

Can patients with pulmonary hypertension travel to high altitude?

A physiological basis for better patient counselling

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SUMMARY

Background: Like a majority of people, also patients with pulmonary hypertension (PH) would like to undertake long-distance air travel or journeys to mountain areas. However, patients with pulmonary vascular diseases thereafter as PH are sensitive to low barometric pressure (Pbar) environments, as alveolar Pbar is one of the main drivers of gas exchange in humans. Low Pbar occurs to similar extents at an altitude of approximately 2500m above sea level and during commercial long-haul flights.

Sensitised by the media, their peers, or care providers, patients with PH are often concerned about their own fitness-to-fly or ability to take part in activities in mountain areas. Due to a lack of scientific knowledge – and because recommendations are mainly expert-based, with a lack of clinical and physiological studies in PH – it is challenging to provide adequate counselling for hypoxic exposure.

Objectives & specific aims: This PhD thesis has the overall objective to identify physiologic and symptomatic changes under hypoxic conditions at rest and during constant-loaded exercise tests in patients with PH as a basis for better patient counselling. The specific aims are threefold:

1. To identify physiological and symptomatic changes under normobaric hypoxia with a fraction of inspired oxygen of 15.1% equivalent to 2500m at rest and under constant load exercise.
2. To assess physiological changes and symptoms during a daytrip of 4-6 hours to real altitude (2500m) compared to low altitude (LA) at rest and during exercise with focus on blood and tissue oxygenation, right ventricular function and other parameter.
3. To identify differences between exposure to normobaric hypoxia (first project) and to hypobaric hypoxia at real altitude (second project) in terms of blood oxygenation, right ventricular functions and other parameter.

Methods: First, we conducted a randomised controlled crossover trial in a safe environment, where we exposed PH patients to normobaric hypoxia equivalent to 2500m for up to 2 hours in a laboratory setting.

Second, we travelled with stable PH patients to a Swiss mountain (Mt. Säntis, 2500m) by shuttle and cable car, where they were tested for physiological and symptomatic changes during a daytrip.

Third, we investigated differences between LA data whilst breathing normobaric hypoxia (NH) and high altitude (HA) data whilst breathing hypobaric hypoxia (HH).

Results: An exposure of 28 stable patients (13 women) with PH exposed to NH (fraction of inspired O₂: 15% equivalent to 2500m) for up to 2 hours revealed an overall good tolerance

with a significant reduction in exercise cycle time (median-difference & 95% Confidence interval) of -0.7(-3.1 to 0.0) minutes and lower oxygenation in PaO_2 -1.7(-2.7 to -1.1) kPa compared to ambient air.

A subsequent daytrip with 28 stable PH-patient to 2500m confirmed the reduced exercise test time by mean-difference (95% CI) -6(-10 to -3) minutes, the reduced oxygenation by -3.2(-3.6 to -2.8) kPa in line with a significant increase in tricuspid pressure gradient of 17(9 to 24) mmHg. Overall this daytrip to 2500m was well tolerated, however 3 patients were treated with supplemental low flow nasal oxygen according to predefined safety criteria ($\text{SpO}_2 < 80\%$ for >30 minutes).

When comparing similar exposure times and hypoxic conditions from NH to HH in 21 stable PH-patients, HH induced more pronounced hypoxemia and larger pulmonary artery pressure increase compared to NH. Changes under NH failed to predict physiologic and symptomatic changes at HH.

Conclusion: This thesis provides valuable information about physiological and symptomatic changes under normobaric and hypobaric hypoxia within one day while addressing the uncertainty about potential adverse health effects of an increasing number of stable patients with PH travelling to HA or by aeroplane. Physiological changes were more prominent under HH compared to NH and a short exposure to high altitude simulation testing (NH) to predict physiological changes at altitude remains further questionable. This PhD thesis could provide valuable information necessary to counsel patients with PH who are travelling to hypoxic environments. However, future research with bigger sample size and longer exposure time is needed.

LIST OF ABBREVIATIONS

ARAHE	Altitude-related adverse health events
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CWRET	Constant loaded work-rate exercise test
FiO ₂	Fraction of inspired oxygen
HA	High altitude
HAST	High altitude simulation test
HH	Hypobaric hypoxia
HPV	Hypoxic pulmonary vasoconstriction
LA	Low altitude
NH	Normobaric hypoxia
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
Pbar	Barometric pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
SpO ₂	Peripheral oxygen saturation
WHO FC	World Health Organisation functional class

CHAPTER 1 Introduction

1.1. Background

1.1.1. State of research

Ease of access to mountain areas for tourist or business-related purposes is increasing thanks to modern means of transportation, such as trains, cable cars, and aeroplanes. Additionally, long-distance air travel has become affordable for most people. This trend allows not only healthy and well-trained athletes to travel to hypobaric environments, but also people suffering from cardiopulmonary diseases. Barometric pressure (P_{bar}), which is reduced at altitude and during commercial flights, is a main driver of gas exchange in humans. People with cardiopulmonary diseases are particularly sensitive to hypobaric hypoxia (HH). Some people unknowingly expose themselves to additional risk of altitude-related adverse health events (ARAHE), whilst others, as observed in our daily practice, are cautious and seek advice about their risk of hypoxic exposure. Owing to the lack of clinical trials, current scientific knowledge only allows expert-based recommendations for altitude exposure in pulmonary hypertension (PH), as opposed to evidence-based practice.

Therefore, the purpose of my thesis was to investigate whether high altitude (HA) or similar conditions, such as HH, during commercial long-haul flights are tolerable for patients with PH. The goal of this was to support evidence-based counselling for patients with PH who wish to engage in air travel.

1.1.2. Pulmonary hypertension

PH is a rare and progressive cardiopulmonary disease. The two major forms of precapillary PH, in the absence of underlying lung diseases, are pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH).

Up to 2022, the gold standard definition of PH was a mean pulmonary artery pressure (PAP) of >25 mmHg, measured at rest, during right-heart catheterisation and a pulmonary artery wedge pressure of ≤ 15 mmHg to exclude post capillary mechanisms. The novel PH guidelines decreased the threshold to a mean PAP of >20 mmHg, a pulmonary artery wedge pressure of ≤ 15 mmHg, and a pulmonary vascular resistance (PVR) of >2 Wood units.^[1] Precapillary PH is a life-threatening disorder with an elevated PAP and an increased PVR caused by a loss or obstructive remodelling of the pulmonary vascular bed. Without adequate therapy, affected

patients may suffer from progressive right-heart failure, explained by an increased afterload of the right-heart and functional decline.^[2]

The prevalence of PAH in Europe is 15–60 subjects per million, and the prevalence of CTEPH was recently estimated at 30–50 cases per million in Europe and the United States, with an overall greater predominance among women.^[3] However, the American REVEAL register cites a much higher prevalence of PAH, with up to 93 cases per million^[4] and the Spanish register gives the prevalence of CTEPH as 3.2 cases per million.^[5]

Symptoms

The cardinal symptom of PH is dyspnoea on exertion. Other symptoms are rather unspecific, encompassing fatigue, syncope, and chest pain. Throughout the progression of the disease, patients primarily experience exertional dyspnoea, limited exercise performance, and reduced quality of life.^[6, 7]

Therapy

Specific pharmaceutical therapies are available for precapillary PH (PAH & CTEPH), with the goal of reducing PVR by specific pulmonary vasodilators and antiproliferative agents. Studies have shown that supportive treatment with diuretics, supplemental oxygen, and exercise training may be beneficial.^[1]

Patients suffering from CTEPH with proximal thrombosis may be eligible for the highly invasive surgical pulmonary endarterectomy.^[1, 5, 8, 9]

Since 1995, when the first pharmaceutical therapy for PH came on the market, several other treatment options have been developed. Today, there are three treatment pathways available, and these are often combined to relieve the right-heart overload and improve the World Health Organization functional class (WHO FC).^[1, 5, 9] Progress in pharmaceutical therapy has substantially increased the 5-year survival – from 34% in 1991 to more than 60% in 2015–2018, and even higher for those in the low-risk category defined by several clinical parameters such as WHO FC I and II, 6 Minute walk distance >440m and others.^[1, 8, 9]

1.1.3. Altitude and Hypoxia

Better survival of PH patients – together with the ease of access to hypobaric environments, such as high altitudes and aeroplanes – has increased incidents of hypoxic exposure, including for patients with cardiopulmonary diseases.^[10]

The higher the elevation, the more hypoxic the environment becomes, in line with a decreasing P_{bar} and a consequently reduced alveolar pressure of oxygen. P_{bar} is one of the main drivers of gas exchange in humans. Therefore, a reduction of P_{bar} results in hypoxemia, tissue hypoxia, and thus a higher incidence of ARAHE.^[11, 12]

Several physiological adaptations to hypoxia are known and described in the literature. Reduced P_{bar} is compensated for by hypoxic pulmonary vasoconstriction (HPV). This adaptation mechanism mitigates the ventilation-perfusion mismatch and optimises lung diffusion by activated chemoreceptors that constrict the pulmonary arteries. This mechanism is present in all individuals and occurs after just a few minutes of hypoxia. For patients with PH, an increase in PAP induced by a hypoxic environment may further increase the risk of ARAHE, since their PAP is already elevated at low altitude (LA). This physiological HPV, which results in an additional increase of the right-ventricular afterload and reduced oxygen delivery, should be taken into account when patients with PH wish to travel to high altitudes or by aeroplane.^[13]

Furthermore, altitude triggers chemoreceptors that activate the sympathetic nervous system, which results in increased ventilation and heart rate. Figure 1 (Ulrich et al., 2017)^[13] describes the main adaptive mechanisms to HH.^[13]

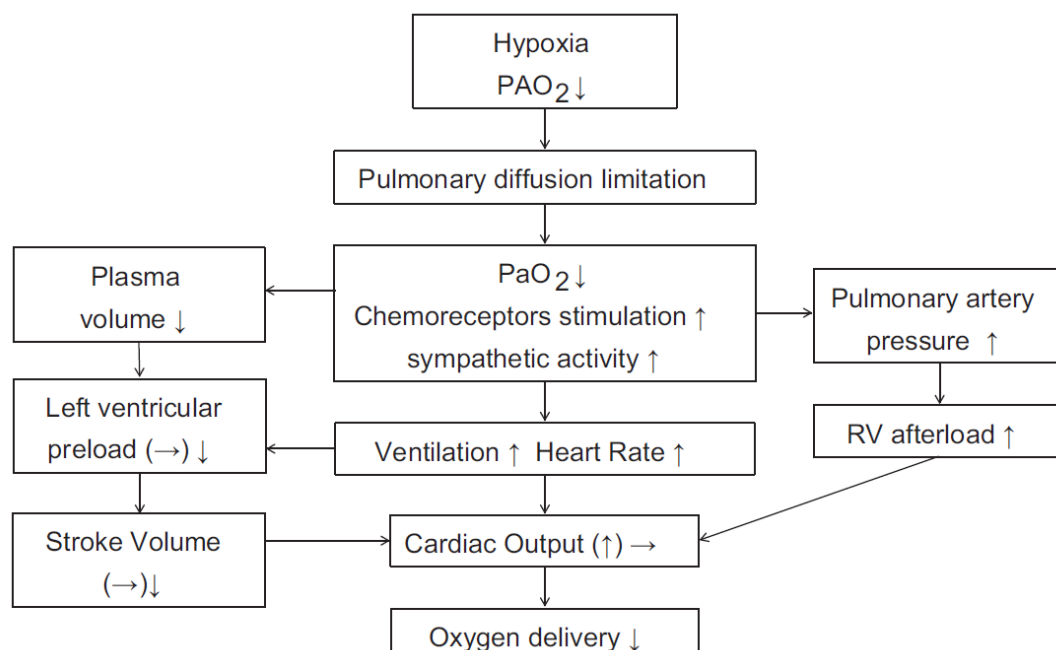


Figure 1: Adaptive mechanisms to exercise under acute exposure to hypobaric hypoxia at altitude by Ulrich et al. 2017^[13]; RV: right ventricle, PaO_2 : arterial partial pressure of oxygen.

1.1.4. Gap of knowledge

Current evidence regarding recommendations for hypoxic exposure in patients with PH remains scarce and is primarily expert-based.^[13]

The British Thoracic Society recommends supplemental oxygen during air travel for those who are clinically unstable or in WHO FC 3 and 4. Furthermore, for certain cardiopulmonary diseases, an HA simulation test (HAST) is recommended, especially for those patients with a peripheral oxygen saturation (SpO₂) near sea level of <95%. More precise recommendations for PH are not available.^[14, 15] Uncertainty about the fitness-to-fly of PH patients – and the concerns of patients going into HA environments, as experienced in our daily practice – provide a clear incentive to tackle this issue in a structured and scientific context.

This PhD thesis focuses on the physiological changes of patients with PH under hypoxia – both in a laboratory setting, with all possible safety equipment close-by, under normobaric hypoxia (NH) at LA (image S1) and under HH at real HA, at similar levels, corresponding to 2500m above sea level (image S2). A further goal of this project is to identify predictors of unfavourable outcomes and to provide generally evidence-based data with which to counsel PH patients travelling to hypoxic environments.

1.2. Overall objectives and specific aims

As a response of unclear recommendation for altitude exposure or air travel in patients with pulmonary hypertension the overall objective of this PhD is to identify relevant changes in physiological parameters under hypoxia and predictors of unfavourable outcomes, which help to counsel patients with pulmonary hypertension travelling to high altitude (2440-4270m) or by airplane.^[16]

The aim of this project is to identify physiological and symptomatic changes under normobaric and hypobaric hypoxia at rest and during a constant-loaded exercise test by investigating right heart function, hemodynamics, and other in patients with pulmonary hypertension.

1.2.1. Objectives and aims project I

Objective

To obtain important information about potential adverse health effect of simulated altitude, normobaric hypoxia at rest and under exercise in patients with pulmonary hypertension.

Specific aim

To identify physiological and symptomatic changes under normobaric hypoxia with a fraction of inspired oxygen of 15.1% equivalent to 2500m at rest and under constant load exercise.

1.2.2. Objectives and aims project II

Objective

To obtain information about altitude-related adverse health effects in patients with pulmonary hypertension exposed to hypobaric hypoxia at high altitude at rest and during exercise.

