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Please cite this article as: Schneider SR, Mayer LC, Lichtblau M, *et al*. Effect of a daytrip to altitude (2500 m) on exercise performance in pulmonary hypertension – randomized cross-over trial. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00314-2021).

# Effect of a daytrip to altitude (2500m) on exercise performance in pulmonary hypertension – randomized cross-over trial

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**Take home**

Short-time exposure to high altitude in pulmonary hypertension induced hypoxemia, reduced constant work-rate cycle time compared to ambient air and was overall well tolerated.

**Keywords**

High altitude, exercise testing, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, echocardiography, randomized controlled trial (RCT)

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 randomized crossover trial in stable (same therapy for >4 weeks) patients with pulmonary arterial or chronic thromboembolic PH (PAH/CTEPH) with resting $PaO_2$ ≥7.3kPa, we compared symptom-limited constant work-rate exercise test (CWRET) cycling time during a daytrip to 2500m vs. 470m. Further outcomes were symptoms, oxygenation and echocardiography. For safety, patients with sustained hypoxemia at altitude ($SpO_2$<80% >30min or <75% >15min) received oxygen therapy. (ClinicalTrials.gov: NCT03637153)

Results

28 PAH/CTEPH-patients (15/13), 13 females, mean±SD age 63±15y were included. After >3h at 2500m vs. 470m, CWRET-time was reduced to 17±11 vs. 24±9min (mean-difference 95%CI) -6(-10 to -3) corresponding to -27.6% (-41.1 to -14.1) p<0.001 but similar Borg-dyspnea scale. At altitude, $PaO_2$ was significantly lower (7.3±0.8 vs. 10.4±1.5kPa; -3.2(-3.6 to -2.8)), whereas heart rate and tricuspid regurgitation pressure gradient (TRPG) were higher (86±18 vs. 71±16 bpm; 15(7 to 23) and 56±25 vs. 40±15mmHg; (17(9 to 24)) and remained so until end-exercise, all p<0.001. The TRPG/cardiac output slope during exercise was similar at both altitudes. Overall, 3/28 (11%) patients received oxygen at 2500m due to hypoxemia.

Conclusion

This randomized cross-over study showed that the majority of PH-patients tolerate a daytrip to 2500m well. At high vs. low altitude, the mean exercise time was reduced, albeit with a high inter-individual 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 became easily accessible by car, train or cable car up to >3500m and many large settlements worldwide situated >2000m are approachable by commercial flights pressurized as well up to 2438m (8000ft., barometric pressure 752hPa). However, with increasing hypobaric hypoxic environment at higher altitude, the prevalence of altitude-related adverse health effects (ARAHE) rises in healthy and even more in patients with cardiorespiratory diseases.[1-5]

In our clinical practice, many patients with cardiorespiratory diseases, including patients with pulmonary arterial and chronic thromboembolic pulmonary hypertension (PAH/CTEPH, summarized as PH) seek medical advice concerning hypoxia-related adverse health effects whilst planning sojourns in the nearby altitude settlements. Recent therapeutic advances improved quality of life and physical performance in many patients with PH and obviously, these patients wish to participate in daily activities including popular mountain travel to at least moderate altitude up to 2500m. However, with increasing severity of PH, worsening hemodynamic may lead to hypoxemia, particularly during exertion, sleep and exposure to a hypoxic environment.[6] Thus, current PH guidelines discourage altitude sojourns 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 ($FiO_2$ 0.15, altitude equivalent 2500m) 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 hemodynamics by echocardiography and that PVR resulted as the best predictor for exercise time.[14]

Tricuspid regurgitation pressure gradient/cardiac output (TRPG/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 (2500m) on exercise capacity, symptoms, hemodynamics, and additional physiological measures.

## Material and methods

### Design

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

### Subjects

Adults diagnosed with PAH/CTEPH according to current guidelines[7] were recruited at PH-centre Zurich if they were clinically stable on the same medication for >4 weeks, lived <1000m, were not on long-term oxygen therapy and had a resting $PaO_2$ ≥7.3kPa, and $PaCO_2$ <6.5kPa. Patients who had travelled to >1500m for ≥3 nights during the previous 4 weeks or had relevant comorbidities, were pregnant, breast-feeding, 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 (470m) and during a 6-7h stay at (2500m) in a randomized order, with washout period of at least 3 days at altitude <800m in-between. Transfers between study locations were by a 2-3h trip by shuttle bus and cable car.

### Safety

During the high altitude sojourn, the clinical condition of the patients and pulseoxymetry were continuously monitored. 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 $SpO_2$ <80% >30 minutes or <75% >15 minutes were given oxygen and descent was arranged.

