Effect of a day-trip to altitude (2500 m) on exercise performance in pulmonary hypertension: randomised crossover trial

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Short-time exposure to high altitude in pulmonary hypertension induces hypoxaemia, reduces constant work-rate cycle time compared to ambient air and is well tolerated overall https://bit.ly/3xUAFMs

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Abstract

Question addressed by the study To investigate exercise performance and hypoxia-related health effects in patients with pulmonary hypertension (PH) during a high-altitude sojourn.

Patients and methods In a randomised crossover trial in stable (same therapy for >4 weeks) patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) with resting arterial oxygen tension (P_{aO_2}) ⩾7.3 kPa, we compared symptom-limited constant work-rate exercise test (CWRET) cycling time during a day-trip to 2500 m *versus* 470 m. Further outcomes were symptoms, oxygenation and echocardiography. For safety, patients with sustained hypoxaemia at altitude (peripheral oxygen saturation <80% for >30 min or <75% for >15 min) received oxygen therapy.

Results 28 PAH/CTEPH patients (n=15/n=13); 13 females; mean±SD age 63±15 years were included. After >3 h at 2500 m *versus* 470 m, CWRET-time was reduced to 17±11 *versus* 24±9 min (mean difference −6, 95% CI −10 to −3), corresponding to −27.6% (−41.1 to −14.1; p<0.001), but similar Borg dyspnoea scale. At altitude, P_{aO_2} was significantly lower (7.3±0.8 *versus* 10.4±1.5 kPa; mean difference −3.2 kPa, 95% CI −3.6 to −2.8 kPa), whereas heart rate and tricuspid regurgitation pressure gradient (TRPG) were higher (86±18 *versus* 71±16 beats·min^{-1}, mean difference 15 beats·min^{-1}, 95% CI 7 to 23 beats·min^{-1}) and 56±25 *versus* 40±15 mmHg (mean difference 17 mmHg, 95% CI 9 to 24 mmHg), respectively, and remained so until end-exercise (all p<0.001). The TRPG/cardiac output slope during exercise was similar at both altitudes. Overall, three (11%) out of 28 patients received oxygen at 2500 m due to hypoxaemia.

Conclusion This randomised crossover study showed that the majority of PH patients tolerate a day-trip to 2500 m well. At high *versus* low altitude, the mean exercise time was reduced, albeit with a high interindividual variability, and pulmonary artery pressure at rest and during exercise increased, but pressure–flow slope and dyspnoea were unchanged.

Introduction

Travelling to the Alps, Rockies and other mountain regions worldwide is increasingly popular, with >120 million visitors per year, including many with pre-existing chronic cardiorespiratory diseases. This is possible as mountains have become easily accessible by car, train or cable car up to >3500 m and many large settlements worldwide situated >2000 m are approachable by commercial flights pressurised up to 2438 m (8000 feet, barometric pressure 752 hPa). However, with an increasing hypobaric hypoxic environment at higher altitudes, the prevalence of altitude-related adverse health effects (ARAHE) rises in healthy individuals, and even more so in patients with cardiorespiratory diseases [1–5].

In our clinical practice, many patients with cardiorespiratory diseases, including patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH; summarised together as PH) seek medical advice concerning hypoxia-related adverse health effects while planning sojourns to settlements at altitude. Recent therapeutic advances have improved quality of life and physical performance in many patients with PH and these patients wish to participate in daily activities including popular mountain travel to at least moderate altitudes up to 2500 m. However, with increasing severity of PH, worsening haemodynamics may lead to hypoxaemia, particularly during exertion, sleep and exposure to a hypoxic environment [6]. Thus, current PH guidelines discourage sojourns at altitude in fear of ARAHE [7]. Alveolar hypoxia at high altitude leads to immediate hypoxic pulmonary vasoconstriction (HPV) to distribute pulmonary blood flow to alveolar areas with higher oxygen partial pressure and it is feared that PH patients might be particularly affected by hypoxia due to an accelerated rise of pulmonary artery pressure (PAP) augmenting pulmonary vascular resistance (PVR) [8]. Upon long-term hypoxic exposure in high-altitude dwellers, this may induce pulmonary vascular remodelling, leading to sustained PH in susceptible individuals [9–11]. Alternatively, HPV could be diminished in already remodelled lung vessels in patients with PH [12]. Overall, there is still insufficient scientific knowledge on pathophysiological changes of PH under hypoxic conditions and their clinical implications, which impedes adequate counselling of PH patients for their upcoming mountain journey [13]. In a recent study in patients with PH exposed to simulated altitude by breathing hypoxic air (F_{IO_2} 0.15, altitude equivalent 2500 m) we found that short-term exposure to normobaric hypoxia was well tolerated, but reduced median constant work-rate exercise test (CWRET) cycling time without significantly altering pulmonary haemodynamics by echocardiography and that PVR resulted as the best predictor for exercise time [14]. Tricuspid regurgitation pressure gradient (TRPG)/cardiac output (CO) ratio is an established measure to assess total pulmonary resistance and potential surrogate of PVR, especially during exercise, and was shown to predict survival in PH [15, 16]. In the present trial we investigated effects of a day-trip to real altitude (2500 m) on exercise capacity, symptoms, haemodynamics and additional physiological measures.

Material and methods

Design

This randomised controlled crossover trial was conducted between August and December 2018 at the University Hospital Zurich (470 m) and in the Swiss Alps at 2500 m.

Subjects

Adults diagnosed with PAH/CTEPH according to current guidelines [7] were recruited at the PH centre, Zurich, if they were clinically stable on the same medication for >4 weeks, lived <1000 m, were not on long-term oxygen therapy and had a resting arterial oxygen tension (P_{aO_2}) ⩾7.3 kPa and arterial carbon dioxide tension (P_{aCO_2}) <6.5 kPa. Patients who had travelled to >1500 m for ⩾3 nights during the previous 4 weeks or had relevant comorbidities, were pregnant, breastfeeding or unable to follow the study protocol were excluded.