Specific aim

To assess physiological changes and symptoms during a daytrip of 4-6 hours to high altitude (2500m) compared to low altitude at rest and during exercise with focus on blood and tissue oxygenation, right ventricular function and other parameter.

1.2.3. Objectives and aims project III

Objective

To investigate the predictive value of low altitude baseline parameters and parameters assessed during normobaric hypoxia at low altitude to evaluate pulmonary hypertension-patients' risk for hypoxia exposure at altitude and during air travel.

Specific aim

To identify differences between exposure to normobaric hypoxia (first project) and to hypobaric hypoxia at real altitude (second project) in terms of blood oxygenation, right ventricular functions and other parameter.

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CHAPTER 2 Results

2.1. Project I

Effect of Normobaric Hypoxia on Exercise Performance in Pulmonary Hypertension: Randomized Trial

Citation:

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Effect of Normobaric Hypoxia on Exercise Performance in Pulmonary Hypertension Randomized Trial



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BACKGROUND: Many patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (PH) wish to travel to altitude or by airplane, but their risk of hypoxia-related adverse health effects is insufficiently explored.

RESEARCH QUESTION: How does hypoxia, compared with normoxia, affect constant work-rate exercise test (CWRET) time in patients with PH, and which physiologic mechanisms are involved?

STUDY DESIGN AND METHODS: Stable patients with PH with resting $Pao_2 \geq 7.3$ kPa underwent symptom-limited cycling CWRET (60% of maximal workload) while breathing normobaric hypoxic air (hypoxia; FIO_2 , 15%) and ambient air (normoxia; FIO_2 , 21%) in a randomized cross-over design. Borg dyspnea score, arterial blood gases, tricuspid regurgitation pressure gradient, and mean pulmonary artery pressure/cardiac output ratio (mean PAP/CO) by echocardiography were assessed before and during end-CWRET.

RESULTS: Twenty-eight patients (13 women) were included: median (quartiles) age, 66 (54; 74) years; mean pulmonary artery pressure, 41 (29; 49) mm Hg; and pulmonary vascular resistance, 5.4 (4; 8) Wood units. Under normoxia and hypoxia, CWRET times were 16.9 (8.0; 30.0) and 6.7 (5.5; 27.3) min, respectively, with a median difference (95% CI) of -0.7 (-3.1 to 0.0) min corresponding to -7 (-32 to 0.0)% ($P = .006$). At end-exercise in normoxia and hypoxia, respectively, median values and differences in corresponding variables were as follows: Pao_2 : 8.0 vs 6.4, -1.7 (-2.7 to -1.1) kPa; arterial oxygen content: 19.2 vs 17.2, -1.7 (-3 to -0.1) mL/dL; $Paco_2$: 4.7 vs 4.3, -0.3 (-0.5 to -0.1) kPa; lactate: 3.7 vs 3.7, 0.9 (0.1 to 1.6) mM ($P < .05$ all differences). Values for Borg scale score: 7 vs 6, 0.5 (0 to 1); tricuspid pressure gradient: 89 vs 77, -3 (-9 to 16) mm Hg; and mean PAP/CO: 4.5 vs 3.3, 0.3 (-0.8 to 1.4) Wood units remained unchanged. In multivariable regression, baseline pulmonary vascular resistance was the sole predictor of hypoxia-induced change in CWRET time.

INTERPRETATION: In patients with PH, short-time exposure to hypoxia was well tolerated but reduced CWRET time compared with normoxia in association with hypoxemia, lactic acidemia, and hypocapnia. Because pulmonary hemodynamics and dyspnea at end-exercise remained unaltered, the hypoxia-induced exercise limitation may be due to a reduced oxygen delivery causing peripheral tissue hypoxia, augmented lactic acid loading and hyperventilation.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT03592927; URL: www.clinicaltrials.gov;

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KEY WORDS: altitude; chronic thromboembolic pulmonary hypertension; echocardiography; exercise testing; pulmonary arterial hypertension

FOR EDITORIAL COMMENT, SEE PAGE 484

ABBREVIATIONS: CO = cardiac output; CTEPH = chronic thromboembolic pulmonary hypertension; CTO = cerebral tissue oxygenation; CWRET = constant work-rate exercise test; LLS = Lake Louise score; MTO = muscular tissue oxygenation; NYHA = New York Heart Association; PAH = pulmonary arterial

hypertension; PAP = pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SpO_2 = arterial oxygen saturation as determined by pulse oximetry; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid regurgitation pressure gradient

Take-home Point

Short-time exposure to normobaric hypoxia was well tolerated in patients with pulmonary hypertension but induced hypoxemia and reduced constant work-rate cycle time compared with ambient air.

An increasing number of people worldwide travel to mountain areas and by airplane, exposing themselves to hypoxia; these include many patients with cardiopulmonary diseases. Pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH), hereafter summarized as PH, is associated with reduced exercise performance, quality of life, and survival. With progression of PH, worsening hemodynamics may lead to hypoxemia, particularly during exercise and sleep.¹ Recent therapeutic advances have improved quality of life and physical performance in PH, enabling stable patients with PH to travel, but current PH guidelines discourage altitude sojourns in fear of adverse health effects.²

The hypoxic environment induces distinct acute effects on human physiology, potentially inducing adverse health effects. The cardiovascular response to hypoxia is characterized by an increase in heart rate, which directly elevates the cardiac output (CO), whereas the stroke volume may not immediately be influenced.³ The

hypoxia-induced chemoreceptor response increases ventilation through a higher respiratory rate,⁴ enhancing dyspnea perception.⁵ In addition, alveolar hypoxia at high altitude leads to immediate hypoxic pulmonary vasoconstriction distributing blood flow to alveolar areas with higher oxygen partial pressure.⁶ In susceptible individuals this may induce pulmonary vascular remodeling leading to sustained PH.^{7,8}

High altitude-related health problems are of importance for mountaineers, particularly at altitudes > 3,500 m, but may occur at much lower altitude in patients with preexisting hypoxemic lung diseases including PH.^{9,10} Patients with PH might be affected more severely by hypoxia because of an accelerated rise in pulmonary arterial pressure (PAP) augmenting pulmonary vascular resistance (PVR). On the other hand, hypoxic pulmonary vasoconstriction could be dampened in lung vessels already remodeled by PH.¹¹

We showed that exposure of patients with PAH/CTEPH to normobaric hypoxia corresponding to approximately 2,500 m was not associated with a rise in PVR, unlike in control subjects.¹¹ Therefore, the objective of the current study is to investigate whether exposure to normobaric hypoxia reduces exercise capacity in patients with PH and to study symptoms and physiologic effects of hypoxia at rest and under exercise.

Methods

Design

This is a randomized-controlled, single-blinded crossover trial conducted in August 2018 to April 2019 at the University Hospital of Zurich.

Pulmonary Hypertension Unit University Hospital of Zurich

Subjects

Adult patients who had received a diagnosis of PAH/CTEPH according to current guidelines¹² were recruited from among outpatients at the

Pulmonary Hypertension Unit, University Hospital of Zurich, on receipt of written informed consent. Patients were clinically stable, lived at an elevation < 1,000 m, and had a resting $\text{PaO}_2 \geq 7.3$ kPa and $\text{PaCO}_2 < 6.5$ kPa. Patients exposed to > 1,500 m for ≥ 3 nights during the previous 4 weeks, were unable to follow the study protocol, had relevant comorbidities, or were pregnant or breastfeeding women were excluded.

The study was performed according to the principles of the Declaration of Helsinki and was approved by Cantonal Ethics Zurich (KEK 2018-00455) and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03592927).

Intervention/Hypoxic Challenge

Patients were randomly allocated to breathe ambient air first and then exposed to normobaric hypoxia (FiO_2 , 15%), or vice versa, via a sealed facemask with a nonrebreathing two-way valve (T-shape; Hans Rudolph) during ≥ 20 min of rest followed by a symptom-limited cycle-ergometer constant work-rate exercise test (CWRET) to exhaustion (ergoselect 100; ergoline GmbH).¹³ Work rate was determined at 60% of maximal work rate achieved during an incremental ramp test at ambient air > 1 day before the first intervention. Maximal cycling time was set at 30 min. Gas mixtures were provided by Altitrainer (SMTEC-SA) as nitrogen-enriched air simulating 2,500 m (FiO_2 , 15%) or ambient air (FiO_2 , 21%). Interventions were separated by a washout period of > 2 h.

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Assessment

Demographics, PH group, actual medication, the 6-min walk distance,¹⁴ and New York Heart Association (NYHA) functional class were assessed.

The following parameters were assessed by echocardiography at rest and exercise^{15,16}: fractional area change, tricuspid annular plane systolic excursion (TAPSE), CO calculated from the left ventricular outflow tract velocity time integral,¹⁷ and maximal systolic velocity of the tricuspid regurgitation to derive the tricuspid regurgitation pressure gradient (TRPG). Right atrial pressure (RAP) was estimated from the dimension and respiratory variability of the inferior vena cava at rest and assumed constant during exercise. PAP was calculated as follows: systolic PAP = TRPG + RAP, mean PAP as 0.61 systolic PAP + 2 mm Hg.¹⁸

Arterial blood was sampled from a radial artery under both interventions, while breathing normobaric hypoxic air and ambient air, after 20 min of rest and at peak exercise, and each sample was immediately analyzed (ABL90 FLEX; Radiometer GmbH).

We continuously assessed three-lead electrocardiography, breathing rate, fingertip pulse oximetry (arterial oxygen saturation [SpO₂]) (Alice PDx; Philips Respironics), cerebral and muscle tissue oxygenation (CTO/MTO) by near-infrared spectroscopy at the forehead and quadriceps,¹⁹ and systemic BP, heart rate, stroke volume, and CO by finger cuff manometry (Finapres Medical Systems BV).²⁰

Symptoms were assessed using a 10-cm visual analog scale for general health and the Borg CR-10 dyspnea and leg fatigue scales.²⁰⁻²³ At the end of each sequence, while still exposed to hypoxia or breathing ambient air, participants were asked to fill out the new Lake Louis score (LLS) questionnaire.²⁴

Outcomes

The primary outcome was the difference in CWRET time under normobaric hypoxia vs ambient air.

Additional outcomes were differences of above-described assessments at rest (20 min), end-exercise, or predefined isotimes (3 min, 6 min) under hypoxia vs ambient air.

Sample Size Estimation

To detect an estimated minimally important difference of 1.75 min with an SD of 1.7 in CWRET time with a power of 0.8 (α , 0.05), 18 patients were required.²⁵ To account for potential dropouts, we included 28 participants.

Randomization and Blinding

The randomization was performed balanced in blocks of four, using a computer algorithm (Stata statistical software, version 15; StataCorp). Participants were fully blinded to the gas mixtures. Blinding of investigators during the study sequences was not possible for safety reasons; however, data analysis was performed by blinded investigators.

Data Analysis and Statistics

Data are summarized as medians (quartiles) and median difference (95% CI) according to nonnormality distribution by Shapiro-Wilk. Between-groups comparison was performed with the Wilcoxon matched-pairs test. Continuous data from Finapres, PDx, and near-infrared spectroscopy were imported to LabChart, and averaged over 30 s at respective time points. Predictors of the change in CWRET time with hypoxia vs ambient air were explored by linear regression and univariable predictors with $P < .1$ entered in the multivariable model. Characteristics and outcomes of patients who decreased their cycling time by > 1.75 min were compared with remaining patients. A two-sided P value $< .05$ was considered statistically significant. The somersd package was used to calculate nonparametric CIs to reflect the spread of changes in parameters with hypoxia vs ambient air.²⁶ Statistical analysis was conducted with Stata statistical software, version 15.

Results

Patients

From 91 patients assessed for eligibility, 28 were included on receipt of written informed consent (Fig 1, Table 1).

Primary Outcome

The median exercise time was reduced by more than one-half with hypoxia vs ambient air (from 16.9 [8.0; 30.0] to 6.7 [5.5; 27.3] min; $P = .006$) and the relative decrease in exercise time under hypoxia was 7 (0; 32)% ($P = .018$), with high interindividual differences. Sixteen of 28 of the participants reduced their cycling time under hypoxia (Table 2, Fig 2).

Additional Outcomes

SpO₂, SaO₂ (arterial oxygen saturation as determined by blood gas analysis), and Pao₂ were significantly lower after 20 min of rest ($P = .013$, $< .001$, and $< .001$, respectively) and at peak exercise ($P = .036$, $.003$, $.003$,

respectively) under hypoxia vs ambient air, resulting in lower arterial oxygen content (Tables 2, 3, Fig 3). CTO and MTO were similar at rest and peak exercise under both conditions. Paco₂ was similar at rest but lower at peak exercise under hypoxia. At isotimes of 3 and 6 min, SpO₂ and CTO were lower under hypoxia vs ambient air (Table 4). Exercise induced significant changes compared with rest in almost all parameters under both conditions except for mean PAP/CO with ambient air and for mean PAP/CO and TRPG under hypoxia (Table 3).