Assessment

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

During the study, assessments were performed at 470m or after >3h at 2500m 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 <40rpm or after 30min.[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 velocity time integral (LVOT VTI)*π*(LVOT diameter/2)$^2$) and cardiac output (CO)=SV*heart rate (HR). TRPG was derived using the simplified Bernoulli equation $\Delta P=4*Vmax^2$. 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 GmbH, Switzerland). Oxygen content ($CaO_2$) was calculated by (Hb*1.36*($SaO_2$/100))+((7.5*$PaO_2$)*0.0031) and multiplied by CO for oxygen delivery ($DaO_2$).[23]

HR, breathing rate (BR) and fingertip $SpO_2$ were continuously recorded by Alice-PDX® (PhilipsRespironics, Switzerland). Cerebral and muscle tissue oxygenation (CTO/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, Netherlands).[25]

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

Outcomes

The primary outcome was the difference in CWRET-time at 2500m compared to 470m.

Additional outcomes were differences of above-described assessments at rest, end-exercise and predefined isotimes at 3 and 6 minutes of exercise.

Sample size estimation

To detect a minimal clinically important difference in CWRET-time of 1.75±1.7min suggested for chronic obstructive pulmonary disease with a power of 0.8 (alpha 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.

Randomization and blinding

Randomization was performed balanced in blocks of 4 using (Stata® statistics, Texas, USA, v16). Due to study settings, blinding was not possible, however investigators were blinded for the data analysis including echocardiography.

Data analysis and statistics

Data are summarized as means±SD and mean-difference (95% CI). Comparisons between outcomes at 2500m and 470m were performed with the student's 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 0min 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 seconds at respective 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 by Stata® statistics, Texas, USA, v16.

## Results

### Patients

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

The daytrip to 2500m was well tolerated. 3/28 (10.7%) of patients fulfilled the predefined safety criteria and received oxygen therapy (2-3 litres/min) and did not undergo further testing at 2500m.

### Primary Outcome

The ITT-analysis based mean CWRET-time at 470m was 23.9±8.9min, at 2500m 17.4±11.3min, 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 randomization order, the order had no significant effect on the CWRET-time (e-table 1). 16 patients revealed a reduced CWRET-time at 2500m vs. 470m by more than the predefined minimal important difference of 1.75min,[27] 10 revealed similar and two improved CWRET-time (figure 2). Per-protocol analysis of 25 patients after exclusion of the 3 patients that did not cycle at altitude as they received oxygen according to safety criteria revealed a mean CWRET-time at 470m of 25.6±7.1 min, at 2500m of 19.5±10.1 min; mean-difference (95%CI) -6.1 (-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 (e-table 2a).

Additional Outcomes

Assessments at rest are shown in table 2, at end-exercise in table 3. At rest after >3 hours at 2500m vs. 470m $SpO_2$, $SaO_2$, $PaCO_2$, $PaO_2$ and $CaO_2$ were reduced, whereas the pH, $HCO^{3-}$ and $DaO_2$ were increased.

Exercise at altitude was associated with a lower blood oxygenation and a higher increase in lactate (difference of the change 2mmol/l (0 to 3), p=0.009), a smaller decrease in $PaO_2$ (2kPa (0 to 3, p=0.011) but a higher decrease in $CaO_2$ (-1mg/dl (-2 to 0), p<0.001) and a smaller increase in $DaO_2$ (-193ml/min (-357 to -28), 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 2500m (figure 3).

HR was significantly higher at 2500m vs. 470m at rest and end-exercise, whereas BR was similar. At both altitudes, HR and BR significantly increased during exercise to a similar extent. The TRPG, CO, TRPG/CO and PVR at rest were significantly higher at 2500m vs. 470m. The RAP, SV, $DaO_2$, TAPSE und FAC were similar. At end exercise, the TRPG and CO were higher at 2500m vs 470m, other hemodynamics including the pressure-flow slope (TRPG/CO) (figure 4) were unchanged and hemodynamic changes during exercise were similar at both altitudes.

Logistic regression to predict a difference in cycling time >1.75 minutes at 2500m vs. 470m revealed no significant predictors, also not the diagnostic group (PAH/CTEPH) with p-values <0.1 univariable, therefore multivariable effects were not further investigated. (e-table 2b)

At isotime 3 and 6 min of CWRET at 2500m vs. 470m, $SpO_2$ was lower whereas HR was higher (e-table 3). At isotime 3min at 2500m vs. 470m, echocardiographically assessed PAP and CO were higher, whereas PVR and TRPG/CO were unchanged, at isotime 6min, the only remaining difference was a higher CO at 2500m. (e-table 3)

## Discussion

The current randomized cross-over trial in patients with stable PAH/CTEPH revealed that a daytrip to moderate altitude of 2500m was well tolerated by 25/28 (89%) of patients. Three patients revealed significant hypoxemia, which improved immediately with oxygen therapy given according to safety rules. The mean CWRET cycling-time significantly decreased by 6.4min (22.9%) at altitude with large inter-individual variability (figure 3). The TRPG was increased at high vs. low altitude at rest and during exercise along with an increased HR and CO but with unchanged pressure-flow slope during exercise and symptoms by Borg dyspnoea scale. We found no significant predictors amongst measures at low altitude for clinically relevant reduction in CWRET time >1.75min during the altitude sojourn (e-table 2b).