Participants provided written informed consent, the study was approved by Cantonal Ethics Zurich and registered at clinicaltrials.gov (NCT03637153).

Intervention/altitude exposure

Participants were assessed in Zurich (470 m) and during a 6–7 h stay at 2500 m in a randomised order, with washout period of ⩾3 days at altitude <800 m in-between. Transfers between study locations were by a 2–3 h trip by shuttle bus and cable car.

Safety

During the high-altitude sojourn, the clinical condition of the patients and pulse oximetry were monitored continuously. Patients who reported general discomfort or findings such as severe dizziness, ataxia, confusion, muscle weakness or cardiac deterioration (arrhythmia, hypotension, severe dyspnoea) or who revealed a peripheral oxygen saturation (S_{pO_2}) <80% for >30 min or <75% for >15 min were given oxygen and descent was arranged.

Assessment

Demographics, PH classification, current medication, a cycle incremental ramp cardiopulmonary exercise test, the 6-min walk distance (6MWD) and New York Heart Association (NYHA) functional class were assessed during screening [7].

During the study, assessments were performed at 470 m or after >3 h at 2500 m at rest and during a symptom-limited cycle-ergometer CWRET to exhaustion at 60% of maximal work-rate (Ergoselect100;

Geratherm, Germany), which was terminated when pedalling frequency was exhaustive <40 rpm or after 30 min [17].

The following echocardiographic parameters (CX50; Philips Respironics, Switzerland) were assessed at rest and repetitively during exercise according to guidelines [18]: fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), stroke volume (SV)=the left ventricular outflow tract (LVOT) velocity time integral×π×(LVOT diameter/2)^2) and CO=SV×heart rate. TRPG was derived using the simplified Bernoulli equation $\Delta P=4\times V^2_{max}$. Resting right atrial pressure (RAP) was estimated from the respiratory variability of the inferior vena cava and assumed constant during exercise, despite potential exercise-induced RAP change [19]. Systolic PAP was calculated as TRPG+RAP and mean PAP=0.61×systolic PAP+2 [20]. Pulmonary artery wedge pressure (PAWP) was computed by 1.24×(E/E′) +1.9 [21]. PVR was calculated by (mean PAP – PAWP)/CO [18]. The TRPG/CO was used as simplified surrogate during exercise [22].

Radial artery blood was sampled at rest and end-exercise and immediately analysed (ABL90 Flex; Radiometer, Switzerland). Oxygen content (C_{aO_2}) was calculated by (haemoglobin×1.36×(arterial oxygen saturation (S_{aO_2})/100))+((7.5×P_{aO_2})×0.0031) and multiplied by CO for oxygen delivery (D_{aO_2}) [23].

Heart rate, breathing rate and fingertip S_{pO_2} were recorded continuously by Alice-PDX (PhilipsRespironics, Switzerland). Cerebral (CTO) and muscle tissue oxygenation (MTO) were assessed by near-infrared spectroscopy (NIRS) (NIRO-200NX; Hamamatsu, Japan) at the forehead and quadriceps lateralis during CWRET, as described [24]. Additionally, subjects underwent continuous assessments of systemic blood pressure by continuous finger-cuff manometry (Finapres Medical Systems, the Netherlands) [25].

The Borg category ratio (CR)-10 dyspnoea and leg fatigue scale was assessed at end-exercise [26].

Outcomes

The primary outcome was the difference in CWRET-time at 2500 m compared to 470 m. Additional outcomes were differences of earlier-described assessments at rest, end-exercise and pre-defined isotimes at 3 and 6 min of exercise.

Sample size estimation

To detect a minimal clinically important difference in CWRET-time of 1.75±1.7 min suggested for COPD with a power of 0.8 (α=0.05), 18 patients were required [27]. As the dropout rate in a logistically demanding study was not known, we scheduled 28 participants to participate.

Randomisation and blinding

Randomisation was performed balanced in blocks of four using Stata software (version 16; TX, USA). Due to study settings, blinding was not possible; however, investigators were blinded for the data analysis including echocardiography.

Data analysis and statistics

Data are summarised as mean±SD and mean difference (95% CI). Comparisons between outcomes at 2500 m and 470 m were performed using the t-test for matched pairs. The analysis of the main outcome was by intention to treat (ITT), where patients not able to exercise due to ARAHE were set as 0 min CWRET time. In addition, the primary outcome was analysed by a linear mixed-effect regression model. Secondary outcomes were analysed per protocol. Continuous data from Finapres, PDX and NIRS were imported in LabChart, and averaged over 30 s at specific time points. Predictors of the change in CWRET-time were explored by univariate and multivariable linear regression models together with age, sex and allocation sequence. A two-sided p-value <0.05 was considered as statistically significant. The statistical analysis was conducted in Stata.

Results

Patients

Out of 124 patients assessed for eligibility from outpatient consultations and mouth-to-mouth advertising, 28 were recruited and all completed this trial without any dropouts. Baseline characteristics and resting measurements are shown in tables 1 and 2 and the patient flow in figure 1.

The day-trip to 2500 m was well tolerated. Three out of (10.7%) 28 patients fulfilled the pre-defined safety criteria and received oxygen therapy (2–3 L·min^{-1}) and did not undergo further testing at 2500 m.