Heart and breathing rates were unchanged while breathing hypoxic vs ambient air at rest and end-exercise, whereas resting but not exercise systemic BPs were higher (Tables 2, 3). Pulmonary hemodynamics assessed by echocardiography (PAP, CO) as well as hemodynamic parameters assessed by finger-tip manometry (Finapres) did not differ after 20 min of rest and at end-exercise while breathing hypoxic vs ambient air (Tables 2, 3), but despite a similar CO, oxygen

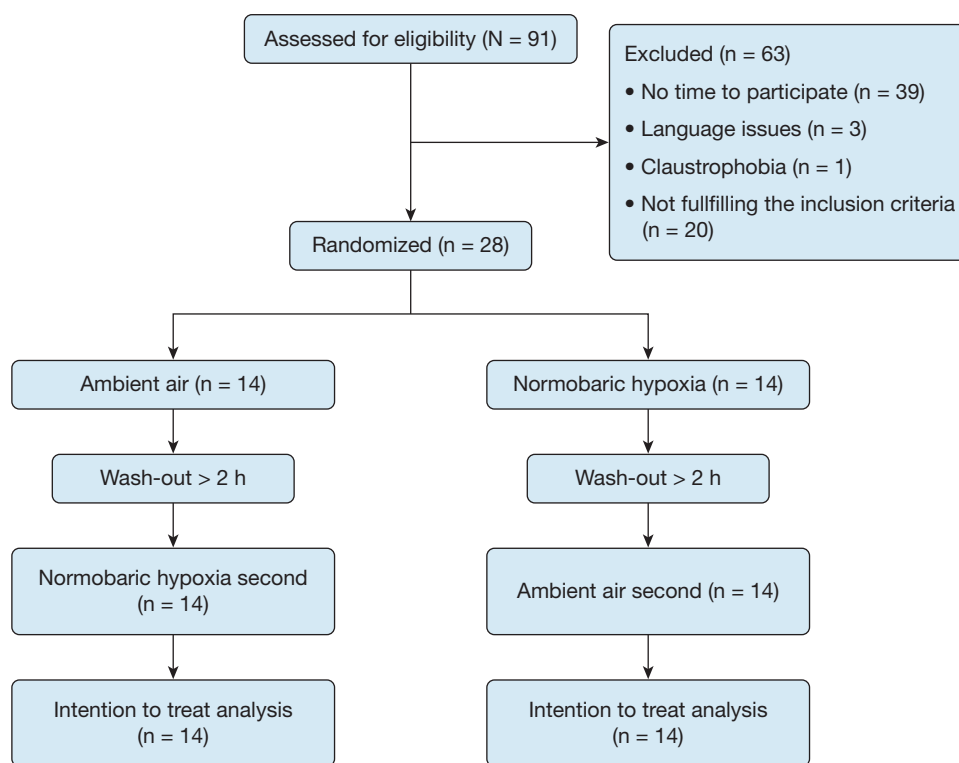


Figure 1 – Patient's flow.

TABLE 1] Patient Characteristics

Characteristic	Value
Participants, total/women	28/13 (46)
Age, y	66 (54; 74)
BMI, kg/m ²	25.6 (22.9; 29.5)
Pulmonary hypertension classification	
1. Pulmonary arterial hypertension	16 (57)
1.1. Idiopathic	11 (39)
1.4.1. Connective tissue disease	4 (14)
1.4.3. Portal hypertension	1 (4)
4. Chronic thromboembolic pulmonary hypertension	12 (43)
6-min walk distance, m	515 (454; 585)
New York Heart Association functional class I, II, III	8 (29), 13 (46), 7 (25)
Incremental ramp cycle exercise, W	95 (80; 123)
Resting Pao ₂ , kPa	10.2 (8.4; 11.6)
Pulmonary vascular resistance, Wood units	5.4 (4; 8.4)
Mean pulmonary arterial pressure, mm Hg	41 (29; 49)
Targeted therapy	
Endothelin receptor antagonist	19 (70)
Phosphodiesterase-5 inhibitor	13 (46)
Soluble guanylate cyclase stimulators	2 (7)
Prostacyclin receptor agonist or prostacyclin	5 (18)
Combination therapy	12 (43)

Data are shown as No. (%) or median (quartiles).

TABLE 2] Assessments After 20 Minutes of Normobaric Hypoxia (Fio₂, 15%) vs Ambient Air at Rest

	Ambient Air (F _{IO} ₂ , 21%)	Normobaric Hypoxia (F _{IO} ₂ , 15%)	Ambient Air vs Normobaric Hypoxia	
Parameter	Median (Quartiles)	Median (Quartiles)	Median Difference (95% CI)	P Value
Noninvasive blood and tissue oxygenation				
Pulse oximetry, %	93 (90; 95)	90 (86; 93)	−3 (−5 to −1)	.013
Cerebral tissue oxygen saturation, %	64 (51; 71)	64 (58; 69)	−1 (−7 to 4)	.949
Muscular tissue oxygen saturation, %	71 (63; 80)	68 (63; 77)	−3 (−9 to 5)	.703
Arterial blood gases				
pH	7.44 (7.43; 7.47)	7.50 (7.40; 7.50)	0 (−0 to 0.01)	.493
P _{CO} ₂ , kPa	4.8 (4.6; 5.2)	4.8 (4.5; 5.1)	0 (−0.1 to 0.1)	.558
P _O ₂ , kPa	9.7 (9; 10.8)	7.9 (7.2; 9)	−1.6 (−2.8 to −1.2)	< .001
Hydrogen carbonate, mM	26 (24; 27)	25 (24; 27)	0 (−0.6 to 0.4)	.700
Lactate, mM	0.8 (0.6; 1.5)	0.9 (0.5; 1.5)	0.1 (−0.3 to 0.3)	1
Arterial oxygen saturation, %	95 (93; 96)	90 (87; 94)	−3 (−6 to −2)	.001
Hemoglobin, g/dL	13.8 (13.2; 14.9)	13.9 (13; 14.9)	0.1 (0 to 0.2)	.216
Arterial oxygen content, mL/dL	17.7 (16.9; 19.3)	16.7 (16; 18.6)	−0.9 (−1.7 to 0)	.004
Oxygen delivery by echocardiography, mL/min	96 (81; 106)	97 (78; 108)	−2 (−15 to 9)	.446
Oxygen delivery by Finapres, mL/min	78 (66; 88)	71 (49; 100)	−4 (−22 to 16)	.685
Circulatory and respiratory parameters by Finapres and PDx				
Heart rate, beats/min	69 (61; 74)	69 (65; 75)	2 (−2 to 7)	.270
Breathing rate, breaths/min	16 (13; 20)	16 (13; 20)	0 (−1 to 2)	.443
Systolic arterial pressure, mm Hg	106 (86; 129)	118 (108; 135)	12 (−3 to 25)	.026
Diastolic arterial pressure, mm Hg	61 (53; 74)	70 (62; 87)	13 (1 to 24)	.010
Cardiac output, L/min	4.1 (3.7; 5.4)	4.3 (2.8; 5.3)	0.3 (−1.2 to 0.8)	.696
Systemic vascular resistance, Wood units	19 (13; 23)	20.2 (13.6; 23.9)	3 (−5 to 5)	.842
Echocardiography				
Tricuspid regurgitation pressure gradient, mm Hg	40 (30; 58)	42 (29; 52)	−0 (−8 to 7)	.809
Right atrial pressure, mm Hg	3 (3; 4)	3 (3; 3)	0 (0 to 0)	1
Systolic pulmonary arterial pressure (PAP), mm Hg	43 (33; 66)	46 (36; 60)	0 (−9 to 7)	.851
Cardiac output (CO), L/min	5.4 (4.4; 6.3)	5.3 (4.4; 6)	−0.1 (−0.7 to 0.4)	.592
Mean PAP/CO, Wood units	5.8 (4.5; 7.8)	6.2 (5.1; 8.5)	0.6 (0 to 1.2)	.615
Tricuspid annular plane systolic excursion (TAPSE), cm	2 (1.7; 2.2)	1.9 (1.7; 2.2)	0 (−0.2 to 0.1)	.666
Fractional area change, %	30 (30; 40)	30 (20; 40)	0 (0 to 0)	.396
Tricuspid regurgitation velocity, m/s	3.2 (2.8; 3.8)	3.3 (2.7; 3.6)	0 (−0.3 to 0.2)	.798
TAPSE/systolic PAP, mm/mm Hg	4.7 (2.9; 6.4)	3.9 (3.3; 5.8)	0.1 (−1.4 to 0.9)	.864
Patient-reported outcomes				
Visual analog scale (general status), cm	0.8 (0.4; 1.7)	0.8 (0.2; 2.3)	0.1 (−0.2 to 0.4)	.699
Borg dyspnea scale	1.5 (0.3; 3)	1.5 (0; 3)	0 (0 to 0)	.300
Borg leg fatigue scale	0 (0; 1.8)	0 (0; 1.3)	0 (0 to 0)	.989

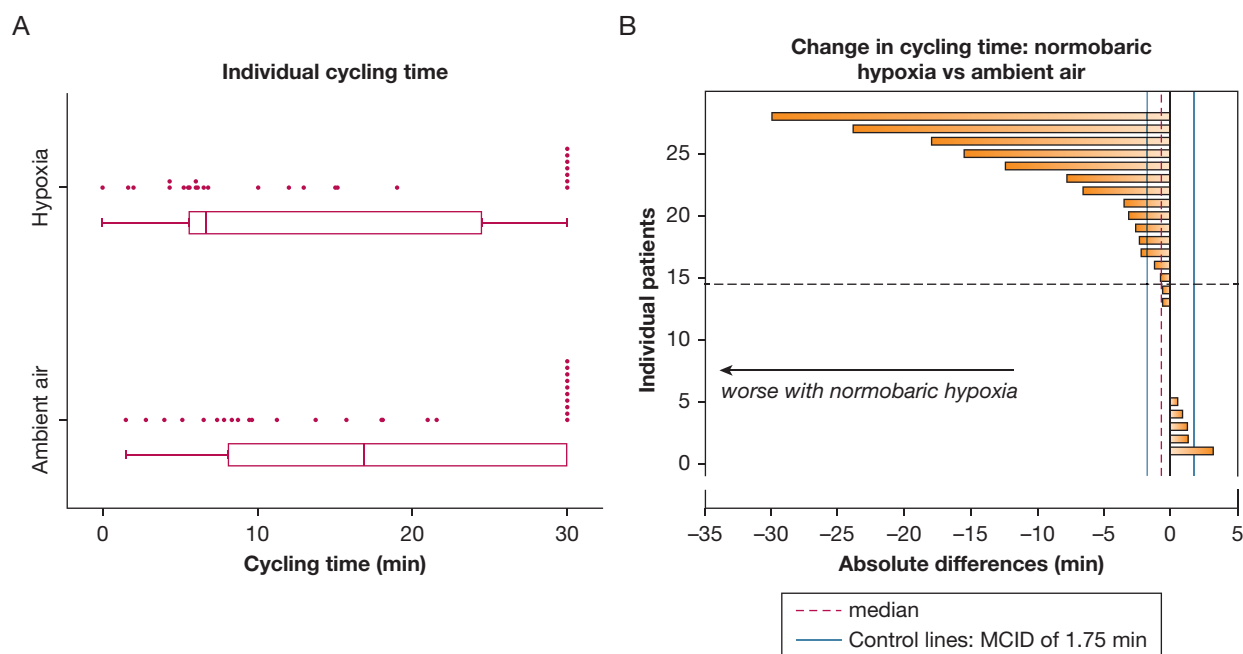


Figure 2 – A and B, Constant work-rate cycling time with normobaric hypoxia (F_{IO_2} , 15%) and ambient air in patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (A) and the individual changes in cycling time with hypoxia vs ambient air (B). A, Individual cycling times (points) and boxplots indicating medians with quartiles (square ends), the quartiles ± 1.5 SD (whiskers), and outliers, with the upper boxplot/ data points representing measurements under normobaric hypoxia, the lower under ambient air. B, Individual absolute changes in cycling time under normobaric hypoxia compared with ambient air. The dashed lines after 14 patients reflect the median change of -0.7 (-3.1 to 0.0) min ($P = .006$). Vertical lines at 1.75 min reflect the minimal clinical important difference (MCID) of constant work-rate cycling time as suggested for patients with COPD.

delivery was reduced because of the significantly lower arterial oxygen content. At isotimes under both conditions, pulmonary hemodynamic parameters were not significantly different except for the diastolic systemic BP at 6 min, which was higher under hypoxia (89 vs 94 mm Hg; $P = .017$) (Table 4). Significant changes in parameters were found from rest to end-exercise under both conditions (Table 3).

Dyspnea perception scores by Borg scale and visual analog scale-general at end-exercise were similar under hypoxia vs ambient air, whereas Borg leg fatigue score was increased. All symptom scale scores increased from rest to end-exercise under both conditions (Tables 2 and 3). Normobaric hypoxia at rest and under exercise was well tolerated; all patients completed the study without serious adverse events. The most frequently reported side effect was headache (five times during ambient air, eight times during hypoxia; $P =$ not significant). Exploratory analysis indicated that symptoms that might occur after prolonged hypoxia, defined as acute mountain sickness with LLS > 3 plus headache, were detected in six patients under hypoxia, and three under ambient air. The LLS was significantly higher under hypoxia at the end of the intervention. Hypoxia-induced

symptoms disappeared promptly with access to ambient air.

Univariable linear regression revealed that the PVR assessed during the last right heart catheterization is significantly correlated with the reduction in CWRET time induced by hypoxia whereas age, sex, the order of interventions, and further outcome measures were not associated. In the predefined multivariable model, higher PVR remained the sole significant predictor of a reduction in CWRET time under hypoxia vs ambient air, whereas the randomized order of intervention did not affect the change in cycle time (Table 5). The same multivariable model performed with exclusion of the four patients with PAH associated with connective tissue disease revealed comparable results with a slightly higher R^2 of 0.49.

TAPSE at rest was significantly lower in patients who decreased their cycling time > 1.75 min compared with those who did not (Table 6).