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 2590m,[30] the corresponding reduction of 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 2340m.[31] Of interest, in a recent study in patients with PH exposed to normobaric hypoxia ($FiO_2$ 15%) for 30-60min corresponding to an altitude equivalent of 2500m 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 6-7h. In parallel, a pilot-trial investigating 9 patients with PAH/CTEPH at 2048m found a reduction in 6MWD and CWRET-time compared to 490m.[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 $SpO_2$ 82% vs. 87%) contributed to an earlier exhaustion during CWRET. However, exposure to the hypobaric hypoxic environment at altitude in this stable, non-hypoxemic PH-collective in NYHA functional class I-III was for the vast majority of patients safe with only 3/28 (about 10%) needing oxygen therapy according to predefined 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 hypoxemia and consecutive anaerobic metabolism, the exercise-induced rise in lactate concentration of 5.0mmol/l at 2500m (table 3) was greater than the corresponding rise in lactate of 3.0mmol/l in the previous study with short-term exposure to normobaric hypoxia.[30] Not only resting but also end-exercise blood oxygenation was lower at altitude despite the reduced exercise time.

The PAP was significantly higher at 2500m vs. 470m both at rest and at end-exercise along with an increased CO, related to the increased HR, and a higher PVR at rest but not end-exercise as assessed by echocardiography. The higher TRPG and PVR at rest suggests that the effect of HPV was present after >3h at altitude which is consistent with existing literature,[33, 34] although in previous studies PAP remained unchanged by exposing patients with precapillary PH to normobaric hypoxia for 20min [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 2500m vs. 470m. 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- vs. 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 hypoxemia.

The significantly lower $PaCO_2$ at rest and end-exercise at 2500m vs. 470m was most probably due to the adaptively increased ventilation, albeit the BR in our trial was similar, but tidal volume and thus minute ventilation was not assessed.[28, 35] In addition to the lower $PaCO_2$, the adaptive response was also shown by the increased HR at rest and during exercise, resulting in a higher CO, as measured by echocardiography at rest and end-exercise at 2500m vs. 470m. This resulted in an increased $DaO_2$ at rest but not end-exercise at 2500m vs. 470m. The increase in $DaO_2$ during cycling exercise was higher at 470m compared to 2500m, potentially contributing to the longer exercise time (table 3). The similar $DaO_2$ at end-exercise in the presently investigated PH-patients is in line with our previous study investigating PH-patients under normobaric hypoxia vs. ambient air but also in PH-patients whilst breathing oxygen-enriched air.[10, 14]

CTO and MTO did not differ between altitudes. Thus, it seems that adaptive mechanisms protected the brain, but also skeletal muscle from deoxygenation during symptom-limited exercise at altitude, which can probably be explained by the preserved $DaO_2$ due to the increased HR and herewith CO and/or preferential redistribution of blood flow to working muscles and the brain.[36] The unchanged MTO during CWRET at 470m may indicate that the reason for stopping was unrelated to muscular deoxygenation. In contrast, muscular along with 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]

Limitation

The presently investigated PH population was relatively low risk (23/28 with NYHA class I or II), stable, non-hypoxemic 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% Wmax for the CWRET might have been relatively low at 470m but it was selected to assure that the majority of PH-patients would be able to cycle at least for some minutes also at 2500m.

**Interpretation**

This first randomized-sequence crossover trial in stable, non-hypoxemic PH-patients exposed to an altitude of 2500m during a daytrip reveals that the vast majority of patients tolerated the hypoxic environment well, but CWRET-cycling time was moderately reduced by almost one quarter albeit with high inter-individual variability. The TRPG reflecting PAP significantly increased with altitude at rest and during exercise, however, along with and increased CO, driven by the increased HR, the pressure-flow slope during exercise was similar. Along with similar dyspnoea at end-exercise, the more pronounced hypoxemia and lactic acidosis, exercise limitation was combined due to peripheric hypoxia and the cardiopulmonary limitation. These novel findings represent long needed evidence required to counsel stable non-hypoxemic PH patients planning altitude travel 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.

**Acknowledgements**

Guarantor: S. Ulrich is the guarantor and takes responsibility for the content of the manuscript, including the data and analysis.

Author contributions: S. Ulrich, K.E. Bloch and S.R. Schneider contributed to the conception and design. S.R. Schneider, L.C. Mayer, M. Lichtblau, C. Berlier, S. Saxer, E.I. Schwarz, M. Furian, L. Tan, K.E. Bloch and S. Ulrich contributed to acquisition, analysis, or interpretation of data. S.R Schneider and S. Ulrich drafted the manuscript. All authors revised the manuscript critically for important intellectual content.

Financial support: Unrestricted research grant from Actelion SA supported this work.

Disclosure: S.U. reports grants from Johnson and Johnson SA, Switzerland, during the conduct of the study; grants from Swiss National Science Foundation, grants from Zurich Lung, grants and personal fees from Orpha Swiss, personal fees from Actelion SA, personal fees from MSD SA, outside the submitted work. S.R.S., L.C.M., M.L., C.B., E.I.S., S.S., L.T., M.F., and K.E.B. have nothing to disclose.

Role of the sponsor: S Ulrich had a role as the sponsor and the investigator.