TABLE 1 Patient characteristics

Patients total/female	28/13 (46)
Age, years	63±15
Body mass index, kg·m^{-2}	24.9±4.0
Pulmonary hypertension classification	
1 Pulmonary arterial hypertension	15 (54)
1.1 Idiopathic	13 (46)
1.4.1 Connective tissue disease associated	1 (4)
1.4.3 Portal hypertension	1 (4)
4 Chronic thromboembolic pulmonary hypertension	13 (46)
Inoperable	6 (21)
Post-endarterectomy	4 (14)
Potentially operable, patients yet undecided	2 (7)
6-min walk distance, m	558±95
NYHA functional class I, II, III	9 (32), 14 (50), 5 (18)
N-terminal pro-brain natriuretic peptide, ng·L^{-1}	412±583
Maximal incremental ramp cycle exercise, W	121±43
Maximal oxygen uptake, mL·min^{-1}·kg^{-1}	18.5±4
Resting arterial partial pressure of oxygen, kPa	10.4±1.5
Pulmonary vascular resistance, WU	5.8±2.8
Mean pulmonary arterial pressure, mmHg	39±11
PH targeted therapy	
Endothelin receptor antagonist	18 (64)
Phosphodiesterase-5 inhibitor	13 (46)
Soluble guanylate cyclase stimulators	10 (36)
Prostacyclin receptor agonist or prostacyclin	3 (11)
Combination therapy	8 (29)

Data are presented as n (%) or mean±SD. NYHA: New York Heart Association; PH: pulmonary hypertension.

Primary outcome

The ITT analysis based mean CWRET-time at 470 m was 23.9±8.9 min and at 2500 m was 17.4 ±11.3 min, with a mean difference (95% CI) of −6.4 (−9.5 to −3.3) min (p<0.001) (table 3). In a mixed-effect linear regression model evaluating the CWRET-time including intervention altitude and the randomisation order, the order had no significant effect on the CWRET-time (supplementary table S1). 16 patients revealed a reduced CWRET-time at 2500 m *versus* 470 m by more than the pre-defined minimal important difference of 1.75 min [27], 10 revealed similar CWRET-times and two had improved CWRET-times (figure 2). Per-protocol analysis of 25 patients after exclusion of the three patients that did not cycle at altitude (because they received oxygen according to safety criteria) revealed a mean CWRET-time at 470 m of 25.6±7.1 min and at 2500 m of 19.5±10.1 min (mean difference −6.1, 95% CI −9.2 to −2.9 min; p<0.001). In a mixed-effect linear regression model with change in CWRET-time (min) as dependent variable, a predefined p-value <0.1 in univariable models could not be found and therefore multivariable models were not further investigated (supplementary table S2a).

Additional outcomes

Assessments at rest are shown in table 2 and at end-exercise in table 3. At rest after >3 h at 2500 m *versus* 470 m, S_{pO_2}, S_{aO_2}, P_{aCO_2}, P_{aO_2} and C_{aO_2} were reduced, whereas the pH, hydrogen carbonate and D_{aO_2} were increased.

Exercise at altitude was associated with a lower blood oxygenation and a higher increase in lactate (difference of the change 2 mmol·L^{-1}, 95% CI 0–3 mmol·L^{-1}; p=0.009), a smaller decrease in P_{aO_2} (2 kPa, 0 to 3 kPa; p=0.011) but a higher decrease in C_{aO_2} (−1 mg·dL^{-1}, −2 to 0 mg·dL^{-1}; p<0.001) and a smaller increase in D_{aO_2} (−193 mL·min^{-1}, −357 to −28 mL·min^{-1}; p=0.021). CTO and MTO were similar at both altitudes at rest and end-exercise. During exercise, CTO decreased at both altitudes, whereas MTO decreased only at 2500 m (figure 3).

Heart rate was significantly higher at 2500 m *versus* 470 m at rest and end-exercise, whereas breathing rate was similar. At both altitudes, heart rate and breathing rate significantly increased during exercise to a similar extent. The TRPG, CO, TRPG/CO and PVR at rest were significantly higher at 2500 m *versus* 470 m. The RAP, SV, D_{aO_2}, TAPSE and FAC were similar. At end-exercise, the TRPG and CO were higher at 2500 m *versus* 470 m; other haemodynamics including the pressure–flow slope (TRPG/CO) (figure 4) were unchanged; and haemodynamic changes during exercise were similar at both altitudes.

TABLE 2 Resting assessments after >3 h at high altitude (2500 m) *versus* low altitude (470 m)

	Low altitude (470 m)	High altitude (2500 m)	2500 m *versus* 470 m	p-value
Noninvasive blood and tissue oxygenation				
Pulse oximetry, %	94±2	87±8	−7 (−10 to −4)	<0.001
Cerebral tissue oxygen saturation, %	61±12	61±9	1 (−4 to 5)	0.707
Muscular tissue oxygen saturation, %	67±11	66±9	−1 (−5 to 2)	0.506
Arterial blood gases				
pH	7.45±0.03	7.50±0.04	0.04 (0.03 to 0.06)	<0.001
Partial pressure of carbon dioxide, kPa	4.6±0.6	4.3±0.6	−0.3 (−0.4 to −0.1)	<0.001
Partial pressure of oxygen, kPa	10.4±1.5	7.3±0.8	−3.2 (−3.6 to −2.8)	<0.001
Hydrogen carbonate, mmol·L^{-1}	25.0±2.8	26.0±1.8	1.2 (0.3 to 2.0)	0.007
Lactate, mmol·L^{-1}	0.8±0.4	0.9±0.3	0.1 (−0.1 to 0.2)	0.450
Haemoglobin, g·dL^{-1}	14.7±1.6	14.9±1.3	0.2 (−0.1 to 0.6)	0.235
Arterial oxygen saturation, %	94±2	88±4	−6 (−7 to −5)	<0.001
Arterial oxygen content, mL·dL^{-1}	19±2	18±2	−1 (−2 to 0)	<0.001
Circulatory and respiratory parameters by polygraphy (PDX) and finger-cuff manometry (Finapres)				
Heart rate, beats·min^{-1}	71±16	86±18	15 (7 to 23)	<0.001
Breathing rate, breaths·min^{-1}	19±5	20±6	1 (−1 to 4)	0.373
Systolic arterial pressure, mmHg	112±23	119±27	8 (−1 to 16)	0.068
Diastolic arterial pressure, mmHg	69±18	76±16	7 (−2 to 17)	0.136
Echocardiography				
TRPG, mmHg	40±15	56±25	17 (9 to 24)	<0.001
Right atrial pressure, mmHg	4±3	5±3	1 (−1 to 2)	0.363
Systolic pulmonary arterial pressure, mmHg	44±17	60±25	17 (9 to 25)	<0.001
Stroke volume, mL	73±15	75±18	2 (−4 to 8)	0.556
CO, L·min^{-1}	4.6±1.0	5.3±1.3	0.8 (0.4 to 1.2)	<0.001
Oxygen delivery, mL·min^{-1}	980±214	1148±410	174 (8 to 339)	0.040
Pulmonary vascular resistance, WU	4.0±3.0	5.2±3.9	1.4 (0.2 to 2.7)	0.025
TRPG/CO, WU	8.1±4.5	9.8±6.0	1.7 (0.1 to 3.3)	0.040
Tricuspid annular plane systolic excursion, cm	2.0±0.4	2.1±0.3	0.0 (−0.1 to 0.2)	0.650
Fractional area change, %	30±12	32±10	2 (−1 to 7)	0.209