Discussion

The current randomized, ambient air (placebo)-controlled cross-over trial is the first randomized trial to investigate the effect of normobaric hypoxia equivalent

TABLE 3] Symptom-Limited Maximal Cycling Constant Work-Rate Exercise Test Results Under Normobaric Hypoxia (Fio₂, 15%) vs Ambient Air

Parameter	Ambient Air				Normobaric Hypoxia			
	End-Exercise Ambient Air (Fio ₂ , 21%)	Change From Rest to End-Exercise	P Value	End-Exercise Normobaric Hypoxia (Fio ₂ , 15%)	Change From Rest to Peak Exercise	P Value	Difference at End-Exercise Between Ambient Air and Normobaric Hypoxia	P Value
	Median (Quartiles)	Median Difference (95% CI)		Median (Quartiles)	Median Difference (95% CI)		Median Difference (95% CI)	
Cycling time, min	16.9 (8.0; 30.0)	6.7 (5.5; 27.3)	-0.7 (-3.1 to 0.0)	.006
Relative cycling time to ambient air, %	100 (100; 100)	93.2 (58.1; 100)	-6.8 (-32.2 to 0)	.018
Noninvasive blood and tissue oxygenation								
Pulse oximetry, %	90 (87; 92)	-4 (-6 to -2)	< .001	87 (81; 91)	-5 (-7 to -2)	< .001	-3 (-7 to 0)	.036
Cerebral tissue oxygen saturation, %	61 (57; 69)	-2 (-3 to -1)	.049	59 (53; 64)	-2 (-6 to -1)	.003	-6 (-8 to -2)	.091
Muscular tissue oxygen saturation, %	63 (59; 73)	-3 (-4 to -1)	.005	60 (52; 71)	-6 (-9 to -4)	< .001	-5 (-11 to 4)	.280
Arterial blood gases								
pH	7.4 (7.38; 7.45)	-0.03 (-0.04 to -0.02)	.009	7.42 (7.4; 7.44)	-0.02 (-0.04 to -0.02)	.002	0.01 (-0.02 to 0.02)	.421
Pco ₂ , kPa	4.7 (4.3; 4.8)	-0.3 (-0.4 to -0.2)	.001	4.3 (4; 4.7)	-0.3 (-0.7 to -0.2)	.003	-0.3 (-0.5 to -0.1)	.012
Po ₂ , kPa	8.0 (7.3; 9.9)	-1.6 (-2.6 to -0.5)	.003	6.4 (5.4; 7.9)	-1.2 (-1.9 to -1.0)	.002	-1.7 (-2.7 to -1.1)	.003
Hydrogen carbonate, mM	23 (21; 25)	-3 (-3.5 to -1.1)	< .001	23 (22; 24)	-2.7 (-4.1 to -1.5)	< .001	-0.4 (-0.7 to -0.1)	.031
Lactate, mM	3.7 (2.4; 5)	2.9 (1.4 to 3.9)	< .001	3.7 (2.6; 5.8)	3 (2.5 to 5.1)	< .001	0.9 (0.1 to 1.6)	.014
Arterial oxygen saturation, %	90 (87; 95)	-3.7 (-5.8 to -0.7)	.001	84 (76; 92)	-7.6 (-9.6 to -1.6)	.001	-5.3 (-9.2 to -2.0)	.003
Hemoglobin, g/dL	15.2 (14.7; 16.2)	1.4 (1.3 to 1.4)	< .001	15.3 (14.1; 16)	1.4 (0.9 to 1.7)	< .001	0.1 (-0.1 to 0.4)	.356
Arterial oxygen content, mL/dL	19.2 (17.6; 20.1)	0.9 (-0.1 to 2)	< .001	17.2 (15.5; 19.5)	0.2 (-1.2 to 1.3)	.498	-1.7 (-3 to -0.1)	.010
Oxygen delivery by echocardiography, mL/min	190 (144; 259)	89 (46 to 89)	.003	167 (133; 202)	80 (48 to 110)	.017	-24 (-85 to 26)	.063
Oxygen delivery by Finapres, mL/min	108 (76; 140)	31 (2 to 31)	.010	67 (50; 116)	3 (-20 to 32)	.370	-27 (-60 to 7)	.028
Circulatory and respiratory								

(Continued)

TABLE 3] (Continued)

Parameter	Ambient Air				Normobaric Hypoxia			
	End-Exercise Ambient Air (Fio ₂ , 21%)	Change From Rest to End-Exercise	P Value	End-Exercise Normobaric Hypoxia (Fio ₂ , 15%)	Change From Rest to Peak Exercise	P Value	Difference at End-Exercise Between Ambient Air and Normobaric Hypoxia	P Value
	Median (Quartiles)	Median Difference (95% CI)		Median (Quartiles)	Median Difference (95% CI)		Median Difference (95% CI)	
parameters by Finapres and PDx								
Heart rate, beats/min	107 (84; 123)	27 (16 to 41)	< .001	110 (92; 124)	26 (17 to 35)	< .001	7 (−9 to 13)	.808
Breathing rate, breaths/min	25 (21; 31)	9 (4 to 14)	< .001	29 (26; 33)	12 (10 to 13)	< .001	3 (−2 to 5)	.136
Systolic arterial pressure, mm Hg	128 (102; 162)	13 (4 to 33)	.004	131 (109; 152)	13 (3 to 29)	.028	−3 (−14 to 18)	.838
Diastolic arterial pressure, mm Hg	77 (63; 95)	7 (−1 to 16)	.081	85 (69; 102)	10 (5 to 22)	.012	9 (−3 to 20)	.249
Cardiac output, L/min	6 (3.8; 7.9)	2.1 (0.7 to 3)	< .001	4.5 (3.1; 6.2)	1.3 (0.5 to 1.7)	.006	−0.7 (−1.3 to 0.6)	.191
Systemic vascular resistance, Wood units	16 (10; 23)	5 (1 to 8)	.01	17 (14; 30)	5 (2 to 8)	.046	−1 (−6 to 2)	.260
Echocardiography								
Tricuspid regurgitation pressure gradient, mm Hg	77 (62; 118)	56 (34 to 91)	.012	89 (64; 115)	35 (34 to 147)	.068	−3 (−9 to 16)	.953
Systolic pulmonary arterial pressure (PAP), mm Hg	83 (69; 125)	56 (34 to 91)	.012	95 (67; 121)	35 (34 to 147)	.068	−3 (−9 to 16)	.593
Cardiac output (CO), L/min	10.8 (8.6; 8.8)	5.5 (4 to 5.8)	.028	10.6 (9.8; 9.9)	4.5 (2.3 to 6.1)	.109	1.4 (−6.3 to 3.7)	1
Mean PAP/CO, Wood units	4.5 (2.8; 8.5)	0.5 (−2.4 to 2.9)	.655	3.3 (2.7; 3.9)	3.2 (0.6 to 5.7)	.277	0.3 (−0.8 to 1.4)	.655
Tricuspid annular plane systolic excursion (TAPSE), cm	2.4 (2.3; 2.7)	0.5 (0.2 to 0.7)	.018	2.4 (2.2; 2.9)	0.7 (−0.6 to 1.2)	.068	−0.2 (−0.8 to 0.6)	.588
Tricuspid regurgitation velocity, m/s	5.2 (4.2; 5.6)	1.3 (0.6 to 2)	.043	4.3 (4; 5.3)	1.3 (0.9 to 4)	.066	−0.1 (−0.2 to 0.1)	.285
TAPSE/systolic PAP, mm/mm Hg	2.2 (1.8; 3.8)	−1.6 (−3.3 to −0.7)	.155	2.6 (2.1; 3.6)	−1.7 (−2.4 to −0.5)	.156	0.3 (−0.9 to 1.3)	.138

(Continued)

TABLE 3] (Continued)

Parameter	Ambient Air				Normobaric Hypoxia		
	End-Exercise Ambient Air (FIO ₂ , 21%)	Change From Rest to End-Exercise	P Value	End-Exercise Normobaric Hypoxia (FIO ₂ , 15%)	Change From Rest to Peak Exercise	P Value	Difference at End-Exercise Between Ambient Air and Normobaric Hypoxia
	Median (Quartiles)	Median Difference (95% CI)		Median (Quartiles)	Median Difference (95% CI)		Median Difference (95% CI)
							P Value
Patient-reported outcomes							
Visual analog scale (general status), cm	3.5 (1.5; 6.4)	1.6 (0.8 to 3.8)	< .001	3.9 (1.2; 7.6)	2.1 (0.6 to 3.9)	< .001	0.3 (−0.5 to 0.8)
Borg dyspnea scale	6 (5; 8)	5 (3 to 5)	< .001	7 (5; 8)	5 (4 to 6)	< .001	0.5 (0 to 1)
Borg leg fatigue scale	6 (3; 8)	5 (3 to 6)	< .001	5 (3; 8)	5 (3 to 6)	< .001	0 (0 to 0)
Lake Louise score	0 (0; 0)			0 (0; 1.8)			0 (0 to 0)
							.015
							.295
							.125
							< .001

to approximately 2,500 m on exercise performance, hemodynamics, oxygenation, and physiologic measures in stable patients with PAH/CTEPH without severe resting hypoxemia. The results show that breathing hypoxic air significantly reduces the median constant work-rate cycling time compared with ambient air along with reduced arterial oxygen content, increased ventilation as reflected by the lower PaCO₂, but with similar symptoms and pulmonary hemodynamics at end-exercise. However, high individual variability was found in response to hypoxia, as more than one-half the patients did not change their exercise time by more than 1.75 min, a value considered the minimally important difference in CWRET in COPD.²⁵ Hypoxic air breathing was generally well tolerated; the occurrence of occasional headaches was similar as with ambient air.

Millions of people regularly use airplanes or travel to regions at altitudes > 2,500 m, exposing themselves to a hypoxic environment. Among them there are increasingly more patients with cardiopulmonary diseases including a population of well-treated, stable, and physically active patients with PH. In healthy subjects it has been reported that hypoxia reduces exercise performance, due to the reduced oxygen delivery reflected by a lower arterial oxygen content and inadequate CO increase, increased PAP by hypoxic pulmonary vasoconstriction, altered central control and impaired diffusion in the lungs and muscles,^{3,27,28} but randomized controlled trials on the effect of hypoxia on different outcomes are scarce in healthy subjects and even more in patients with PAH.⁸ Altitude-related adverse health effects are more common in patients with cardiopulmonary diseases during mountain sojourns.^{10,29} However, less is known about the exercise performance, in a hypoxic environment, of patients who already have cardiopulmonary limitations and hypoxemia at low altitude. Eight patients with revascularized stable coronary artery disease were found to have similar exercise limitation at 4,200 m as healthy subjects,³⁰ whereas 38 patients with heart failure reduced their exercise capacity with a decreasing FIO₂.³¹ A randomized trial investigated patients with COPD at 2,590 vs 490 m and reported a 54% mean reduction in CWRET cycling time performed at 60% of the maximal workload at 490 m along with significantly reduced arterial and cerebral oxygen availability.³² The current study is the first to investigate CWRET cycling time in patients with PAH/CTEPH randomly exposed to normobaric hypoxia vs ambient air in a safe environment under laboratory conditions. In accordance

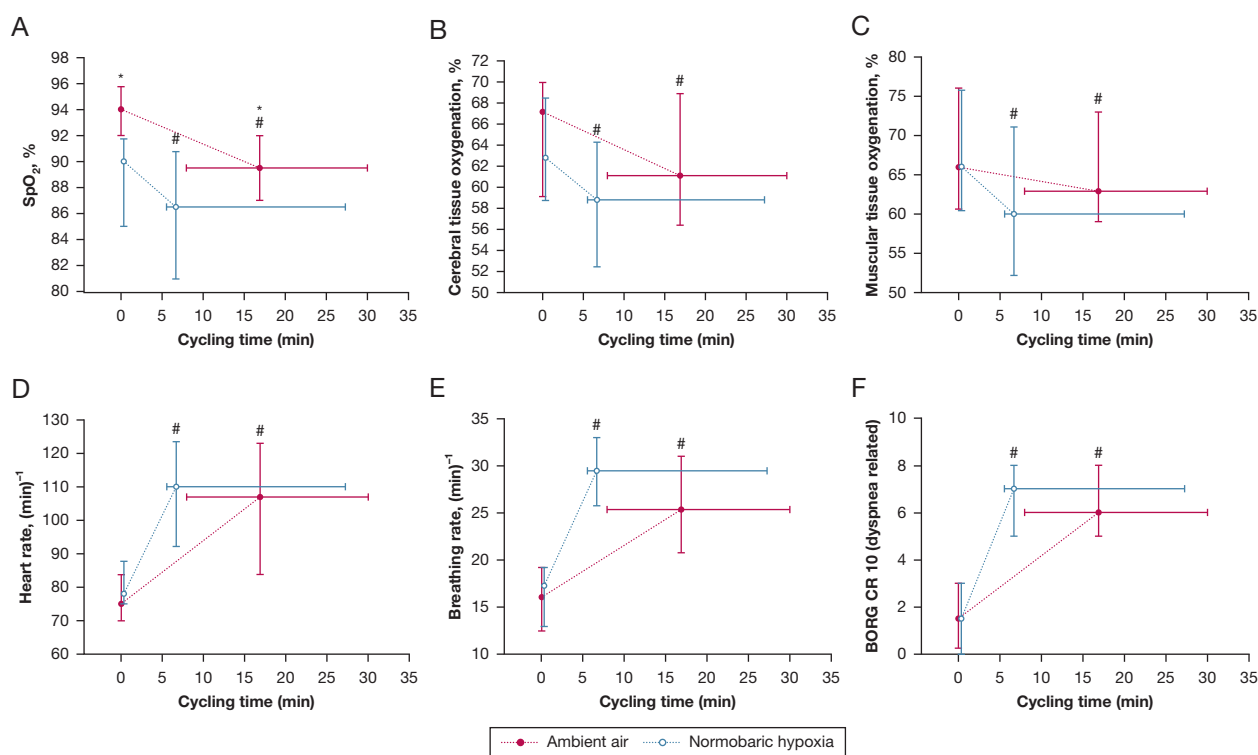


Figure 3 – Effects on physiologic parameters during cycle constant work-rate exercise test. Statistically significant changes ($P < .05$) are indicated by an asterisk (*) compared with ambient air and by a hash mark (#) compared with baseline. The bidirectional error bars indicate the nonparametric 95% CI. SpO₂ = arterial oxygen saturation as determined by pulse oximetry.

with healthy subjects and patients with COPD, we also found a significantly reduced CWRET time under hypoxia vs ambient air. The median relative reduction in patients with PH was 7% and thus markedly less reduced compared with patients with COPD exposed to a similar degree of hypoxia. However, these patients with COPD were investigated after a night at 2,590 m,³² so that the shorter exposure time in the present patients with PH might explain this difference. This is supported by the fact that despite a comparable baseline SpO₂, the cited patients with COPD revealed a lower PaO₂ of 6.8 kPa at altitude compared with the present PH cohort with a PaO₂ of 7.9 kPa.