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## Table 1. Patient characteristics

| | |
|---|---|
| Patients / women | 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-minute walk distance, m | 558 ± 95 |
| New York Heart Association functional class I,II,III | 9 (32), 14 (50), 5 (18) |
| N-terminal pro brain natriuretic peptide, ng/l | 412 ± 583 |
| Maximal incremental ramp cycle exercise, watts | 121 ± 43 |
| Maximal oxygen uptake, ml/min/kg | 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 shown as number (%) or mean ± SD

## Table 2. Resting assessments after >3 hours at high altitude (2500m) vs. low altitude (470m)

| | Low altitude (470m) | High altitude (2500m) | 2500m vs. 470m | |
|---|---|---|---|---|
| **Parameter** | mean ± SD | mean ± SD | mean difference (95% CI) | p- value |
| **Non-invasive 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 | 25.0 ± 2.8 | 26.0 ± 1.8 | 1.2 (0.3 to 2.0) | 0.007 |
| Lactate, mmol/l | 0.8 ± 0.4 | 0.9 ± 0.3 | 0.1 (-0.1 to 0.2) | 0.450 |
| Haemoglobin, g/dl | 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 | 19 ± 2 | 18 ± 2 | -1 (-2 to 0) | <0.001 |
| **Circulatory and respiratory parameters by polygraphy (PDX) and finger-cuff manometry (Finapres®)** | | | | |
| Heart rate, $min^{-1}$ | 71 ± 16 | 86 ± 18 | 15 (7 to 23) | <0.001 |
| Breathing rate, $min^{-1}$ | 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** | | | | |
| Tricuspid regurgitation pressure gradient (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 |
| Cardiac output (CO), l/min | 4.6 ± 1.0 | 5.3 ± 1.3 | 0.8 (0.4 to 1.2) | <0.001 |
| Oxygen delivery, ml/min | 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 |

CI = Confidence Interval, CO = Cardiac output, SD = standard deviation, TRPG = Tricuspid regurgitation pressure gradient

## Table 3. Symptom-limited maximal cycling constant work-rate exercise test at high altitude (2500m) vs. low altitude (470m)

| Parameter | End-exercise low altitude (470m) | Change from rest to end-exercise | | End exercise high altitude (2500m) | Change from rest to end-exercise | | Difference at end-exercise between 2500m vs. 470m | |
|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | mean difference (95% CI) | p-value | Mean ± SD | mean difference (95% CI) | p-value | mean difference (95% CI) | 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 % of value at 470 m, % | 100.0 ± 0.0 | | | 77.1 ± 31.6 | | | -22.9 (-35.1 to -10.8) | <0.001 |
| **Non-invasive 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 | 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 | 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 | 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 | 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, $min^{-1}$ | 116 ± 26 | 45 (34 to 55) | <0.001 | 130 ± 20 | 44 (36 to 52) | <0.001 | 15 (7 to 23) | <0.001 |
| Breathing rate, $min^{-1}$ | 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** | | | | | | | | |
| Tricuspid regurgitation pressure gradient (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 pulmonary arterial pressure (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 |
| Cardiac output (CO), l/min | 9.4 ± 2.4 | 4.3 (-0.4 to -2.1) | <0.001 | 10.5 ± 2.5 | 4.0 (-0.4 to -1.8) | <0.001 | 1.1 (0.1 to 2.1) | 0.036 |
| Oxygen delivery, ml/min | 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 (-0.6 to -2.9) | 0.348 | 8.4 ± 3.9 | -0.9 (-0.6 to -2.7) | 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 |

CI = Confidence Interval, SD = Standard deviation, * significant difference of changes during exercise at 2500m- vs. 470m