Data are presented as mean±SD or mean difference (95% CI), unless otherwise stated. CO: cardiac output; TRPG: tricuspid regurgitation pressure gradient.

Logistic regression to predict a difference in cycling time >1.75 min at 2500 m *versus* 470 m revealed no significant predictors (also not the diagnostic group (PAH/CTEPH)) with p-values <0.1 univariable, therefore multivariable effects were not further investigated (supplementary table S2b).

At isotime 3 and 6 min of CWRET at 2500 m *versus* 470 m, S_{pO_2} was lower, whereas heart rate was higher (supplementary table S3). At isotime 3 min at 2500 m *versus* 470 m, echocardiographically assessed PAP and CO were higher, whereas PVR and TRPG/CO were unchanged, at isotime 6 min; the only remaining difference was a higher CO at 2500 m (supplementary table S3).

Discussion

This randomised crossover trial in patients with stable PAH/CTEPH revealed that a day-trip to moderate altitude of 2500 m was well tolerated by 25 (89%) out of 28 patients. Three patients revealed significant hypoxaemia, which improved immediately with oxygen therapy given according to safety rules. The mean CWRET cycling-time significantly decreased by 6.4 min (22.9%) at altitude with large interindividual variability (figure 3). The TRPG was increased at high *versus* low altitude at rest and during exercise along with an increased heart rate and CO, but with unchanged pressure–flow slope during exercise and symptoms by Borg dyspnoea scale. We found no significant predictors among measures at low altitude for clinically relevant reduction in CWRET time >1.75 min during the altitude sojourn (supplementary table S2b).

It is known from several studies that exercise performance is reduced with increasing altitude in healthy individuals and to an even greater extent in patients with chronic cardiorespiratory diseases [4, 28, 29]. In the present study, we extend these findings by showing for the first time the decrement in exercise performance at altitude in patients with PAH/CTEPH. Compared to patients with moderate to severe COPD experiencing a 54% reduction in CWRET-time at 2590 m [30], the corresponding reduction of