The pathophysiologic mechanisms leading to the significantly reduced CWRET time with hypoxia in the present PH cohort are not entirely clear. The most suggestive explanation in a PH collective would be a circulatory limitation due to the increased right ventricular afterload limiting oxygen delivery to tissues. Indeed, we found that under both conditions, patients stopped cycling with similar hemodynamics and symptoms, which indicates that the circulatory limitation occurred earlier under hypoxia because of the reduced arterial oxygen content that would have called

for further CO increase, which was not possible because of the pulmonary vascular disease. Under hypoxia we found highly significantly reduced oxygen content, whereas the oxygen delivery tended to be reduced only at end-exercise. The latter might be due to imprecise echocardiographic CO values calculated from the left ventricular output tract velocity time integral, which is difficult to trace under exercise. Using the CO provided from finger-tip manometry, the oxygen delivery was indeed significantly reduced. The best predictor of the decrease in cycling time with hypoxia vs ambient air was the PVR obtained during the last right heart catheterization, whereas age, sex, and resting SpO₂ were significant predictors only in multivariable models including the PVR. This indicates that in more severe PH there is less cardiopulmonary reserve to exercise under hypoxic conditions, leading to reduced arterial oxygen content.

Healthy subjects and patients with COPD exposed to hypobaric hypoxia at altitude reveal increased resting systolic PAP and tend to have reduced CO compared with those living in lowland.³³⁻³⁵ The nonsignificant changes in PAP and cardiac function assessed by echocardiography or Finapres under normobaric

TABLE 4] Isotime at 3 and 6 Minutes Under Ambient Air and Normobaric Hypoxia During the Constant Work-Rate Cycling Exercise Test

Parameter	Isotime 3 Minutes				Isotime 6 Minutes			
	3-Min Exercise Under Ambient Air (n = 25)	3-Min Exercise Under Normobaric Hypoxia (n = 25)	Median Difference (95% CI)	P Value	6-Min Exercise Under Ambient Air (n = 20)	6-Min Exercise Under Normobaric Hypoxia (n = 20)	Median Difference (95% CI)	P Value
	Median (Quartiles)	Median (Quartiles)			Median (quartiles)	Median (Quartiles)		
Noninvasive blood and tissue oxygenation								
Pulse oximetry, %	91 (87; 94)	85 (81; 92)	-6 (-6 to -2)	.006	90 (85; 93)	85 (80; 92)	-5 (-6 to 0)	.007
Cerebral tissue oxygen saturation, %	65 (57; 70)	60 (53; 63)	-6 (-11 to -3)	.026	63 (8; 70)	59 (54; 63)	-5 (-13 to 0)	.049
Muscular tissue oxygen saturation, %	64 (59; 73)	59 (53; 70)	-5 (-13 to 4)	.426	64 (60; 74)	60 (53; 69)	-8 (-14 to 4)	.093
Circulatory and respiratory parameters by Finapres and PDx								
Heart rate, beats/min	98 (69; 109)	100 (78; 111)	4 (-3 to 11)	.632	101 (72; 114)	101 (86; 111)	4 (-1 to 7)	.975
Breathing rate, breaths/min	22 (19; 27)	23 (21; 28)	2 (1 to 3)	.184	23 (21; 30)	30 (22; 34)	2 (-1 to 6)	.064
Systolic arterial pressure, mm Hg	143 (115; 166)	144 (124; 162)	2 (-7 to 21)	.637	143 (123; 175)	153 (132; 180)	13 (-13 to 35)	.163
Diastolic arterial pressure, mm Hg	83 (68; 93)	89 (75; 110)	10 (-2 to 20)	.083	89 (73; 106)	94 (81; 112)	13 (1 to 23)	.017
Cardiac output, L/min	5.7 (4.7; 7.4)	5.3 (3.3; 7.6)	-0.3 (-1.1 to 1.3)	.910	5.8 (4.1; 7.9)	5.1 (2.9; 6.8)	-0.2 (-1.6 to 1.2)	.868
Systemic vascular resistance, Wood units	16 (14; 27)	15 (11; 25)	1 (-7 to 4)	.687	15 (11; 28)	18 (11; 26)	4 (-7 to 5)	.972
Echocardiography								
Tricuspid regurgitation pressure gradient, mm Hg	67 (55; 80)	61 (58; 92)	0 (-14 to 0)	.323	64 (58; 90)	71 (62; 110)	4 (-3 to 16)	.142
Systolic pulmonary arterial pressure (PAP), mm Hg	70 (58; 84)	69 (61; 100)	0 (-14 to 0)	.356	68 (61; 99)	75 (65; 113)	4 (-4 to 16)	.182
Mean pulmonary arterial pressure, mm Hg	45 (37; 53)	44 (39; 63)	0 (-8 to 0)	.356	43 (39; 63)	48 (42; 71)	3 (-3 to 10)	.066
Cardiac output (CO), L/min	7.3 (1.3; 7.5)	7.7 (3.7; 7.9)	-0.1 (-1.2 to 2)	.836	8.3 (4.0; 10.1)	8.1 (1.3; 10.4)	-0.1 (-1 to 0.8)	.678
Mean PAP/CO	7.1 (4.4; 38.4)	5.7 (4; 51.6)	0 (-33.9 to 10)	.859	5.1 (3.7; 14.2)	7.8 (5.2; 36.8)	1.8 (-1.7 to 20.2)	.237
Tricuspid annular plane systolic excursion, cm	2.1 (2; 2.4)	2.3 (2; 2.6)	0.1 (-0.1 to 0.4)	.269	2.3 (2.1; 2.5)	2.4 (2.3; 2.5)	0.1 (-0.1 to 0.3)	.381
Tricuspid regurgitation velocity, m/s	4.1 (3.7; 4.5)	3.9 (3.8; 4.8)	0 (-0.4 to 0)	.323	4 (3.8; 4.8)	4.2 (4; 5.3)	0.1 (-0.1 to 0.5)	.181
Left ventricular outflow tract velocity time integral, cm	21.7 (19.2; 23.4)	22 (18; 24.4)	-0.2 (-2 to 1.3)	.698	22.9 (22.3; 24.3)	21.6 (18.6; 23.9)	-0.7 (-3.7 to -0.3)	.260

Data summarize all subjects who managed to cycle up to a certain isotime.

TABLE 5] Predictors of Change in Constant Work-Rate Exercise Time With Normobaric Hypoxia vs Ambient Air

Predictor of Change in Cycling Time (s) From Ambient Air to Normobaric Hypoxia	Univariable Linear Regression			Multivariable Linear Regression		
	Coefficient	95% CI	P Value	Coefficient	95% CI	P Value
Intervention order, ambient air first	-117.3	-502.3 to 267.7	.537
Age, y	-0.3	-13.2 to 12.6	.961
Sex, male	-245	-621.2 to 131.1	.192
Spo ₂ at rest, %	-52.1	-108.7 to 4.4	.069	-40	-88 to 6.2	.086
Change in partial oxygen pressure, kPa	8.6	-72.7 to 89.9	.829
Pulmonary vascular resistance, Wood units	-109.8	-164.3 to -55.3	< .001	-95.3	-172.8 to -17.8	.018
6-min walk distance, m	-1.7	-3.8 to 0.4	.112
Spo ₂ at peak 6-min walk test, %	-4.1	-30 to 21.5	.746
New York Heart Association functional class	174.1	-81.7 to 430	.174
Cycling time under ambient air, s	-0.3	-0.6 to 0.0	.054	-0.0	-0.3 to 0.2	.814
Maximal oxygen uptake, L	1.6	-33.3 to 36.5	.927

Linear regression models with the change in constant work-rate exercise test time (s) as dependent variable. Negative coefficients indicate greater decrease with normobaric hypoxia. Univariable parameters with a *P* value < .1 were included in the multivariable model. Univariable model: $R^2 = 0.41$, $P < .001$; multivariable model: $R^2 = 0.45$, $P = .048$. Spo₂ = arterial oxygen saturation as determined by pulse oximetry.

hypoxia vs ambient air, also at rest, are in line with a previous study in which we exposed patients with PH to hypoxia during right heart catheterization at rest and found no change in PVR under hypoxia.¹¹ Similarly, a case-control study comparing patients with PAH with healthy subjects under hypoxia (Fio₂, 15.1%) did not reveal differences in right ventricular size and function under hypoxia at rest or under mild exercise.³⁶ However, this nonrandomized, nonblinded study revealed a slight and similar systolic PAP increase in patients with PAH and healthy subjects under hypoxia. A relevant factor limiting exercise performance under hypoxia might be tissue hypoxemia with compensatory hyperventilation. In line with this, our study revealed significantly lower PaCO₂, Pao₂, HCO₃⁻, and Sao₂ along with a higher lactate concentration at end-exercise under hypoxia compared with ambient air. These findings correspond to findings in healthy subjects and patients with COPD exercising at altitude.^{32,37} The decreased PaCO₂ at end-exercise under hypoxia signifies compensatory hyperventilation, which has been consistently shown in healthy and diseased subjects.^{22,28} Although breathing rate at end-exercise tended to be higher under hypoxia, the difference was not significant compared with ambient air. This is potentially due to a more pronounced increase in tidal volume, which was not measured in the present cohort. Increased lactate with exercise under hypoxia, as found in our study, has been previously shown in healthy subjects and was explained by premature anaerobic muscle metabolism due to hypoxemia³⁸; however, this was not associated with

increased leg fatigue, which was even higher under ambient air, and potentially related to the longer exercise duration.

Another contribution to reduced exercise capacity under hypoxia would be a dysfunction of the CNS, which fails to adequately activate muscle cells; however, this remains to be elucidated.³⁹ In our study, both the CTO and MTO significantly decreased from rest to end-exercise under both hypoxia and air breathing, without significant differences at end-exercise. This is in line with previous findings in highlanders living at approximately 3,250 m where CTO was unchanged, potentially related to physiologic adaption to protect the brain.⁴⁰ Whether the decrease in MTO during exercise under hypoxia contributes to the reduced exercise performance remains to be scrutinized.

Limitations

The presently investigated patients with PH were in good physical condition with a median 6-min walk distance of 515 m, and most were in NYHA functional class I/II under established therapy. Thus, our results may not apply for less fit, more symptomatic patients with PH. In accordance with the experience of patients with COPD,³² and for safety reasons regarding absent data on exercise under hypoxia in PH, we choose a CWRET load at 60% of patient maximal workload in an incremental ramp protocol, which might have been too low as many patients cycled > 20 min.⁸ We did not include ergospirometry and thus cannot provide

TABLE 6] Comparison Between Patients Who Decreased Their Constant Work-Rate Cycling Time With Hypoxia More Than 1.75 Minutes and Patients Who Did Not

Parameter	Patients Who Decreased Their Cycling Time Under Hypoxia vs Ambient Air		Patients Who Maintained or Improved Their Cycling Time Under Hypoxia vs Ambient Air		Wilcoxon Rank-Sum Test
	No.	Median (Quartiles)	No.	Median (Quartiles)	P Value
Clinical parameters					
Age, y	12	64 (55; 73)	16	66 (53; 79)	.781
Heart rate, beats/min	7	70 (62; 78)	16	64 (59; 70)	.228
BMI, kg/m ²	12	25 (22; 28)	16	27 (24; 31)	.227
Pulse oximetry, %	11	93 (91; 95)	16	93 (88; 94)	.551
Peripheral oxygen saturation measured at peak 6-min walk test, %	11	88 (82; 92)	15	91 (84; 95)	.420
Breathing rate, breaths/min	11	16 (14; 18)	16	20 (16; 22)	.061
New York Heart Association functional class	12	2 (1; 3)	16	2 (1; 3)	.764
Maximal oxygen uptake, L/min	12	15 (13.2; 19.3)	16	16.5 (12.7; 19.6)	.853
NT-pro-brain natriuretic peptide, ng/L	12	194.5 (93.3; 487.3)	16	254.5 (123.3; 422)	.643
Hemodynamics measured during the last right heart catheterization					
Mean pulmonary arterial pressure, mm Hg	12	43 (37; 54.3)	16	33.5 (27.3; 45.5)	.162
Pulmonary arterial wedge pressure, mm Hg	11	12 (10; 13)	16	11.5 (8.5; 13)	.424
Cardiac index, L/min/m ²	11	2.5 (2.1; 3.2)	16	2.5 (2.3; 2.8)	.824
Pulmonary vascular resistance, Wood units	11	7.8 (5; 10)	16	4.9 (3.6; 7.6)	.084
Arterial oxygen saturation, %	8	93 (90.5; 95)	16	93 (90; 95.8)	.901
Mixed venous oxygen saturation, %	11	68 (54; 73)	16	66 (63; 71)	.767
Assessments after 20 min of normobaric hypoxia (FiO₂, 15%)					
pH	10	7.5 (7.4; 7.5)	15	7.5 (7.4; 7.5)	.677
Pco ₂ , kPa	10	4.8 (4.6; 5.1)	15	4.9 (4.2; 5.1)	.824
Po ₂ , kPa	10	7.6 (6.7; 9.2)	15	8 (7.4; 8.9)	.579
Lactate, mM	10	0.8 (0.6; 1.2)	14	0.9 (0.5; 1.7)	.883
Arterial oxygen saturation, %	10	89 (85; 94.6)	15	92 (88; 94)	.244
Breathing rate, breaths/min	10	15 (13; 19)	15	17 (13; 20)	.542
Heart rate, bpm	10	73 (68; 83)	15	68 (65; 74)	.095
Pulse oximetry, %	10	90 (86; 93)	15	90 (83; 92)	.597
Diastolic BP, mm Hg	11	79 (66; 88)	16	66 (56; 77)	.139
Systolic BP, mm Hg	11	117 (108; 126)	16	119 (107; 136)	.980
Echocardiography assessed after 20 min of normobaric hypoxia (FiO₂, 15%)					
Left ventricular ejection fraction, %	10	60 (60; 70)	11	60 (60; 70)	.136
Systolic pulmonary arterial pressure, mm Hg	11	41 (30; 57)	15	52 (37; 67)	.349
Cardiac output, L/min	12	5.1 (4; 6.6)	14	5.5 (4.9; 5.8)	.817
Tricuspid annular plane systolic excursion, cm	12	1.7 (1.7; 1.9)	14	2 (1.8; 2.3)	.037

Relevant decrease in cycling time was assumed according to the minimal importance difference in change in constant work-rate cycling time of 1.75 min as derived for patients with COPD.

information on oxygen uptake, CO₂ output, minute ventilation, or end-tidal Paco₂, but did measure respiratory rate by plethysmography and Paco₂ in

blood gases. Assessing hemodynamics by echocardiography, especially under exercise, may have limits of accuracy.⁴¹

Interpretation

An increasing number of stable and active patients with PH ask about potential adverse health effects of altitude or air travel. This first randomized, placebo-controlled trial shows that in accordance with healthy control subjects and patients with COPD, patients with PH also reveal a reduced exercise capacity under hypoxic conditions albeit with high interindividual variability. Because pulmonary

hemodynamics, cardiac output, and dyspnea at end-exercise, together with deoxygenation during exercise, remained unaltered, exercise limitation under hypoxia may be caused by lower oxygen content and excessive ventilation reflected by lower Paco_2 at end-exercise. Further studies at real altitude should explore longer-term changes and adaptive mechanisms to hypoxia in PH, potential adverse health effects, and their risk factors.

