mm Hg, mean difference 0.39 mL/mm Hg, 95% CI 0.15–0.94 mL/mm Hg, $p = 0.004$; Fig. 3; Table 2) at rest significantly increased from baseline to 15 weeks. Analysis of covariance with baseline mean pulmonary arterial pressure and PVR as covariates led to consistent results for both SV ($p < 0.0001$) and PAC ($p = 0.031$). The training and the control group showed an increase of sPAP, dPAP, and PP in the control group and a decrease in the training group. Together with PAC and SV, EA improved significantly in the training group compared to the control group (−0.16 ± 0.35 mm Hg/mL vs. 0.14 ± 0.31 mm Hg/mL). No significant changes were found in right atrial pressure between both groups. The training group showed significant improvements in SV (increase, $p = 0.001$) and PAC (increase, $p = 0.014$).

Change in Mean Pulmonary Artery Pressure, CO, and PVR at Rest

Resting mean pulmonary artery pressure (mPAP) decreased in the training group after 15 weeks by −5 ± 11 mm Hg versus increase of 5 ± 7 mm Hg in the control group (mean difference training vs. control −8.9 mm Hg; 95% CI −14.3 to −3.6 mm Hg). CO at rest significantly improved in the training group by 0.6 ± 0.9 L/min versus −0.2 ± 0.8 L/min in the control group (mean difference training vs. control 0.8 L/min; 95% CI 0.3–1.3 L/min). PVR at rest changed in the training group after 15 weeks by −1.18 ± 2.13 Wood units (WU) versus 0.83 ± 1.13 WU in the control group

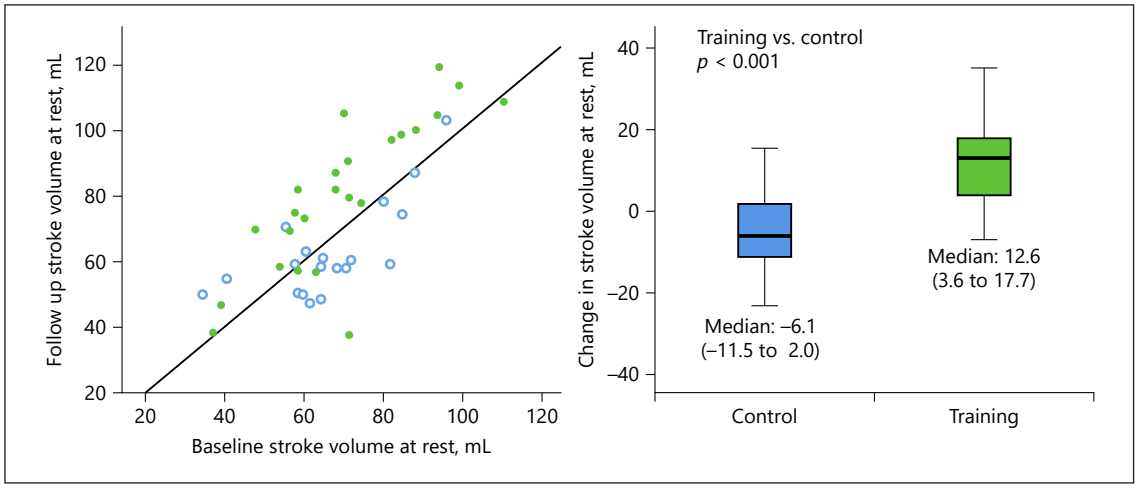

Fig. 2. Change in stroke volume. Left graph: the abscissa shows baseline stroke volume at rest, and the ordinate shows stroke volume at rest after 15 weeks. The solid points represent patients of the training group and the circles represent patients of the control group. Right graph: boxplots at the right side show the distribution of changes between baseline and follow-up in the training and control group. The changes were different between training and control patients, $p < 0.001$, Mann-Whitney U test.