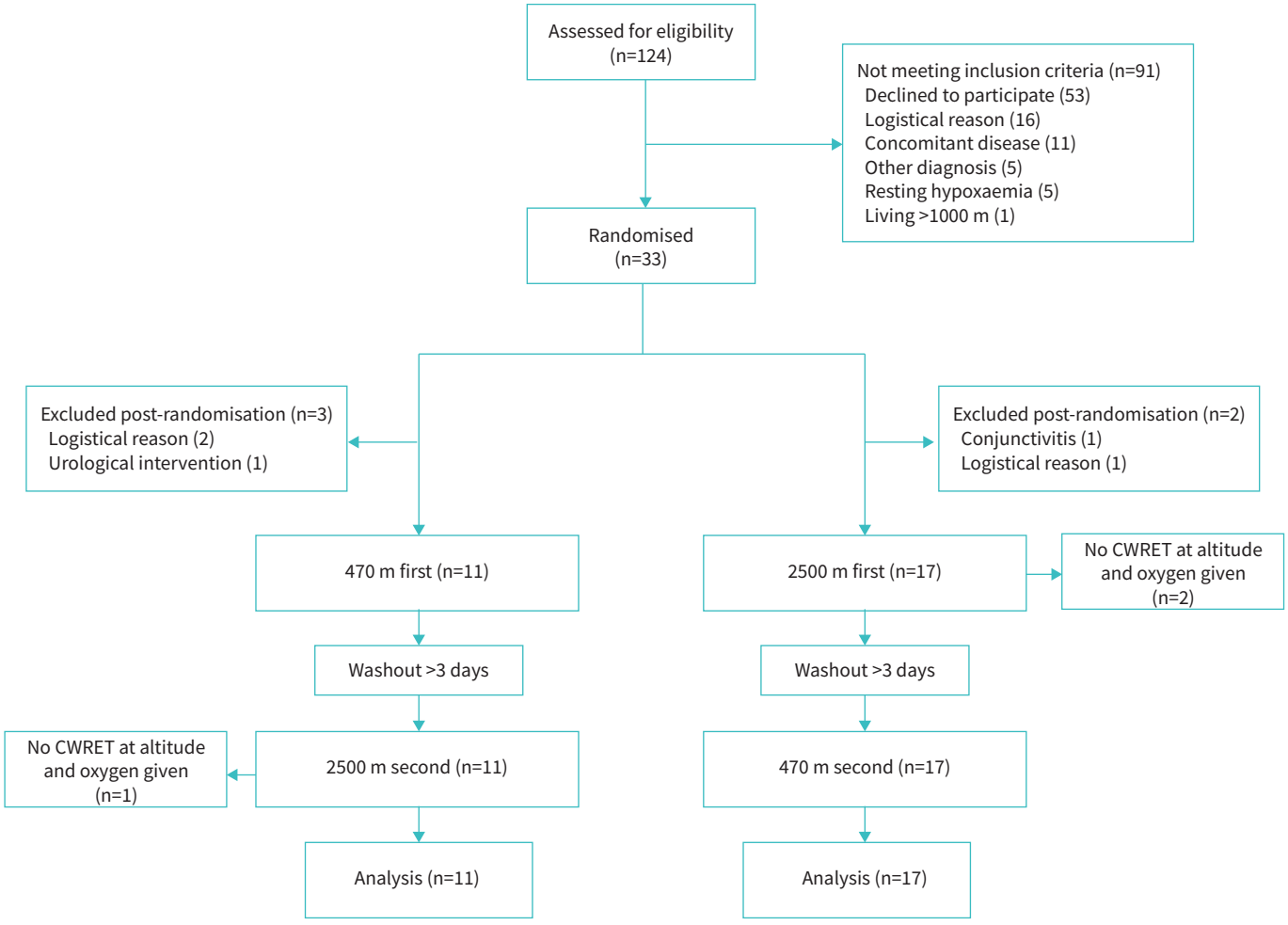

FIGURE 1 Patient flow. CWRET: constant work-rate exercise test.

22.9% we observed in patients with PH at similar altitude was less pronounced, but similar to the reduction in CWRET time of 25.8% reported in elite cyclists at 2340 m [31]. Of interest, in a recent study in patients with PH exposed to normobaric hypoxia (F_{IO_2} 15%) for 30–60 min corresponding to an altitude equivalent of 2500 m we found that the CWRET cycling-time was reduced by 7% [14], *i.e.* to a lesser extent compared to patients in the current study exposed to a comparably reduced inspiratory oxygen partial pressure at real altitude, but for a considerably longer time of 6–7 h. In parallel, a pilot trial investigating nine patients with PAH/CTEPH at 2048 m found a reduction in 6MWD and CWRET-time compared to 490 m [32]. Presumably, the longer hypoxia exposure in association with a more pronounced oxygen desaturation in the current study at real altitude compared to the simulation study (end-exercise S_{pO_2} 82% *versus* 87%) contributed to an earlier exhaustion during CWRET. However, exposure to the hypobaric hypoxic environment at altitude in this stable, nonhypoxaemic PH collective in NYHA functional class I–III was safe for the vast majority of patients, with only three (~10%) out of 28 needing oxygen therapy according to pre-defined safety criteria. In the presently investigated PH patient, altitude exposure was associated with an expected significant drop in arterial oxygenation at rest and end-exercise, which may have significantly contributed to exercise cessation in regard of the similar dyspnoea at end-exercise. Consistent with the more severe hypoxaemia and consecutive anaerobic metabolism, the exercise-induced rise in lactate concentration of 5.0 $mmol \cdot L^{-1}$ at 2500 m (table 3) was greater than the corresponding rise in lactate of 3.0 $mmol \cdot L^{-1}$ in the previous study with short-term exposure to normobaric hypoxia [30]. End-exercise blood oxygenation was lower at altitude, as well as resting blood oxygenation, despite the reduced exercise time.

The PAP was significantly higher at 2500 m *versus* 470 m both at rest and at end-exercise along with an increased CO, related to the increased heart rate, and a higher PVR at rest, but not end-exercise as assessed

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TABLE 3 Symptom-limited maximal cycling constant work-rate exercise test (CWRET) at high altitude (2500 m) *versus* low altitude (470 m)