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2.2. Project II

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

Citation:

Schneider SR, Mayer LC, Lichtblau M, Berlier C, Schwarz EI, Saxer S, Tan L, Furian M, Bloch KE, Ulrich S. Effect of a day-trip to altitude (2500m) on exercise performance in pulmonary hypertension: randomised crossover trial. *ERJ Open Res.* 2021 Oct 11;7(4):00314-2021. doi: 10.1183/23120541.00314-2021. PMID: 34651040; PMCID: PMC8502941.



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

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Shareable abstract (@ERSpublications)

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 \pm SD age 63 \pm 15 years were included. After >3 h at 2500 m versus 470 m, CWRET-time was reduced to 17 \pm 11 versus 24 \pm 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 \pm 0.8 versus 10.4 \pm 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 \pm 18 versus 71 \pm 16 beats \cdot min⁻¹, mean difference 15 beats \cdot min⁻¹, 95% CI 7 to 23 beats \cdot min⁻¹) and 56 \pm 25 versus 40 \pm 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 $\times\pi\times(\text{LVOT diameter}/2)^2$ and CO=SV \times heart rate. TRPG was derived using the simplified Bernoulli equation $\Delta P=4\times V_{\text{max}}^2$. 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 \times systolic PAP+2 [20]. Pulmonary artery wedge pressure (PAWP) was computed by $1.24\times(E/E') + 1.9$ [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 $\times 1.36\times$ (arterial oxygen saturation (S_{aO_2})/100)) $+(7.5\times P_{aO_2}\times 0.0031)$ 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 (Philips Respironics, 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 isotime 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 ($\alpha=0.05$), 18 patients were required [27]. As the dropout rate in a logistically demanding study was not known, we scheduled 28 participants to participate.

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 \pm 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 ($2\text{--}3\text{ L}\cdot\text{min}^{-1}$) 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 <i>versus</i> 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

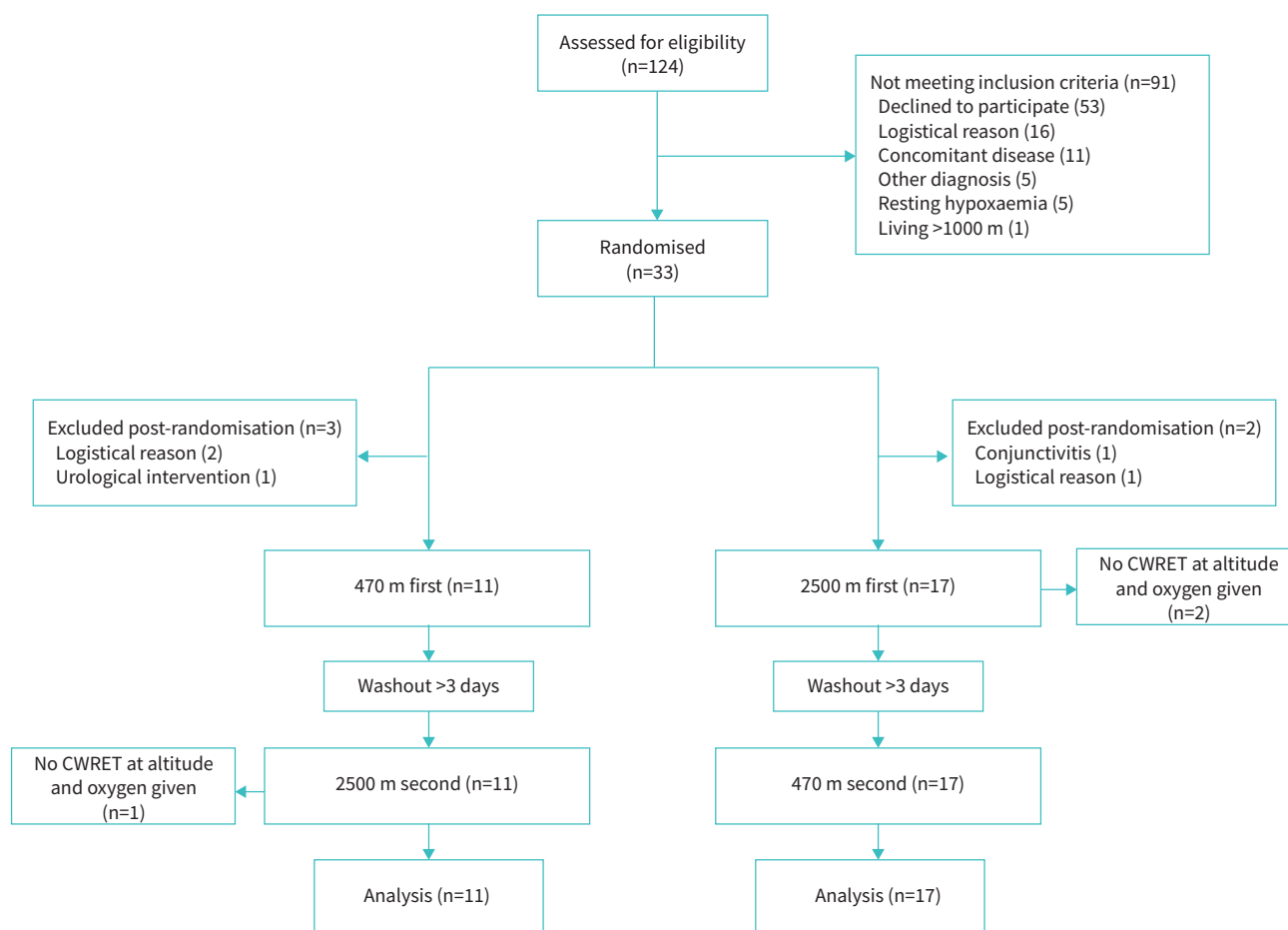


FIGURE 1 Patient flow. CWRET: constant work-rate exercise test.

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 $5.0 \text{ mmol} \cdot \text{L}^{-1}$ at 2500 m (table 3) was greater than the corresponding rise in lactate of $3.0 \text{ mmol} \cdot \text{L}^{-1}$ 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

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 <i>versus</i> 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.

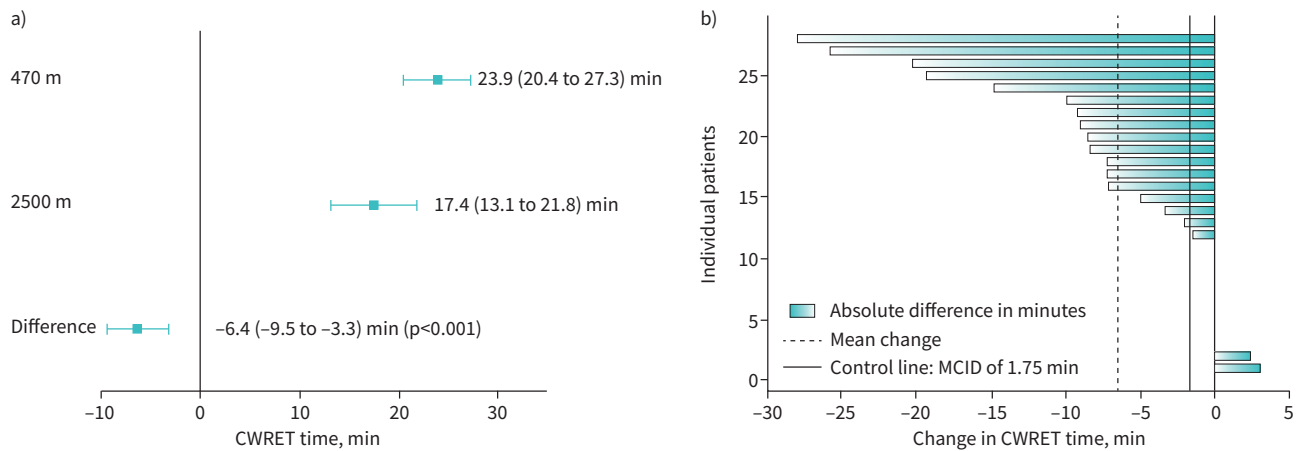


FIGURE 2 Constant work-rate exercise test (CWRET) time at altitude in pulmonary hypertension. **a)** The CWRET cycling time at low altitude (470 m), high altitude (2500 m) and the difference between altitudes presented as mean (95% CI) in patients with pulmonary arterial hypertension or chronic thromboembolic 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.

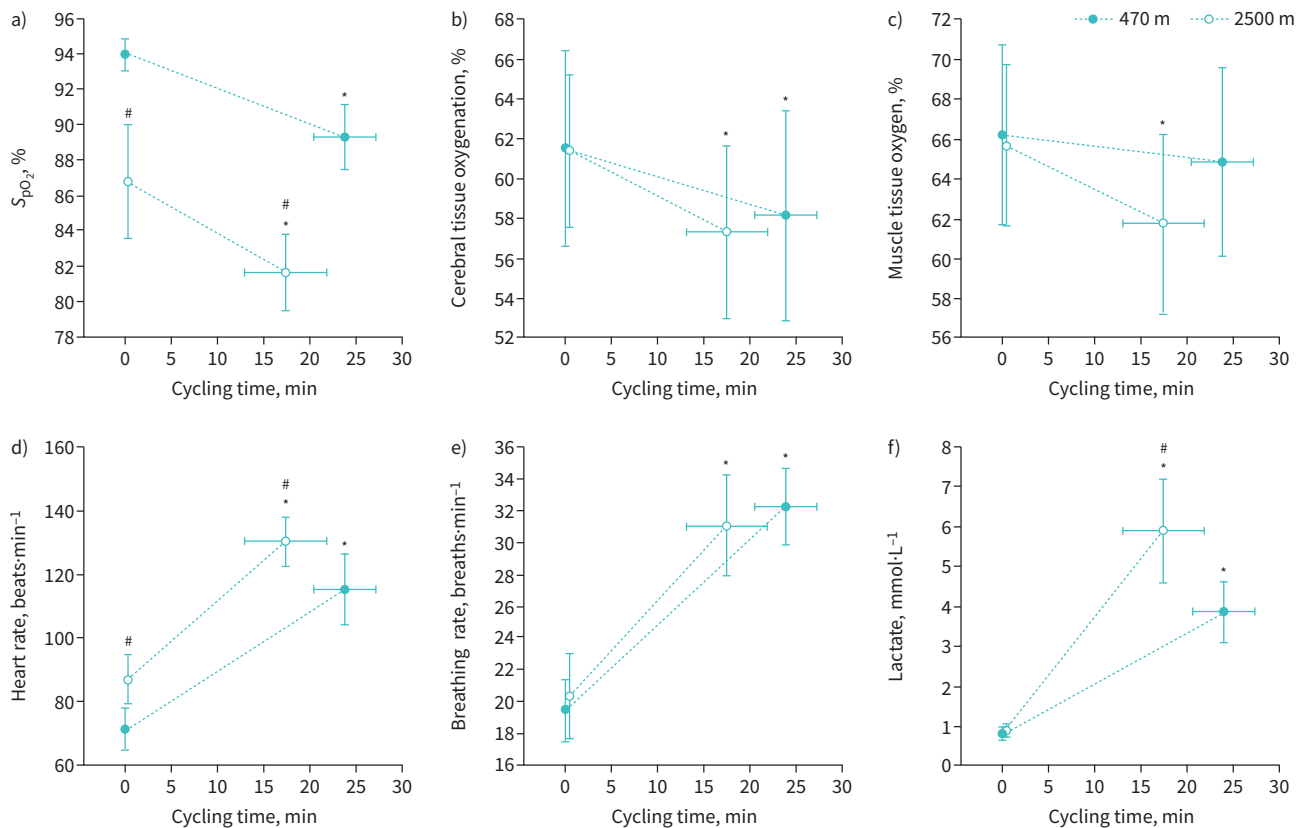


FIGURE 3 Effects of altitude exposure on physiological parameters during the constant work-rate cycle exercise test. The bidirectional error bars indicate 95% confidence intervals. S_{pO_2} : peripheral oxygen saturation. #: p<0.05 at 2500 m compared to 470 m; *: p<0.05 at end-exercise compared to rest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

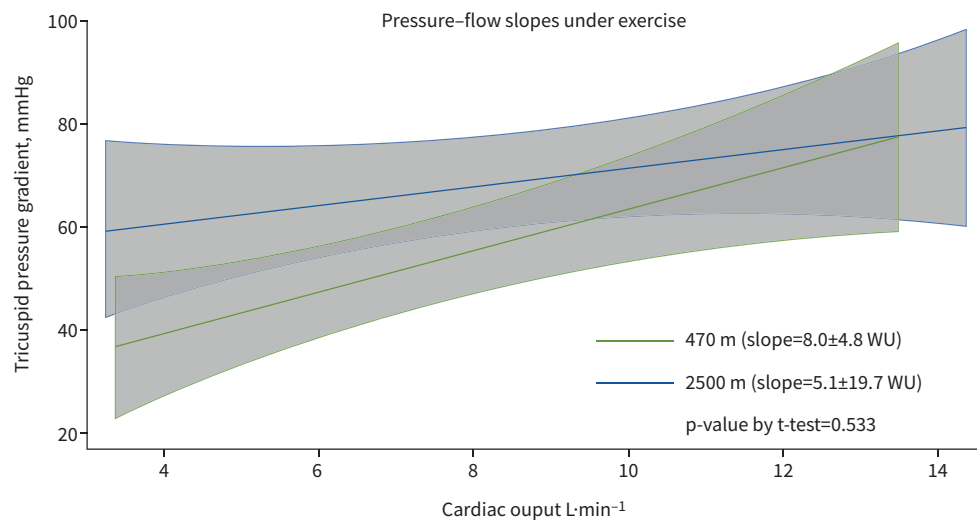


FIGURE 4 Pulmonary artery pressure–flow slopes as tricuspid regurgitation pressure gradient to cardiac output ratio during constant work-rate cycle exercise tests at 470 m and 2500 m shown as mean (95% CI).