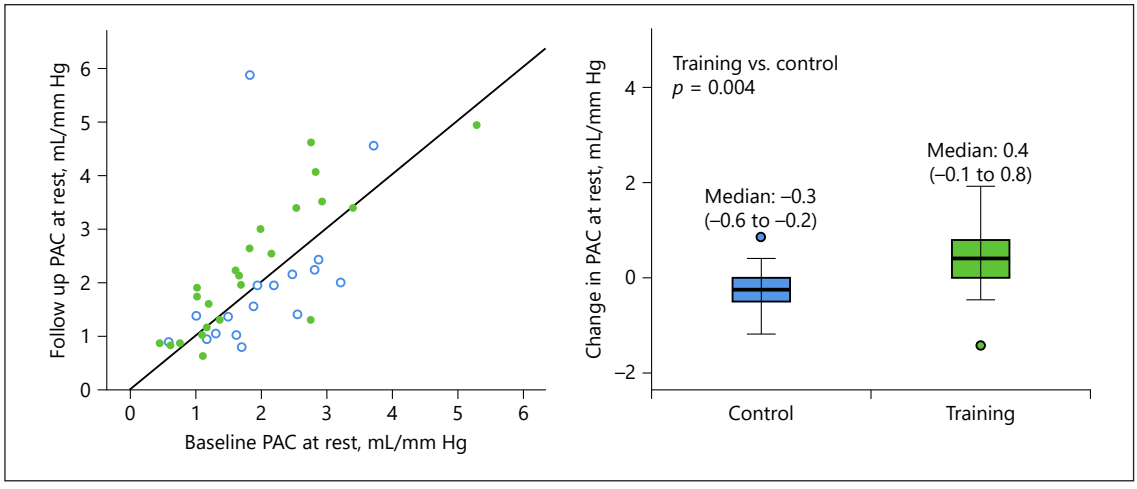

Fig. 3. Change in PAC. Left graph: the abscissa shows baseline PAC at rest, and the ordinate shows PAC at rest after 15 weeks. The solid points represent patients of the training group, and the circles represent patients of the control group. Right graph: boxplots at the right side show the distribution of changes in PAC between baseline and follow-up. The changes are different between training and control patients, $p = 0.004$, Mann-Whitney U test. PAC, pulmonary artery compliance.

(mean difference training vs. control −2.01 WU; 95% CI −3.05 to −0.96 WU, Table 2). The training group significantly improved in PVR (decrease, 0.001), mPAP at rest (decrease, 0.011), and CO at rest (increase, $p = 0.002$).

Change in mPAP, CO, and PVR during Exercise

Patients of the training group showed a lower increase of mPAP during exercise after 15 weeks than patients of the control group (2.2 ± 9.8 mm Hg vs. 6.7 ± 10.1 mm Hg) (mean difference training vs. control −4.5 mm Hg; 95% CI −11.4 to 2.4), although the training group had a higher increase in maximum workload after 15 weeks (16.1 ± 22.7 Watts vs. 1.6 ± 10.0 Watts, mean difference training vs. control 14.5 Watts; 95% CI 3.4 to 25.6 Watts). CO during exercise markedly and significantly increased in the training group by 1.5 ± 2.4