	End-exercise low altitude (470 m)	Change from rest to end-exercise	p-value	End-exercise high altitude (2500 m)	Change from rest to end-exercise	p-value	Difference at end-exercise 2500 m *versus* 470 m	p-value
CWRET cycling time, min	23.9±8.9			17.4±11.3			−6.4 (−9.5 to −3.3)	<0.001
CWRET cycling time percentage of value at 470 m, %	100.0±0.0			77.1±31.6			−22.9 (−35.1 to −10.8)	<0.001
Noninvasive blood and tissue oxygenation								
Pulse oximetry, %	89±4	−5 (−7 to −3)	<0.001	82±5	−5 (−9 to −1)	0.017	−8 (−10 to −5)	<0.001
Cerebral tissue oxygen saturation, %	59±12	−3 (−5 to −1)	0.011	57±10	−4 (−8 to −1)	0.023	−1 (−5 to 4)	0.758
Muscular tissue oxygen saturation, %	66±11	−1 (−5 to 2)	0.469	62±10	−4 (−7 to −1)	0.007	−4 (−8 to 1)	0.107
Arterial blood gases								
pH	7.44±0.03	−0.02 (−0.01 to −0.03)	0.009	7.45±0.04	−0.04 (−0.01 to −0.04)	<0.001	0.01 (0.00 to 0.03)	0.065
Partial pressure of carbon dioxide, kPa	4.3±0.7	−0.3 (−0.1 to −0.4)	0.003	3.9±0.6	−0.4 (−0.1 to −0.5)	0.001	−0.3 (−0.5 to −0.2)	<0.001
Partial pressure of oxygen, kPa	8.3±1.2	−2.0 (−0.4 to −1.8)	<0.001	6.2±1.2	−1.0 (−1.5 to −0.5)[#]	0.001	−2.2 (−2.6 to −1.8)	<0.001
Hydrogen carbonate, mmol·L^{-1}	23.2±2.4	−2.3 (−0.3 to −1.3)	<0.001	22.3±2.6	−3.9 (−0.5 to −2.0)	<0.001	−0.7 (−1.6 to 0.1)	0.096
Lactate, mmol·L^{-1}	3.8±1.7	2.8 (−0.3 to −1.3)	<0.001	5.9±2.7	5.0 (3.9 to 6.1)[#]	<0.001	2.1 (1.3 to 2.8)	<0.001
Haemoglobin, g·dL^{-1}	15.5±1.3	0.8 (−0.1 to −0.6)	<0.001	15.7±1.4	0.8 (0.6 to 0.9)	<0.001	0.2 (−0.1 to 0.5)	0.260
Arterial oxygen saturation, %	91±4	−3 (−5 to −2)	<0.001	81±7	−8 (−11 to −4)	<0.001	−10 (−12 to −8)	<0.001
Arterial oxygen content, mL·dL^{-1}	19±2	0 (−0 to 1)	0.156	17±2	−1 (−1 to −0)[#]	0.028	−2 (−3 to −2)	<0.001
Circulatory and respiratory parameters by PDX and Finapres								
Heart rate, beats·min^{-1}	116±26	45 (34 to 55)	<0.001	130±20	44 (36 to 52)	<0.001	15 (7 to 23)	<0.001
Breathing rate, breaths·min^{-1}	32±6	12 (10 to 15)	<0.001	31±7	11 (6 to 15)	<0.001	−1 (−4 to 3)	0.708
Systolic arterial pressure, mmHg	128±28	14 (3 to 24)	0.012	134±30	15 (3 to 28)	0.017	8 (−4 to 20)	0.213
Diastolic arterial pressure, mmHg	81±14	12 (3 to 21)	0.010	86±21	9 (0 to 18)	0.051	5 (−5 to 15)	0.317
Echocardiography								
TRPG, mmHg	65±29	25 (16 to 35)	<0.001	84±30	28 (20 to 36)	<0.001	18 (9 to 27)	<0.001
Systolic PAP, mmHg	69±30	26 (16 to 36)	<0.001	88±31	28 (20 to 36)	<0.001	18 (9 to 28)	<0.001
Stroke volume, mL	82±16	9 (6 to 12)	<0.001	81±21	6 (3 to 10)	0.002	−1 (−9 to 7)	0.837
CO, L·min^{-1}	9.4±2.4	4.3 (3.4 to 5.2)	<0.001	10.5±2.5	4.0 (3.3 to 4.8)	<0.001	1.1 (0.1 to 2.1)	0.036
Oxygen delivery, mL·min^{-1}	1958±360	936 (762 to 1111)	<0.001	1825±493	629 (401 to 857)[#]	<0.001	−98 (−310 to 114)	0.365
Pulmonary vascular resistance, WU	4.3±3.1	0.3 (−0.6 to 1.2)	0.492	4.8±2.9	−0.5 (−1.2 to 0.3)	0.195	0.7 (−0.2 to 1.6)	0.120
TRPG/CO, WU	7.1±3.4	−0.6 (−1.9 to 0.7)	0.348	8.4±3.9	−0.9 (−2.1 to 0.3)	0.117	1.2 (0.0 to 2.5)	0.050
TRPG/CO slope during exercise, WU		8.0±4.8			5.1±19.7		−2.5 (−10.2 to 5.3)	0.533
Tricuspid annular plane systolic excursion, cm	2.4±0.2	0.6 (0.4 to 0.8)	<0.001	2.4±0.5	0.6 (0.3 to 0.8)	0.001	0 (−0.3 to 0.2)	0.749
Patient-reported outcomes under exercise								
Borg dyspnoea scale	4.5±2.5	4.1 (3.2 to 5)	<0.001	5.0±2.7	4.3 (3.3 to 5.4)	<0.001	0.3 (−0.1 to 0.6)	0.117
Borg leg fatigue scale	4±2.7	3.7 (2.7 to 4.7)	<0.001	4.4±2.8	3.9 (2.8 to 5)	<0.001	0.2 (−0.1 to 0.5)	0.195

Data are presented as mean±SD or mean difference (95% CI), unless otherwise stated. TRPG: tricuspid regurgitation pressure gradient; PAP: pulmonary artery pressure; CO: cardiac output. [#]: significant difference of changes during exercise at 2500 m *versus* 470 m.