## Figure legends

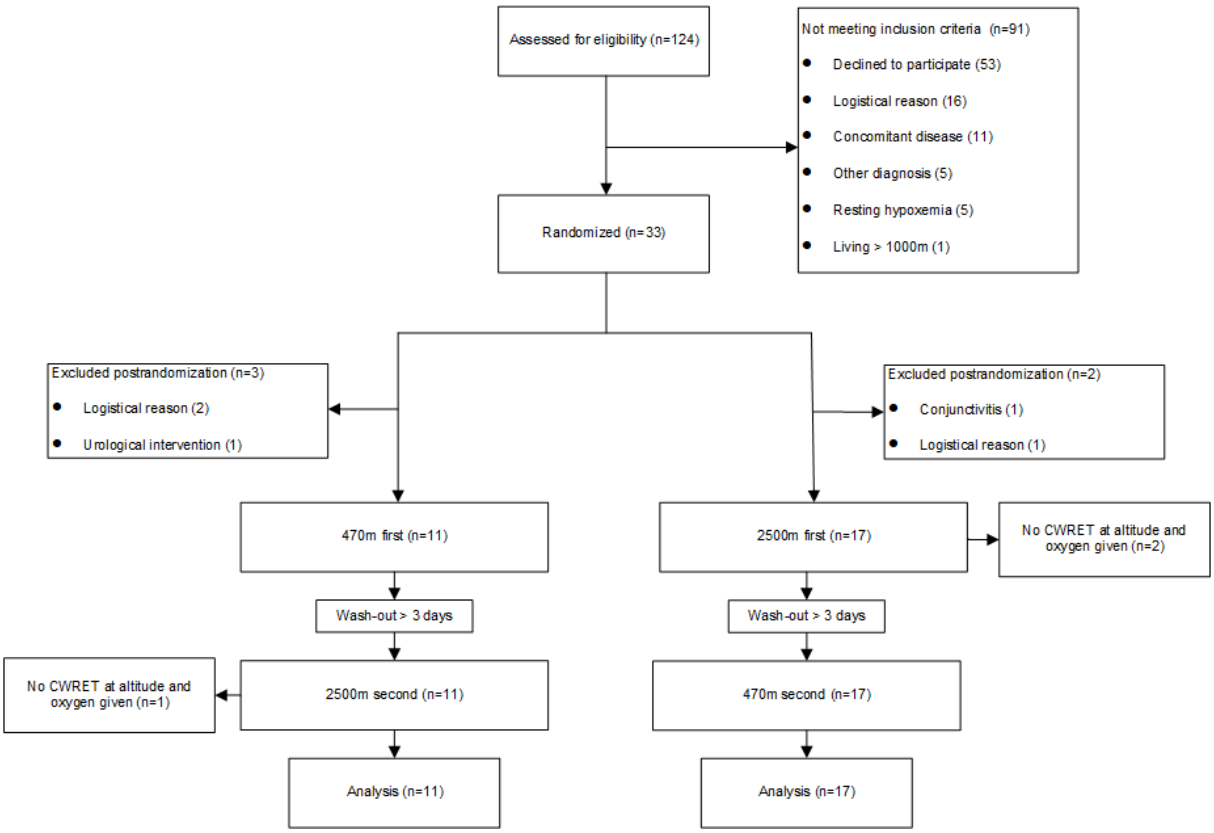


**Figure 1. The patient's flow.**

CWRET = Constant work-rate exercise test

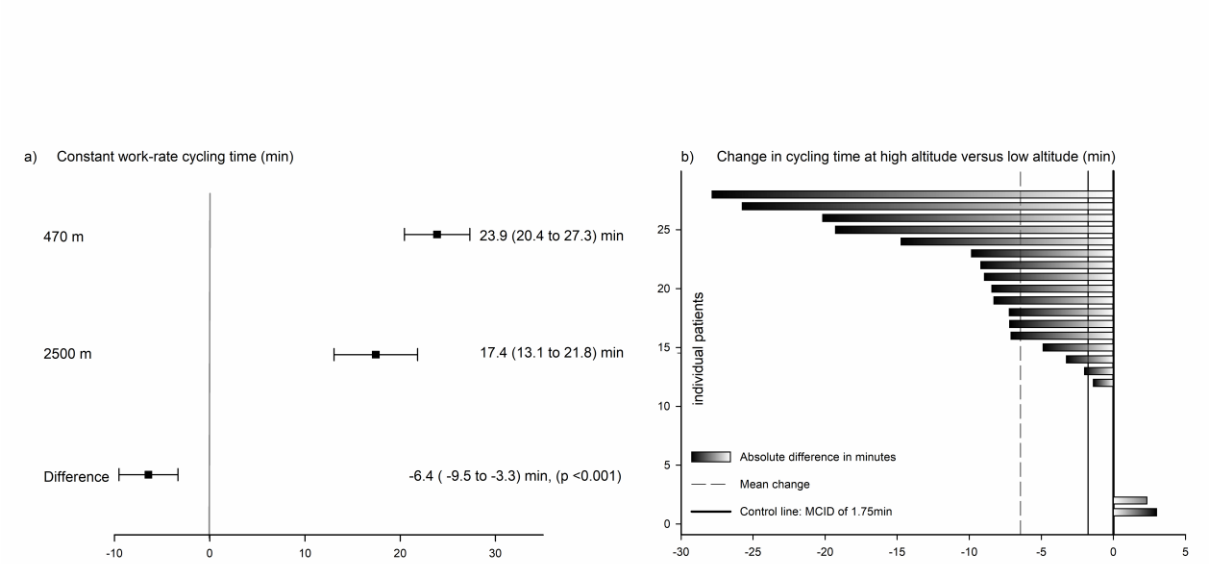


**Figure 2. Constant work-rate exercise test time at altitude in PH:**

Panel a) shows the constant work-rate exercise test cycling time at low altitude (470m), high altitude (2500m) and the difference between altitudes as mean (black square) and 95% confidence intervals (whiskers) in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension.

Panel b) shows the individual changes of cycling time at 2500m vs. 470m. The dashed line reflects the mean change of -6.4 (-9.5 to -3.3) minutes (p=<0.001), vertical lines at ±1.75 min reflect the minimal clinical important difference (MCID) of constant work-rate cycling time as suggested for patients with chronic obstructive pulmonary disease.