Table 2. Change of clinical outcome parameters

Characteristic	Training group		Control group		Training – control		
	baseline	change baseline to 15 weeks	baseline	change baseline to 15 weeks	difference of changes[#]		
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean	95% CI	*p* value
Main parameters SV and PAC							
SV at rest, mL	70.3±18.5	9.9±13.4	66.8±15.3	−4.2±11.0	14.2	6.5 to 21.8	<0.001
PAC at rest, mL/mm Hg	1.86±1.09	0.33±0.65	1.95±0.83	−0.06±1.10	0.39	0.20 to 0.98	0.004
Mean 6MWD, m	442±80	26±51	402±66	−9±51	35.1	0.7 to 69.5	*
Laboratory parameter							
NT-proBNP, pg/mL	1,233±2,586	−394±1,390	1,453±1,659	−105±386	−289	−950 to 372	
Cardiopulmonary exercise testing							
Peak VO_2/kg, mL/min/kg	12.9±3.5	2.9±1.8	12.0±4.0	0.5±2.8	2.4	0.9 to 3.9	*
Peak VO_2, mL/min	993±315	216.0±123.0	974±255	13.5±157.2	203	112 to 293	*
Oxygen pulse, mL/beat	8.3±2.6	0.76±0.82	7.9±2.1	0.29±1.1	0.46	−0.18 to 1.1	*
HR rest, min^{-1}	73±10	1.3±9.8	73±10	−7.5±11.5	8.7	−2.0 to 15.5	
HR max, min^{-1}	131±17	11±11.9	131±38	−0.1±10.4	11.1	−4.0 to 18.1	
BP sys at rest, mm Hg	114±19	−5.3±19.7	111±15	−0.42±15.1	−4.9	−15.7 to 5.9	
BP dia at rest, mm Hg	72±11	−3.4±11.5	73±10	−2.5±11.3	−0.77	−7.9 to 6.4	
BP sys max, mm Hg	152±30	8.2±24.7	156±34	−5.5±22.2	13.7	−1.1 to 28.5	
BP dia max, mm Hg	89±12	1.6±14.7	78±11	1.2±10.5	0.43	−7.6 to 8.4	
Workload max, W	70±26	16.1±22.7	64±12	1.6±10.0	14.5	3.4 to 25.6	*
Right heart catheter at rest							
Right atrial pressure, mm Hg	7.3±3.6	0.3±3.9	6.9±4.3	0.9±4.3	0.6	−2.1 to 11.4	
mPAP, mm Hg	40.4±12.5	−4.5±10.5	38.1±10.8	4.5±6.7	−8.9	−14.3 to −3.6	*
Pulse pressure	45.4±15.9	−1.5±12.4	39.6±14.5	2.9±9.9	4.4	−2.7 to 11.4	
EA	1.19±0.61	−0.16±0.35	0.99±0.38	0.14±0.31	0.30	0.09 to 0.50	*
Cardiac output, L/min	5.0±1.0	0.6±0.9	4.8±7.5	−0.2±0.8	0.8	0.3 to 1.3	*
Cardiac index, $L \times min \times m^{-2}$	2.7±0.7	0.2±0.6	2.5±0.4	−0.1±0.4	0.27	−0.06 to 0.60	
PAWP, mm Hg	8.7±2.4	2±3	10.2±4.5	−0.1±4.1	3.2	0.9 to 5.5	*
PVR, WU	7.36±3.35	−1.18±2.13	5.76±2.63	0.83±1.13	−2.01	−3.05 to −0.96	*
Right heart catheter during exercise							
mPAP, mm Hg	69±20	2.2±9.8	56±16	6.7±10.1	−4.5	−11.4 to 2.4	
Cardiac output, L/min	10.0±2.8	1.5±2.4	8.7±2.0	−0.3±1.4	1.8	0.4 to 3.3	*
Cardiac index, $L \times min \times m^{-2}$	5.2±1.6	0.7±1.2	4.5±1.0	−0.1±0.7	0.8	0.2 to 1.5	*
PAWP, mm Hg	15.1±5.5	−0.3±6.0	16.4±7.9	0.5±4.5	−0.8	−4.4 to 2.9	
PVR, WU	6.05±2.65	−0.28±1.91	5.03±2.49	0.80±1.75	−1.08	−2.36 to 0.20	

PAC analysis set (n = 43; 24 training vs. 19 control). Values are mean ± standard deviation; * denotes CI not including 0. CI, confidence interval; SV, stroke volume; PAC, pulmonary artery compliance; 6MWD, 6-min walking distance; HR, heart rate; BP, blood pressure; sys, systolic; dia, diastolic; mPAP, mean pulmonary arterial pressure; EA, effective arterial elastance; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; peak VO_2, peak oxygen consumption; WU, Wood units; NT-proBNP, N-terminal pro brain natriuretic peptide; p values are calculated with the Mann-Whitney U test. [#] A positive difference denotes higher values in the training group; a negative difference denotes lower values in the training group.

L/min versus −0.3 ± 1.4 L/min in the control group (mean difference training vs. control 1.8 L/min; 95% CI 0.4–3.3). PVR during exercise significantly decreased in the training group after 15 weeks by −0.28 ± 1.91 WU versus 0.80 ± 1.75 WU in the control group (mean difference training vs. control −1.08 WU; 95% CI −2.36 to 0.20 WU) (Table 2). Peak CO significantly improved from baseline to follow-up in the training group (increase, p = 0.008); peak mPAP did not significantly differ between baseline and follow-up.

Change of NT-proBNP

NT-proBNP changed in the training group after 15 weeks by −394 ± 1,390 pg/mL versus −105 ± 386 pg/mL in the control group (mean difference training vs. control −289 pg/mL; 95% CI −950 to 372 pg/mL) (Table 2).

Cardiopulmonary Exercise Testing and 6MWD

Peak VO_2 in the training group increased by 216.0 ± 123.0 mL/min in the training group versus 13.5 ± 157.2 mL/min in the control group (mean difference training vs. control 203 mL/min; 95% CI 112–293 mL/min). Peak VO_2 per kg increased by 2.9 ± 1.8 mL/min/kg in the training group versus 0.5 ± 2.8 mL/min/kg in the control group (mean difference training vs. control 2.4 mL/min/kg; 95% CI 0.9–3.9 mL/min/kg). Oxygen pulse improved in the training group by 0.76 ± 0.82 mL/beat versus 0.29 ± 1.1 mL/beat (mean difference training vs. control 0.46 mL/beat; 95% CI −0.18 to 1.1 mL/beat). 6MWD changed in the training group after 15 weeks by 26 ± 51 m versus −9 ± 51 m in the control group (mean difference training vs. control 35.1 m; 95% CI 0.7–69.5) (Table 2).