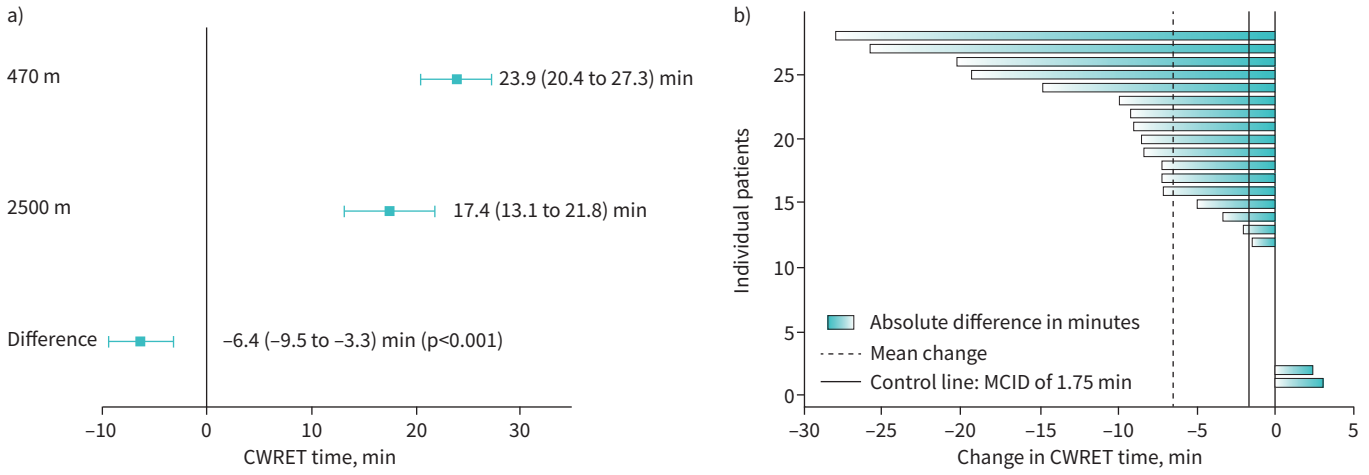

FIGURE 2 Constant work-rate exercise test (CWRET) time at altitude in pulmonary hypertension. a) The CWRET cycling time at low altitude (470 m), high altitude (2500 m) and the difference between altitudes presented as mean (95% CI) in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. b) The individual changes of cycling time at 2500 m *versus* 470 m. The dashed line reflects the mean change of −6.4 (−9.5 to −3.3) min (p<0.001); vertical lines at ±1.75 min reflect the minimal clinical important difference (MCID) of CWRET time as suggested for patients with COPD.

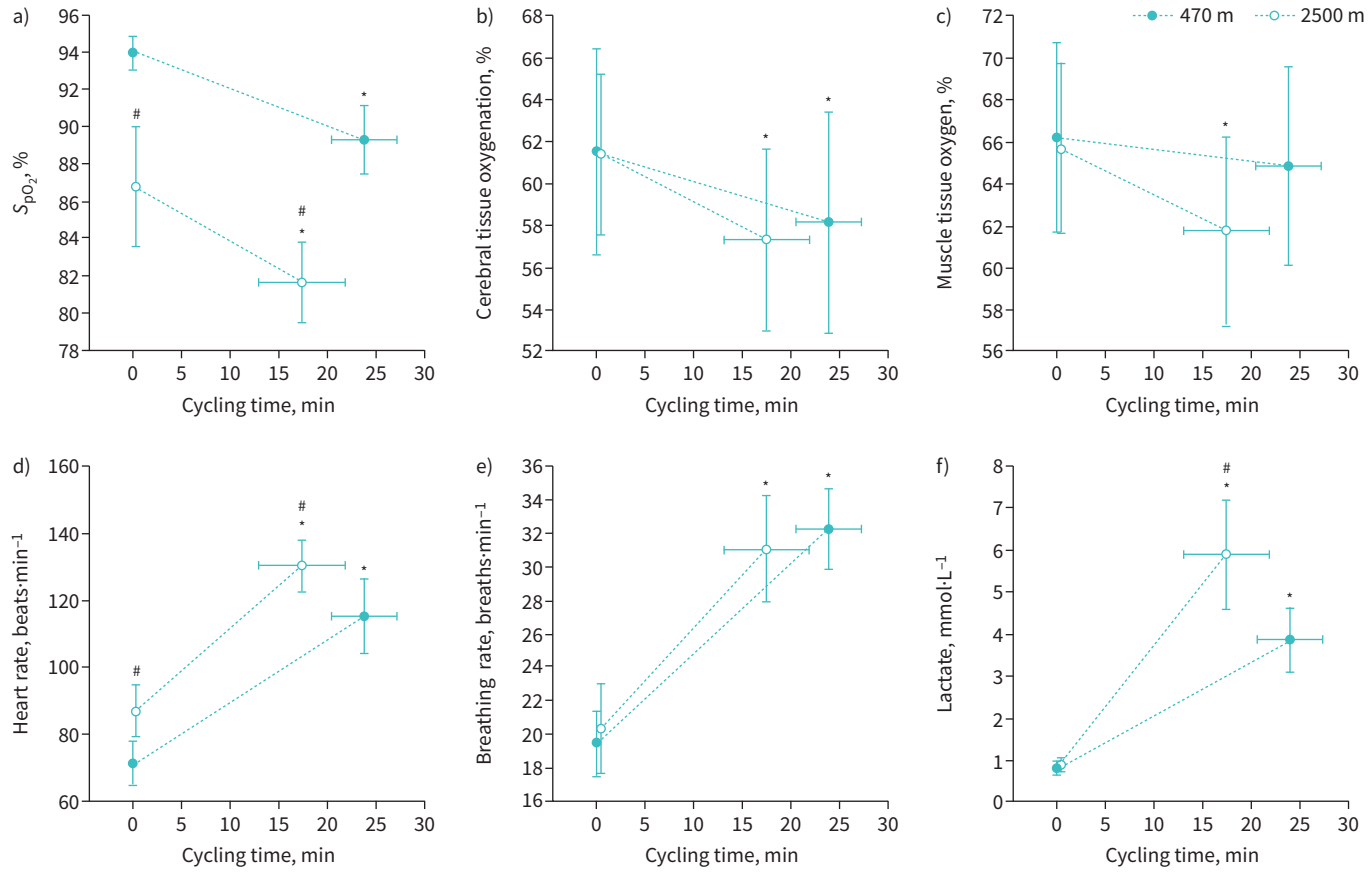

FIGURE 3 Effects of altitude exposure on physiological parameters during the constant work-rate cycle exercise test. The bidirectional error bars indicate 95% confidence intervals. S_{pO_2}: peripheral oxygen saturation. #: p<0.05 at 2500 m compared to 470 m; *: p<0.05 at end-exercise compared to rest (t-test).