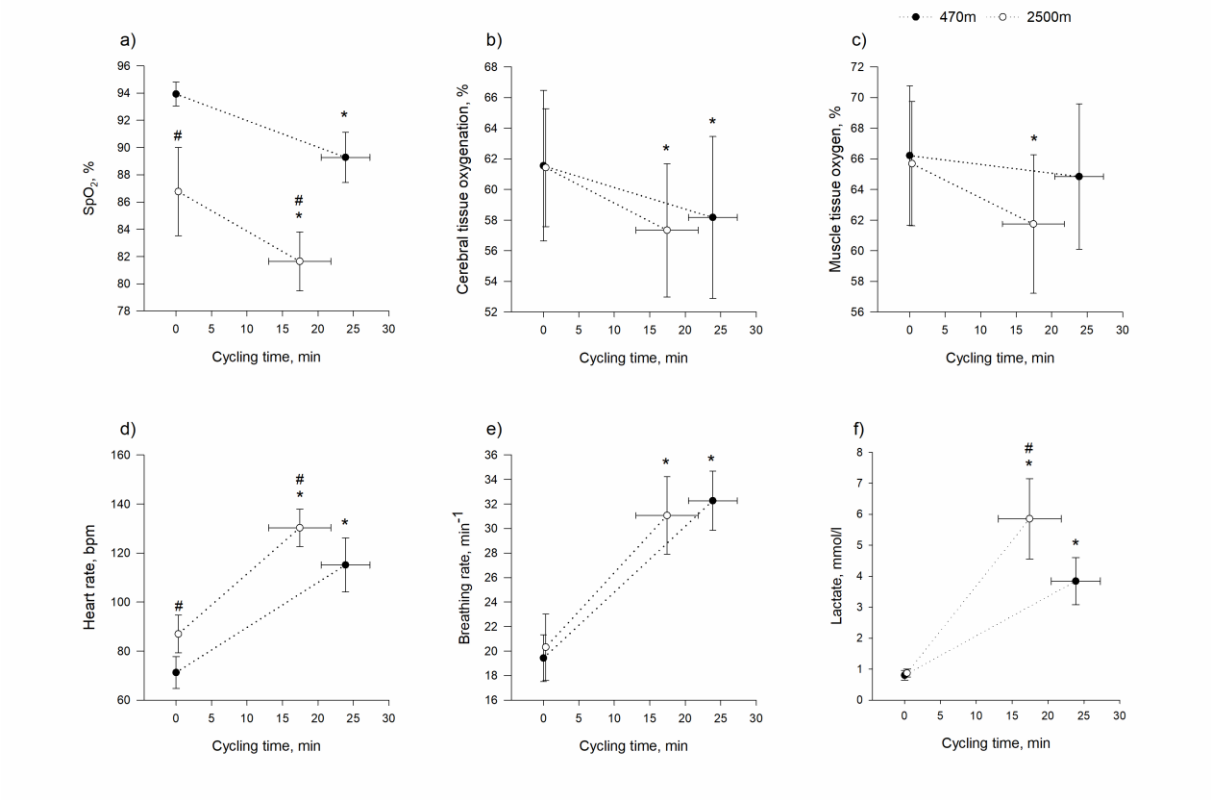


**Figure 3. Effects of altitude exposure on physiological parameters during constant work-rate cycle exercise test**

Statistically significant changes by students ttest ($p<0.05$) are indicated with (#) at 2500m compared to 470m and with (*) at end-exercise compared to rest. Measurements at 470m and 2500 are designated by closed and open circles, respectively. The bidirectional error bars indicate 95% confidence intervals.