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.

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

Conflict of interest: S.R. Schneider has nothing to disclose. L.C. Mayer has nothing to disclose. M. Lichtblau has nothing to disclose. C. Berlier has nothing to disclose. E.I. Schwarz has nothing to disclose. S. Saxer has nothing to disclose. L. Tan has nothing to disclose. M. Furian has nothing to disclose. K.E. Bloch has nothing to disclose. S. Ulrich reports grants from Johnson and Johnson SA, Switzerland, during the conduct of the study; and grants from the Swiss National Science Foundation and Zurich Lung, grants and personal fees from Orpha Swiss, and personal fees from Actelion SA and MSD SA, outside the submitted work.

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2.3. Project III

Cardiorespiratory Adaptation to Short-Term Exposure to Altitude vs. Normobaric Hypoxia in Patients with Pulmonary Hypertension

Citation:

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Article

Cardiorespiratory Adaptation to Short-Term Exposure to Altitude vs. Normobaric Hypoxia in Patients with Pulmonary Hypertension

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Abstract: Prediction of adverse health effects at altitude or during air travel is relevant, particularly in pre-existing cardiopulmonary disease such as pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH, PH). A total of 21 stable PH-patients (64 ± 15 y, 10 female, 12/9 PAH/CTEPH) were examined by pulse oximetry, arterial blood gas analysis and echocardiography during exposure to normobaric hypoxia (NH) (F_{iO_2} 15% \approx 2500 m simulated altitude, data partly published) at low altitude and, on a separate day, at hypobaric hypoxia (HH, 2500 m) within 20–30 min after arrival. We compared changes in blood oxygenation and estimated pulmonary artery pressure in lowlanders with PH during high altitude simulation testing (HAST, NH) with changes in response to HH. During NH, 4/21 desaturated to $SpO_2 < 85\%$ corresponding to a positive HAST according to BTS-recommendations and 12 qualified for oxygen at altitude according to low $SpO_2 < 92\%$ at baseline. At HH, 3/21 received oxygen due to safety criteria ($SpO_2 < 80\%$ for >30 min), of which two were HAST-negative. During HH vs. NH, patients had a (mean \pm SE) significantly lower $PaCO_2$ 4.4 ± 0.1 vs. 4.9 ± 0.1 kPa, mean difference (95% CI) -0.5 kPa (-0.7 to -0.3), PaO_2 6.7 ± 0.2 vs. 8.1 ± 0.2 kPa, -1.3 kPa (-1.9 to -0.8) and higher tricuspid regurgitation pressure gradient 55 ± 4 vs. 45 ± 4 mmHg, 10 mmHg (3 to 17), all $p < 0.05$. No serious adverse events occurred. In patients with PH, short-term exposure to altitude of 2500 m induced more pronounced hypoxemia, hypocapnia and pulmonary hemodynamic changes compared to NH during HAST despite similar exposure times and P_{iO_2} . Therefore, the use of HAST to predict physiological changes at altitude remains questionable. (ClinicalTrials.gov: NCT03592927 and NCT03637153).

Keywords: normobaric hypoxia; hypobaric hypoxia; high altitude; pulmonary hypertension; chronic thromboembolic pulmonary hypertension

1. Introduction

Because of the easy access to mountain areas, mountain tourism, the many populated high altitude areas, and the affordable costs of long-distance flights, the number of people exposing themselves to hypoxia is increasing [1]. Hence, patients with cardiovascular or respiratory disorders such as pulmonary arterial and chronic thromboembolic pulmonary hypertension (PAH/CTEPH, summarized as PH) also wish to undergo high altitude journeys and air travel for various purposes. Hypobaric hypoxia (HH) increases with increasing altitude and decreasing barometric pressure (P_{bar}) resulting in an increasing prevalence of altitude-related adverse health effects (ARAHE) in healthy but particularly in patients with cardiorespiratory diseases [2–6]. The lower P_{bar} resulting

in lower alveolar, blood- and tissue oxygenation leads to immediate hypoxic pulmonary vasoconstriction (HPV) that may put PH-patients at a particularly high risk for a further increase in pulmonary artery pressure (PAP) and vascular resistance (PVR) in response to hypoxia [7]. Comprehensive data on the acute effects of exposure to normobaric hypoxia (NH) in PH have recently been published [8,9] and effects of an exposure to HH of PH patients during a daytrip to altitude (2500 m, Mount Saentis) have been described [10]. However, adequate counselling of PH-patients with regard to altitude or air travel remains challenging, as risk factors and predictors for ARAHE and potential need of supplemental oxygen are largely unknown [8–11]. In patients with chronic obstructive pulmonary disease (COPD), it is recommended to use supplemental oxygen during air travel when in-flight partial pressure of O₂ (PaO₂)-levels drop < 6.6 kPa, albeit this recommendation is not based on robust evidence and the critical blood oxygen level inducing ARAHE is unknown [12,13]. To evaluate the patient's risk for ARAHE during air travel, some experts recommend performing the high altitude simulation test (HAST) [11,12,14]. During the HAST, patients breathe a nitrogen-enriched gas mixture with an inspired O₂ fraction (F_iO₂) of 15% to simulate inflight conditions. The resulting inspired partial pressure of O₂ (P_iO₂) corresponds approximately to the minimally allowed pressure in commercial aircraft cabins (pressurized to 752 hPa, equivalent to 2438 m, 8000 ft) [11]. The HAST is used for COPD-patients with borderline SpO₂ levels < 95% near sea level. It has been shown to predict inflight oxygen saturation with varying accuracy [11,15]. However, evidence-based counseling based on HAST for upcoming air-travel is limited as its ability to predict ARAHE has not been evaluated [11,16,17]. Nevertheless, the British Thoracic Society expert group recommends supplemental inflight oxygen if SpO₂ at the end of HAST is < 85% or PaO₂ < 6.6 kPa [12,13].

The aim of the present analysis was to compare changes in blood oxygenation and echocardiographically assessed PAP in response to exposure to NH during HAST to their respective changes induced by a similar exposure time to HH at the equivalent real altitude (2500 m). Furthermore, we evaluated whether outcomes from HAST predict the occurrence of ARAHE within the first hours at 2500 m altitude.

2. Materials and Methods

2.1. Subjects

Adult outpatients with precapillary PH due to PAH or distal CTEPH diagnosed in accordance with current guidelines [18] were recruited in the reference centre for PH of the University Hospital Zurich and included upon written informed consent. Patients were clinically stable, living at low altitude < 1000 m, had a resting PaO₂ > 7.3 kPa and a PaCO₂ < 6.5 kPa. Patients exposed to >1500 m for >3 nights during the previous 4 weeks, pregnant- or breastfeeding women or patients with relevant comorbidities (PH of other groups such as from heart- or lung disease or miscellaneous reasons, severe concomitant diseases such as cancer, psychological disorders and illicit drugs or alcohol abuse) were excluded. This subgroup analysis where patients participated in two already published randomized cross-over trials investigating the effect of NH vs. placebo (air at 470 m) and the effect of a daytrip to HH at 2500 m vs. 470 m investigates the predictive value from NH to altitude exposure and physiological differences between NH and HH. Part of these data, mainly from the NH group, have been previously published [10]. The studies followed the principles of the declaration of Helsinki, was approved by Cantonal Ethics Committee Zurich (KEK 2018-00455), and registered at ClinicalTrials.gov (NCT03592927 and NCT03637153).

2.2. Design and Interventions

The methods of the trials evaluating arterial blood gas and hemodynamic changes induced by NH and a daytrip to HH, respectively, vs. room air at 470 m at rest and during exercise have been previously reported [9,10]. The present analysis focuses on the difference induced by NH at low altitude (simulated altitude) vs. HH at high altitude (2500 m) in

the same patients during a comparable exposure time and inspired partial pressure of oxygen (P_{iO_2}). NH with an F_{iO_2} of 15% was applied via a tightly-fitted facemask with a non-rebreathing two-way valve (Hans-Rudolph, Shawnee, KS, USA) connected to an ambient air-nitrogen mixing device (AltiTrainer, Lausanne, Switzerland) during 30–45' as described [9]. Measurements during HH were performed 20–30' after patients arrived at 2500 m at Mount Saentis by cable car (10 min ascent) [10].

2.3. Assessments

Baseline measurements included demographics, PH-classification, current medication, and New York Heart Association (NYHA) functional class.

The following assessments were performed 20–30' after exposure to NH during a HAST and 20–30' after arrival on Mount Säntis at 2500 m by cable car:

Transthoracic echocardiography was performed in supine position at rest (CX50, Philips Respironics, Horgen, Switzerland) according to current guidelines [19]. The maximal tricuspid regurgitation velocity was assessed by Doppler to derive the tricuspid regurgitation pressure gradient (TRPG) with the simplified Bernoulli equation $\Delta P = 4 \times V_{max}^2$, which served as surrogate for the PAP. Fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), stroke volume (SV) (=the left ventricular outflow tract velocity time integral (LVOT VTI) $\times \pi \times (LVOT \text{ diameter}/2)^2$), and cardiac output (CO) (=SV \times heart rate (HR)) were measured. We estimated the resting right atrial pressure (RAP) from the respiratory variability of the inferior vena cava. The systolic PAP (SPAP) was calculated as TRPG + RAP and mean PAP as $0.61 \times \text{systolic PAP} + 2$ [20]. Pulmonary artery wedge pressure (PAWP) was computed by $1.24 \times (E/E') + 1.9$ [21]. PVR was calculated by $(\text{mean PAP} - \text{PAWP}) / \text{CO}$ [19,22,23].

Arterial blood was sampled from the radial artery at rest and immediately analyzed (ABL90 Flex, Radiometer GmbH, Switzerland). The oxygen content (CaO_2) was calculated by the following formula: $(Hb \times 1.36 \times (SaO_2/100)) + ((7.5 \times PaO_2) \times 0.0031)$ and was multiplied by CO for oxygen delivery (DaO_2) [24].

HR, breathing rate (BR) and fingertip SpO_2 were continuously recorded by Alice-PDX[®] (Philips Respironics, Horgen, Switzerland).

The 10-cm visual analogue scale was used for assessing general wellbeing and dyspnea at the end of the echocardiography in upright position [25].

2.4. Index and Reference Test

HAST, index test: We applied the same HAST criteria for in-flight supplemental oxygen recommendations as proposed by the British Thoracic Society [26–28]. Therefore, a positive HAST was defined as a $SpO_2 < 85\%$ or a $PaO_2 < 6.6$ kPa after 20 min exposure to NH.

ARAHE, reference test: Patients with severe dyspnea or general discomfort, new onset angina, cardiac deterioration (arrhythmia, dizziness), symptoms of acute mountain sickness or an $SpO_2 < 80\%$ for >30 min or <75% for >15 min were defined as experiencing an ARAHE, and resulted in the indication for oxygen therapy with the aim of achieving an $SpO_2 > 90\%$ and accompanied return to low altitude [6,29].

2.5. Data Analysis and Statistics

Baseline characteristics are summarized as means \pm standard deviation (SD) or number (proportions). Continuous physiological data from Alice-PDX[®] (following 20–30 min of exposure to NH or HH) were imported to LabChart Data analysis software, version 8 and averaged over 30 s. Data are summarized as means \pm standard errors and the difference between NH and HH shown as mean-difference with 95% confidence intervals. Mixed-effects linear regression models with fixed effects (Time, Age, Gender and NYHA-class) and calculated average marginal effects generated by Stata[®]'s linear combinations of parameters (lincom) were used. The sensitivity and specificity to predict ARAHE by BTS-criteria for HAST at low altitude were calculated. A receiver operator-characteristic curve (ROC)

including area under the curve (AUC) for the best predicting cut-off for ARAHE of SpO₂ and PaO₂ during HAST were calculated. A two-sided p -value <0.05 was considered as statistically significant. Statistical analysis was performed with Stata statistical software, version 16.

3. Results

3.1. Study Population

Based on the recruitment structure from the initial trial examining HA-exposure within a daytrip, 124 patients with PH were assessed for eligibility. A total of 21 patients (12 PAH, 9 distal CTEPH, 10 female, age 64 ± 15 years) participated in both trials. Patients performed a HAST within 42 ± 25 days before or after the daytrip to 2500 m (HH) (Figure 1). Demographic characteristics are summarized in Table 1 [9,10].

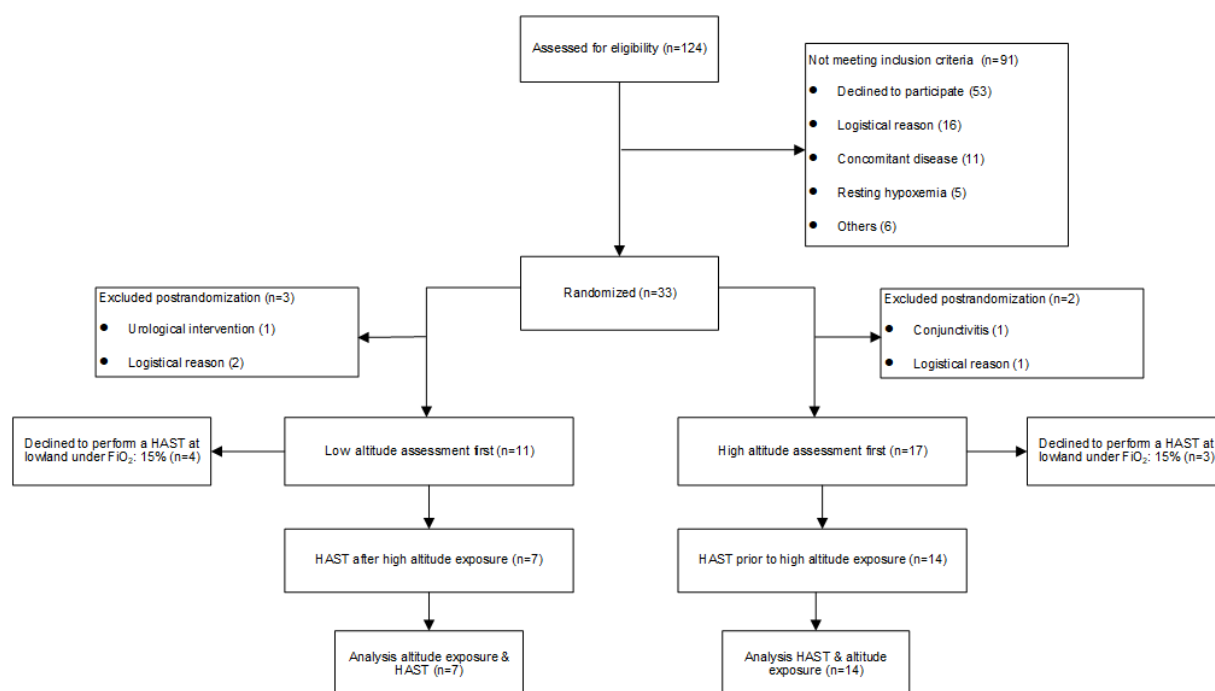


Figure 1. Flow chart: HAST = High altitude simulation test.