Discussion

To our knowledge, this post hoc analysis is the first analysis of an RCT showing the impact of a supervised exercise training therapy on PAC and SV. Exercise training significantly improved vascular stiffness and RV function. Though patients of the training group seemed more severely affected with higher mPAP and PVR at baseline, they showed a significant improvement of PAC and SV compared to the control group.

PAC and PVR follow a predictable inverse, hyperbolic relationship. Any change in PVR meets an inverse change in PAC [20]. Therefore, the RC time (the product of resistance × compliance) in the pulmonary vasculature is constant and provides physiologically a time constant for the pulmonary arterial diastolic pressure decay [20]. In contrast to the pulmonary circulation, compliance can change independently of resistance in the systemic circulation and the RC time is not constant. Mean PVR in our training group was 7.36 ± 3.35 WU and 5.76 ± 2.63 WU in the control group at baseline and therefore moderately high. According to the PAC-PVR relationship [20], an increase or decrease in PVR above 10 WU results in a smaller change in PAC than below 10 WU and vice versa. SV increased in our training group, while PP decreased at the same time, and therefore the improvement of PAC was due to an improvement of both components. With an increase in PAC, PVR decreased to keep a constant RC time in the pulmonary circulation. Presumably, the improvement in vascular stiffness (PAC) resulted in a significant reduction in RV afterload (EA).

Prognostic Importance of PAC

PAC has been shown to be a strong predictor of mortality in a landmark study by Mahapatra et al. [6]. They assessed 109 patients with PAH. In this study, PAC was an independent predictor of mortality and superior to PVR, which is the most common haemodynamic parameter to characterize the resistance of the pulmonary vascular bed. In contrast to PAC, PVR was not associated with increased mortality in this study [6]. The hazard ratio of PAC was higher than that of established haemodynamic parameters like mPAP and cardiac index [6]. The same was observed in patients with PH due to heart failure with preserved ejection fraction [21] and in patients with PH due to left heart failure (World Health Organization Group II) [21–24], underlining the importance of PAC in clinical practice. Furthermore, increased pulmonary artery stiffness measured by cardiac MRI was associated with increased mortality in patients with PAH [25].

Change of PAC under Medical PAH/CTEPH Therapy

At present, current PH therapies are mainly directed at dilatation of small pulmonary arteries to reduce PVR and have only little effect on long-term survival of severe PAH patients [12, 26–28]. In a small single-center study by Brittain et al. [29], PAC improved minimally with parenteral prostacyclin therapy, but not with oral therapies. This was associated with an improvement in exercise capacity measured by 6MWD. Apart from parenteral prostacyclin, no other currently available targeted medical PAH therapy showed an improvement of PAC [29]. Ventetuolo et al. [30] pooled 4 RCTs in PAH and showed a small yet significant improvement of PAC of 0.2 mL/mm Hg but without a reduction in short-term clinical outcomes after 12 weeks of targeted PH medication therapy. Our supervised training therapy successfully addressed all important prognostic aspects of PAH/CTEPH therapy by improving pulmonary artery pressures (mPAP), RV function (CO, cardiac index, and SV), vascular elasticity (PAC), vascular remodelling (PVR), and exercise capacity (6MWD and peak VO_2) at once. This underlines the importance of supervised training therapy in severe but stable PAH and inoperable or persistent CTEPH.

Predictive Value of PAC at Baseline versus Change of PAC over Time

In a retrospective study of 109 patients with severe PAH, Medrek et al. [31] demonstrated for the first time that a decrease of PAC over time was an even better predictor of outcome than PAC at baseline with a hazard ratio of 4.21 (CI 1.77–10.02, $p = 0.004$) in the multivariate analysis. Longitudinal change of PAC was a highly prognostic parameter in this study. Although significant, PVR at baseline only had a hazard ratio of 1.003 ($p = 0.015$). Chemla and colleagues [32] found out that baseline pulmonary artery stiffness did not independently predict outcome in untreated incident idiopathic PAH. In their study, the great dispersion of the PVR × PAC product implied that PVR and PAC were differently affected by the disease process. Our training group showed significant improvements in both parameters at the same time: PAC and PVR. Due to the prognostic meaning of PAC both as assessment at a singular timepoint, as well as of changes due to treatment, the calculation of PAC based on routine right heart catheterization assessments could serve clinical estimation of prognosis and help to optimize and adapt treatment.