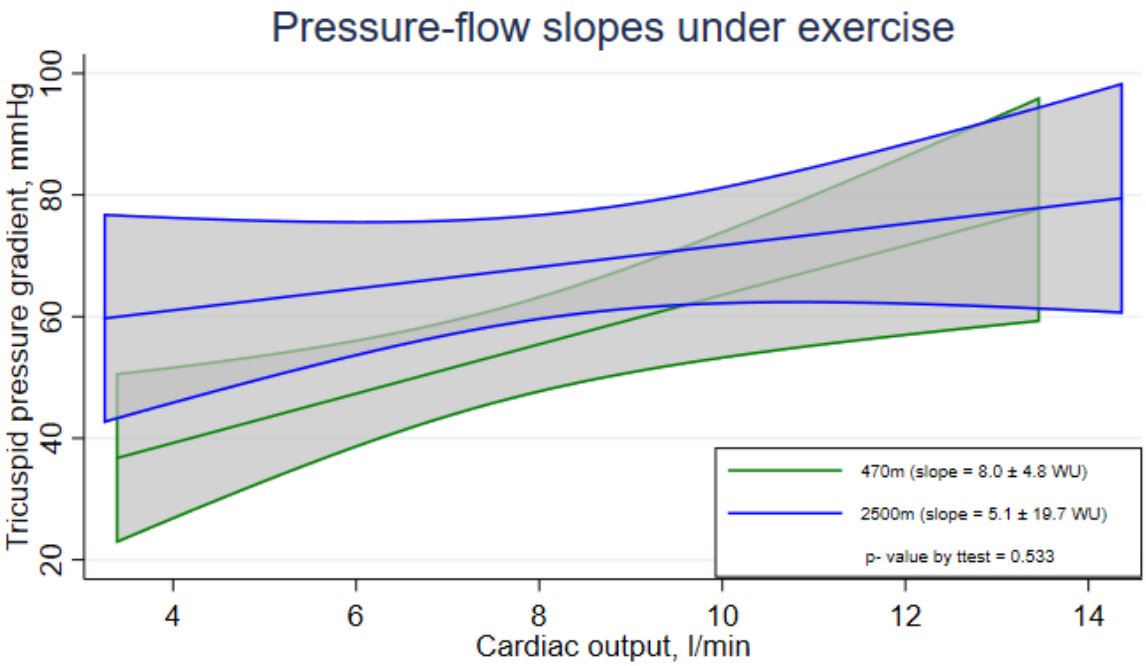


**Figure 4. The pulmonary artery pressure-flow slopes at altitude vs. 470m**

The pulmonary artery pressure-flow slopes as tricuspid regurgitation pressure gradient to cardiac output ratio during constant work-rate cycle exercise tests at 470m (green) and 2500m (blue) are shown as mean (middle line) and 95% confidence (border lines).

## e-table 1. Cycling time at 2500m vs. 470m

| Dependent variable: Cycling time (min) | **Mixed-effect multivariable linear regression** | | |
|---|---|---|---|
| Variables: | Coefficients | 95% Confidence interval | p-value |
| 2500m vs. 470m | -6.44 | -9.47 to -3.40 | <0.001 |
| Intervention order, 470m first | -3.16 | -9.95 to 3.63 | 0.362 |

Mixed linear regression model of the main outcome (Constant work-rate exercise test- time).

## e-table 2a. Predictors of the difference in constant work-rate exercise test cycling time with exposure to 2500m compared to 470m

| Dependent: Change in cycling time (min) from 470m to 2500m (min) | **Mixed- effect univariable linear regression** | | |
|---|---|---|---|
| Variables: | Coefficients | 95% Confidence interval | p-value |
| Intervention order, 470m first | 0.15 | -6.08 to 6.37 | 0.963 |
| Age, year | 0.07 | -0.14 to 0.28 | 0.506 |
| Sex, male | -2.99 | -8.99 to 3.00 | 0.328 |
| Body mass index, kg/m$^2$ | 0.32 | -0.44 to 1.09 | 0.405 |
| PAH (1) vs. CTEPH (2) | 3.36 | -2.60 to 9.33 | 0.270 |
| New York Heart Association class | -0.28 | -4.67 to 4.11 | 0.900 |
| Maximal oxygen uptake at 470m, ml/min/kg | -9.41 | -1.18 to 0.36 | 0.298 |
| Constant work rate exercise test time at 470m | -0.13 | -0.48 to 0.22 | 0.461 |
| Maximal work rate in CPET, Watts | -0.04 | -0.11 to 0.03 | 0.237 |
| Total distance in 6MWT at 470m, m | -0.01 | -0.04 to 0.23 | 0.718 |
| $SpO_2$ at end 6MWT at 470m, % | 0.06 | -0.37 to 0.49 | 0.792 |
| Pulmonary vascular resistance during last right heart catheterization at 470m, WU | 0.32 | -0.81 to 1.44 | 0.580 |
| Mixed venous oxygen saturation during last right heart catheterization at 470m, % | -0.24 | -0.67 to 0.19 | 0.280 |
| Partial pressure of oxygen at rest at 470m, kPa | -0.42 | -2.51 to 1.66 | 0.693 |

Mixed linear regression models with the change in constant work-rate exercise test time (min) as dependent variable. Negative coefficients indicate greater decrease with altitude. 6MWT = 6 minute walk test

## e-table 2b. Predictors to clinically relevantly decrease the cycling time at 2500m vs. 470m

| Dependent: Change in cycling time (min) above minimal clinical relevance difference at altitude | **Logistic univariable linear regression** | | |
|---|---|---|---|
| Variable | Odds ratio | 95% Confidence interval | p-value |
| Intervention order, 470m first | 1.05 | 0.22 to 5.09 | 0.954 |
| Age, year | 0.99 | 0.93 to 1.04 | 0.644 |
| Sex, male | 2.92 | 0.57 to 15.05 | 0.201 |
| Body mass index, kg/m$^2$ | 0.96 | 0.79 to 1.17 | 0.696 |
| PAH (1) vs. CTEPH (2) | 0.93 | 0.55 to 1.56 | 0.778 |
| New York Heart Association class | 2.46 | 0.71 to 8.54 | 0.155 |
| Maximal oxygen uptake at 470m, ml/min/kg | 0.95 | 0.78 to 1.16 | 0.595 |
| Constant work rate exercise test time at 470m | 0.92 | 0.82 to 1.04 | 0.180 |
| Maximal work rate in CPET, Watts | 1.00 | 0.98 to 1.02 | 0.981 |
| Total distance in 6MWT at 470m, m | 1.00 | 0.99 to 1.01 | 0.879 |
| $SpO_2$ at end 6MWT at 470m, % | 0.97 | 0.86 to 1.09 | 0.599 |

| | | | |
|---|---|---|---|
| Pulmonary vascular resistance during last right heart catheterization at 470m, WU | 1.07 | 0.79 to 1.45 | 0.656 |
| Mixed venous oxygen saturation during last right heart catheterization at 470m, % | 0.98 | 0.88 to 1.1 | 0.766 |
| Partial pressure of oxygen at rest at 470m, kPa | 0.67 | 0.36 to 1.22 | 0.191 |