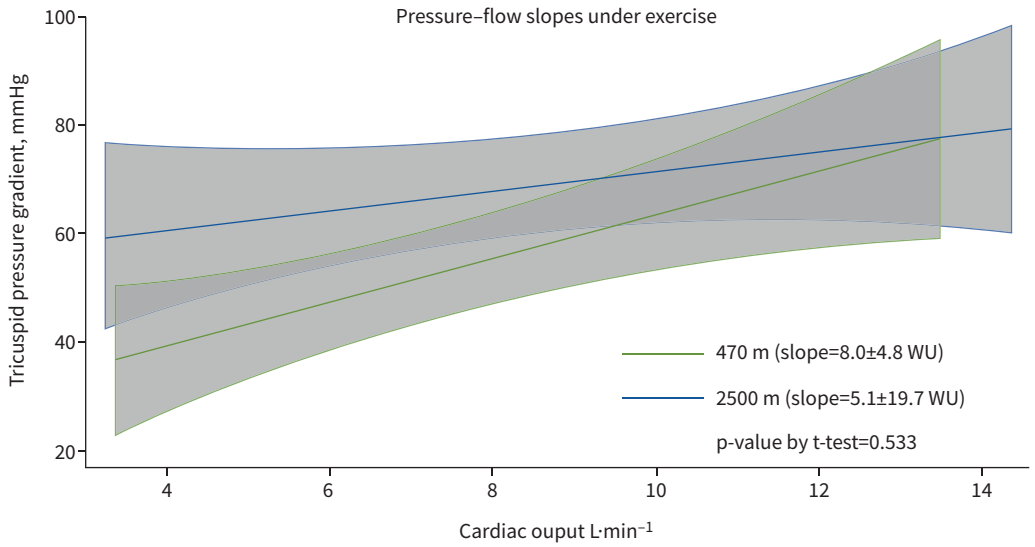

FIGURE 4 Pulmonary artery pressure–flow slopes as tricuspid regurgitation pressure gradient to cardiac output ratio during constant work-rate cycle exercise tests at 470 m and 2500 m shown as mean (95% CI).

by echocardiography. The higher TRPG and PVR at rest suggests that the effect of HPV was present after >3 h at altitude, which is consistent with existing literature [33, 34], although in previous studies PAP remained unchanged by exposing patients with pre-capillary PH to normobaric hypoxia for 20 min [12] and with consecutive CWRET [14] which was probably related to the shorter exposure. The similar change of the TRPG and CO with exercise at both altitudes resulted in an unchanged pressure–flow slope during exercise at 2500 m *versus* 470 m. Since a steeper increase in TRPG/CO slope was linked to worse survival, the similar slope found in our study may be a sign that a short-term exposure to a comparable altitude does not acutely harm the cardiopulmonary system; however, our study was not powered to firmly address safety in PH patients going to altitude [16]. In regard of the reduced exercise-time at high *versus* low altitude, but the similar or slightly increased resistances at end-exercise, the pulmonary circulation may have contributed to exercise limitation along with the blood and tissue hypoxaemia.

The significantly lower P_{aCO_2} at rest and end-exercise at 2500 m *versus* 470 m was probably due to the adaptively increased ventilation, although the breathing rate in our trial was similar, but tidal volume and thus minute ventilation was not assessed [28, 35]. In addition to the lower P_{aCO_2}, the adaptive response was shown by the increased heart rate at rest and during exercise, resulting in a higher CO, as measured by echocardiography at rest and end-exercise at 2500 m *versus* 470 m. This resulted in an increased D_{aO_2} at rest, but not end-exercise at 2500 m *versus* 470 m. The increase in D_{aO_2} during cycling exercise was higher at 470 m compared to 2500 m, potentially contributing to the longer exercise time (table 3). The similar D_{aO_2} at end-exercise in the presently investigated PH patients is in line with our previous study investigating PH patients under normobaric hypoxia *versus* ambient air, but also in PH patients breathing oxygen-enriched air [10, 14].

CTO and MTO did not differ between altitudes. Thus, it seems that adaptive mechanisms protected the brain and skeletal muscle from deoxygenation during symptom-limited exercise at altitude, which can probably be explained by the preserved D_{aO_2} due to the increased heart rate and herewith CO and/or preferential redistribution of blood flow to working muscles and the brain [36]. The unchanged MTO during CWRET at 470 m may indicate that the reason for stopping was unrelated to muscular deoxygenation. In contrast, muscular and cerebral deoxygenation may well have contributed to exercise limitation at altitude, which is further supported by the significantly higher lactate. Our previous study in PH patients under short-term normobaric hypoxia showed comparable results [14]; however, COPD patients at similar altitude revealed a reduction in CTO and MTO [30].

Limitations

The presently investigated PH population was relatively low risk (23 out of 28 with NYHA class I or II), stable, nonhypoxaemic and comparably fit [37]. Thus, the present finding may not apply for patients with

more severe or unstable disease and higher functional class. The chosen work-rate of 60% W_{max} for the CWRET might have been relatively low at 470 m, but it was selected to assure that the majority of PH patients would be able to cycle at least for some minutes at 2500 m.

Interpretation

This first randomised-sequence crossover trial in stable, nonhypoxaemic PH patients exposed to an altitude of 2500 m during a day-trip reveals that the vast majority of patients tolerated the hypoxic environment well, but CWRET-cycling time was moderately reduced by almost a quarter, albeit with high interindividual variability. However, the TRPG reflecting PAP significantly increased with altitude at rest and during exercise, along with increased CO, driven by the increased heart rate; the pressure–flow slope during exercise was similar. Along with similar dyspnoea at end-exercise, the more pronounced hypoxaemia and lactic acidosis, exercise limitation was combined due to peripheral hypoxia and cardiopulmonary limitation. These novel findings represent long-needed evidence required to counsel stable nonhypoxaemic PH patients planning travel to altitude and to plan further studies including larger cohorts of PH patients traveling to altitude in order to investigate longer-term physiological, clinical and altitude-related adverse health effects.

Provenance: Submitted article, peer reviewed

This study is registered at www.clinicaltrials.gov with identifier number NCT03637153.

Data availability: Individual participants' data that underlie the results reported in this article will be shared after deidentification upon request for investigations whose proposed use of data has been approved by an independent review board for potential meta-analysis.

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