Effect on RV Function and Peak Oxygen Uptake

In a study by Ehlken et al. [19], training significantly improved RV function, one of the major predictors of outcome in PH, as measured by an increase in CO and cardiac index as well as SV. Peak VO_2 increased at the same time to levels above 11.4 mL/min/kg, which have been detected to be prognostically relevant by Grünig et al. [33]. Grünig et al. [33] identified two independent prognostic parameters in the multivariate analysis of 124 PAH patients for long-term survival: PASP increase during exercise >30 mm Hg as a correlate for RV contractility and output reserve, and peak VO_2 >11.4 mL/min/kg. Both independent prognostic parameters were improved by our supervised exercise therapy.

Current data raise the possibility that PAC is a critical factor that must be treated in order to improve outcomes for PH patients [7, 15, 17, 25]. There is an unmet need for novel approaches to improve PAC as a promising new parameter and RV function as major predictor of long-term survival in PAH.

Limitations

Our study has several limitations. First, this is a post hoc analysis of the initial RCT that was published previously [19]. As right heart catheterization was an optional assessment in the initial study [19], we only analysed participants with a complete haemodynamic measurement of two right heart catheterizations. Therefore, a referral bias might have occurred. However, both groups were well balanced in their baseline characteristics, with the training patients being slightly more severely affected than patients of the control group.

We received patients from many PH centres throughout Germany, but the training study was performed as a single-center study in Heidelberg. As patients of the control group were also offered to take part in the training program after having completed the study, we are not able to provide long-term and survival data of this cohort.

Conclusion

The findings of this post hoc analysis of our randomized controlled study suggest that supervised exercise training may improve RV function and reduce pulmonary arterial stiffness at the same time as major prognostic parameters of survival in PH, as well as CO, cardiac index, and PVR.

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Statement of Ethics

The original RCT and the post hoc analysis were conducted in accordance with Good Clinical Practice (GCP) and the current version of the revised Declaration of Helsinki (WMA Declaration of Helsinki). The Ethics Committee of the University of Heidelberg, Germany, did not have any objections against the conduct of the RCT. The study was registered at clinicaltrials.gov (NCT01394367). Written informed consent was obtained from each patient prior to enrolment.

Conflict of Interest Statement

C.N. reports honoraria for lectures and participation in clinical trials from Actelion, Bayer/MSD, Novartis, speaker honoraria from Boehringer, Astra Zeneca, and Berlin Chemie and participation in clinical trials from GSK, United Therapeutics outside the submitted work. N.B. received speaker honoraria and travel support from Actelion and Bayer outside the submitted work. B.E. has nothing to disclose. C.A.E. has nothing to disclose. C.F. has noth-

ing to disclose. E.P. has nothing to disclose. J.C. reports honoraria for lectures and participation in clinical trials from Novartis, Amgen, speaker honoraria from Boehringer, Astra Zeneca, and Berlin Chemie outside the submitted work. S.H. received travel support from Actelion and OMT outside the submitted work. E.M. reports non-financial support from the German Centre for Lung Research, during the conduct of the study; personal fees from Actelion Pharmaceuticals, Bayer, Pfizer, GSK, and MSD outside the submitted work. M.N. has nothing to disclose. A.M.M. has received personal fees from Bayer outside the submitted work. E.G. received advisory board member and speaker honoraria from Actelion, Bayer/MSD, GSK, United Therapeutics, Novartis, Pfizer, and OrphaSwiss GmbH outside the submitted work. S.G. reports non-financial support from the German Centre for Lung Research during the conduct of the study and personal fees from Actelion Pharmaceuticals, Bayer, Pfizer, and GSK outside the submitted work.

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Author Contributions

E.G., C.N., S.G., E.M., N.B., and C.F. made substantial contributions to the conception and design of the work. C.N., N.B., B.E., S.H., E.M., A.M.M., E.G., and S.G. acquired the data. N.B. and C.F. analysed the data. All authors were involved in data interpretation. E.G., C.N., and N.B. drafted the work. All authors were involved in manuscript revision, approved the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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