Logistic linear regression models to predict the change in constant work-rate exercise test time (min) at altitude above the minimal clinically important difference of 1.75 minutes. 6MWT = 6 minute walk test, CPET = cardiopulmonary exercise test

## e-table 3. Isotime at 3 and 6 minutes of constant work-rate exercise at low- (470m) and high altitude (2500m)

| Parameter | 3 min exercise at 470m (n=27) Mean ± SD | 3 min exercise at 2500m (n=24) Mean ± SD | Mean difference (95% CI) | p-value | 6 min exercise at 470m (n=27) Mean ± SD | 6 min exercise at 2500m (n=23) Mean ± SD | Mean difference (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Non-invasive blood and tissue oxygenation** | | | | | | | | |
| Pulse oximetry, % | 91 ± 3 | 83 ± 6 | -8 (-10 to -5) | <0.001 | 90 ± 4 | 82 ± 6 | -8 (-11 to -5) | <0.001 |
| Cerebral tissue oxygen saturation, % | 61 ± 13 | 59 ± 9 | -1 (-5 to 3) | 0.670 | 60 ± 12 | 57 ± 10 | -2 (-6 to 3) | 0.448 |
| Muscular tissue oxygen saturation, % | 65 ± 11 | 62 ± 11 | -3 (-7 to 0) | 0.082 | 64 ± 11 | 60 ± 11 | -3 (-7 to 1) | 0.131 |
| **Circulatory and respiratory parameters by PDX and Finapres®** | | | | | | | | |
| Heart rate, $min^{-1}$ | 92 ± 29 | 119 ± 20 | 27 (16 to 38) | <0.001 | 99 ± 28 | 125 ± 14 | 27 (15 to 38) | <0.001 |
| Breathing rate, $min^{-1}$ | 28 ± 5 | 29 ± 7 | 1 (-1 to 3) | 0.461 | 29 ± 5 | 31 ± 6 | 2 (0 to 3) | 0.053 |
| Systolic arterial pressure, mmHg | 133 ± 27 | 140 ± 30 | 7 (-8 to 22) | 0.366 | 133 ± 19 | 153 ± 31 | 19 (6 to 32) | 0.004 |
| Diastolic arterial pressure, mmHg | 84 ± 14 | 82 ± 15 | -1 (-10 to 7) | 0.737 | 84 ± 11 | 87 ± 19 | 3 (-5 to 10) | 0.464 |
| **Echocardiography** | | | | | | | | |
| Tricuspid regurgitation pressure gradient (TRPG), mmHg | 66 ± 23 | 85 ± 25 | 23 (13 to 33) | <0.001 | 76 ± 24 | 79 ± 21 | 5 (-9 to 19) | 0.505 |
| Systolic pulmonary arterial pressure (PAP); mmHg | 70 ± 23 | 90 ± 27 | 23 (13 to 34) | <0.001 | 81 ± 25 | 84 ± 22 | 4 (-11 to 19) | 0.608 |
| Stroke volume, ml | 73 ± 14 | 76 ± 20 | 3 (-8 to 14) | 0.598 | 77 ± 19 | 78 ± 15 | -2 (-12 to 7) | 0.626 |
| CO, l/min | 6.6 ± 2.1 | 8.8 ± 2.2 | 2.2 (0.9 to 3.4) | <0.001 | 7.6 ± 1.7 | 9.6 ± 1.8 | 1.9 (0.8 to 2.9) | <0.001 |
| Pulmonary vascular resistance, WU | 5.9 ± 2.6 | 5.4 ± 2.7 | -0.3 (-2.2 to 1.6) | 0.782 | 6.4 ± 3.1 | 4.7 ± 1.2 | -1.1 (-2.6 to 0.3) | 0.123 |
| TRPG/CO | 11.0 ± 4.0 | 9.8 ± 4.2 | -1.2 (-4.1 to 1.8) | 0.435 | 11.6 ± 4.8 | 8.5 ± 2.0 | -2.0 (-4.2 to 0.2) | 0.072 |
| Tricuspid annular plane systolic excursion, cm | 2.2 ± 0.3 | 2.1 ± 0.3 | -0.1 (-0.3 to 0.0) | 0.101 | 2.4 ± 0.3 | 2.3 ± 0.4 | -0.1 (-0.3 to 0.0) | 0.164 |

Data shows exercise at 3 and 6 minutes of exercise under both altitudes, CI = Confidence Interval, SD = Standard deviation