Table 1. Baseline characteristics.

Participants/women (%)	21/10 (48)
Age, years	64 ± 15
Body mass index, kg/m ²	25.6 ± 3.8
Pulmonary hypertension classification	
1. Pulmonary arterial hypertension	12 (58)
1.1. idiopathic	10 (48)
1.4.1. connective tissue disease	1 (5)
1.4.3. portopulmonary hypertension	1 (5)
4. Chronic thromboembolic pulmonary hypertension	9 (43)
6-min walk distance, m	538 ± 94
New York Heart Association functional class I, II, III	8 (38), 9 (43), 4 (19)
N-terminal pro brain natriuretic peptide, ng/l	427 ± 620
Incremental ramp cycle exercise, Watt	114 ± 36
Maximal oxygen uptake, ml/min/kg	18.2 ± 3.9
Resting arterial partial pressure of oxygen, kPa	10.1 ± 1.6
Mean pulmonary arterial pressure, mmHg *	42 ± 11
Pulmonary vascular resistance, WU *	6 ± 3

Table 1. Cont.

PH targeted therapy	
Endothelin receptor antagonist	14 (67)
Phosphodiesterase-5 inhibitor including Soluble guanylate cyclase stimulators	9 (43)
Soluble guanylate cyclase stimulators	2 (10)
Prostacyclin-receptor agonist or prostacyclin	2 (10)
Combination therapy	8 (38)

Data shown as number (%) or mean \pm SD, * = assessed during last right heart catheter., WU = Wood unit.

3.1.1. Differences between Exposure to Normobaric vs. Hypobaric Hypoxia

Differences between NH and HH are shown in Table 2 and Figure 2. Linear mixed-effect regression models revealed that HR and BR did not significantly differ between NH and HH. Pulse oximetry and arterial blood gas analysis revealed a significantly lower blood oxygenation including PaO_2 , SaO_2 and oxygen content (CaO_2). PaCO_2 and bicarbonate (HCO_3^-) were also significantly lower in HH compared to NH, whereas pH was significantly higher (Figure 2). TRPG was significantly higher during HH compared to NH, which also led to a significant difference in SPAP and the TAPSE/SPAP ratio. Other echocardiographic measurements did not differ significantly between NH and HH. Patient-reported visual analogue scales, dyspnea-related symptoms and general well-being, did not differ among NH compared to HH (Table 2, Figure 3).

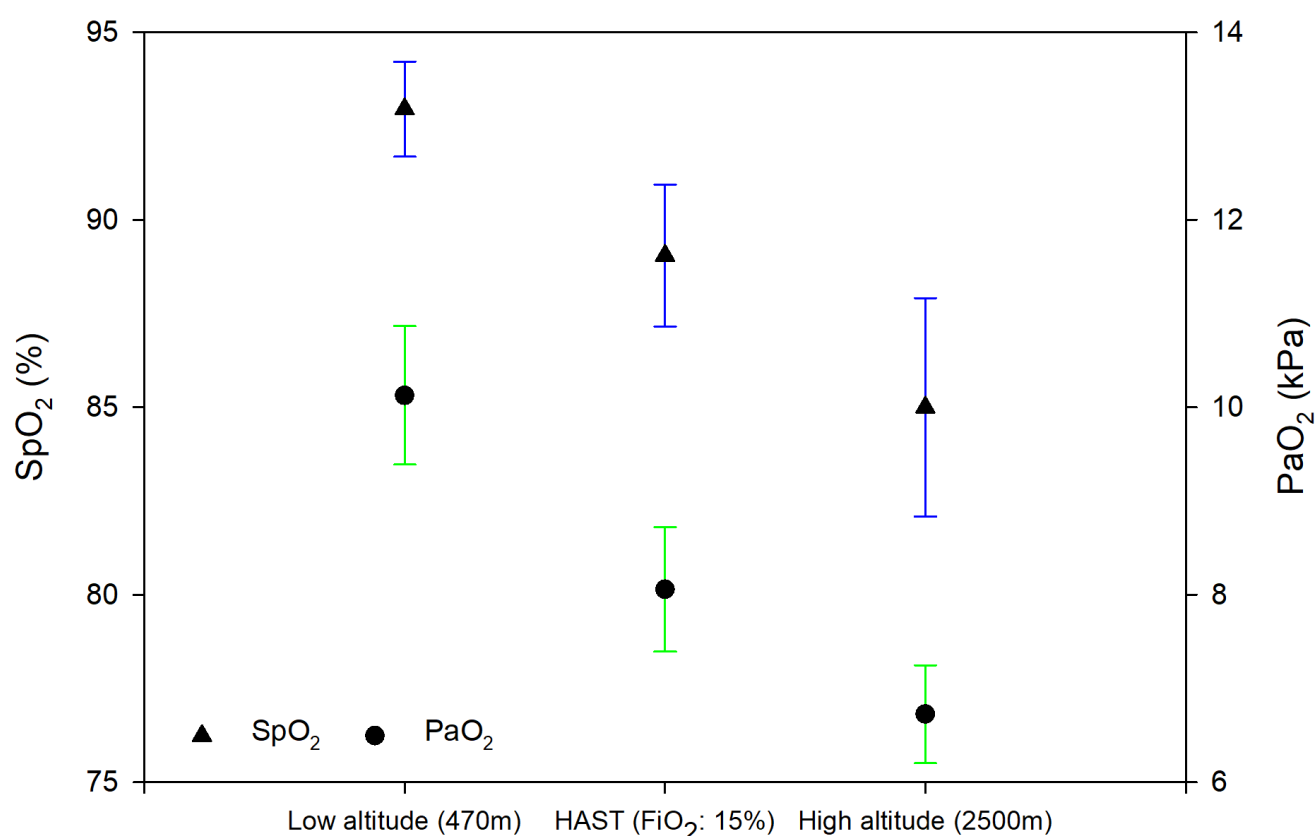
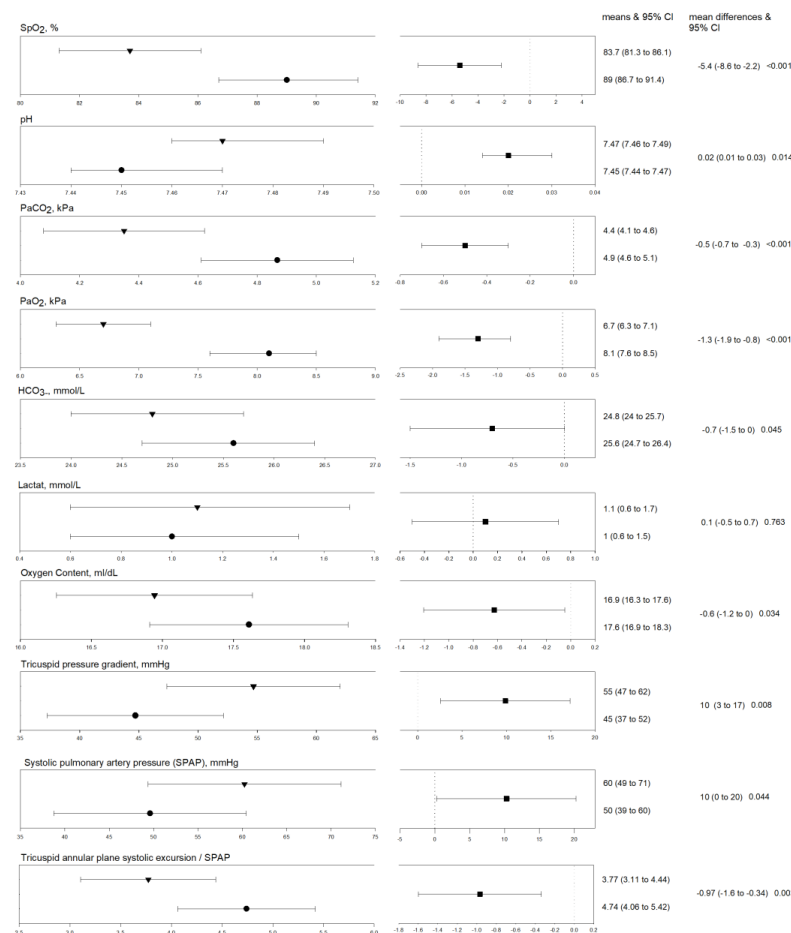


Figure 2. SpO_2 (triangles, blue) and PaO_2 (circles, green) in normobaric normoxia (470 m), normobaric hypoxia (470 m) and at high altitude (2500 m). HAST = High altitude simulation test. Measurements are summarized as means and 95% Confidence Intervals. Data are computed from a mixed-effect regression model with fixed effects variables as time, age, gender and New York Heart Association class.

Table 2. 20–30 min normobaric hypoxia (F_IO₂ 15%) vs. hypobaric hypoxia (2500 m).

Parameter	F _I O ₂ : 15% (Mean ± SE)	Altitude (2500 m) (Mean ± SE)	Mean Difference (95% CI)	p-Value
Peripheral oxygen saturation, %	89 ± 1.2	83.7 ± 1.2	−5.4 (−8.6 to −2.2)	<0.001
pH	7.45 ± 0.01	7.47 ± 0.01	0.02 (0.00 to 0.03)	0.014
Partial pressure of carbon dioxide, kPa	4.9 ± 0.1	4.4 ± 0.1	−0.5 (−0.7 to −0.3)	<0.001
Partial pressure of oxygen, kPa	8.1 ± 0.2	6.7 ± 0.2	−1.3 (−1.9 to −0.8)	<0.001
Hydrogen carbonate, mmol/L	25.6 ± 0.4	24.8 ± 0.4	−0.7 (−1.5 to 0.0)	0.045
Lactate, mmol/L	1 ± 0.2	1.1 ± 0.3	0.1 (−0.5 to 0.7)	0.763
Arterial oxygen saturation, %	90.5 ± 1.2	83.7 ± 1.2	−6.8 (−9.6 to −4.0)	<0.001
Arterial oxygen content, mL/dL	17.6 ± 0.4	16.9 ± 0.4	−0.6 (−1.2 to 0.0)	0.034
Heart rate, min ^{−1}	71 ± 3	69 ± 3	−1.2 (−9 to 6.6)	0.762
Breathing rate, min ^{−1}	16 ± 1	19 ± 1	3 (0 to 7)	0.056
Right atrial pressure, mmHg	4 ± 1	5 ± 1	1 (0 to 1)	0.160
Tricuspid regurgitation pressure gradient (TRPG), mmHg	45 ± 4	55 ± 4	10 (3 to 17)	0.008
Systolic pulmonary arterial pressure (SPAP), mmHg	50 ± 6	60 ± 6	10 (0 to 20)	0.044
Stroke volume, mL	73 ± 4.4	74.3 ± 4.3	0.8 (−9.4 to 11)	0.876
Cardiac output (CO), L/min	5.1 ± 0.4	5.1 ± 0.4	0 (−0.9 to 0.8)	0.920
Oxygen delivery, mL/min	906.6 ± 66.9	854.6 ± 65.6	−44.2 (−192.9 to 104.6)	0.560
Pulmonary vascular resistance, WU	4.3 ± 2.9	5.4 ± 2.6	1.4 (−6.3 to 9.1)	0.718
TRPG/CO, WU	8.4 ± 2	11.3 ± 2	2.8 (−2.5 to 8.2)	0.302
Tricuspid annular plane systolic excursion (TAPSE), cm	2 ± 0.1	2 ± 0.1	0 (−0.2 to 0.1)	0.760
TAPSE/SPAP ratio	4.74 ± 0.35	3.77 ± 0.34	−0.97 (−1.6 to −0.34)	0.003
Fractional area change, %	32 ± 2	30 ± 2	−2 (−6 to 2)	0.422
Visual analog scale (general wellbeing), cm	8.5 ± 0.4	8.7 ± 0.4	0.17 (−0.78 to 1.12)	0.730
Visual analog scale (dyspnea), cm	8.2 ± 0.5	8.4 ± 0.5	0.21 (−0.83 to 1.24)	0.694

Data are computed from a mixed-effect regression model with fixed effects variables as Time, Age, Gender and New York Heart Association class; F_IO₂: fraction of inspired oxygen, CI: Confidence Interval.

**Figure 3.** Physiological outcomes after 20–30 min under normobaric (F_IO₂: 15%) vs. hypobaric hypoxia (2500 m). Triangles and circles indicate mixed-effect model derived means and 95% confidence

intervals (CI) of outcomes during normobaric hypoxia (F_{iO_2} : 15%) and hypobaric hypoxia (2500 m) after 20–30 min of exposure. Fixed effects variables are Time, Age, Gender and New York Heart Association class and random effect is the subject ID. Cubes indicate the mixed-effect model derived mean-differences with associated 95% CI.

3.1.2. HAST and Baseline Measures to Predict Supplemental Oxygen at 2500 m

According to the BTS-recommendations for air travel in respiratory diseases, 12 out of 21 (57%) participants would have qualified for supplemental oxygen due to low SpO_2 (<92%) on room air at 470 m and 8 had an indication for further testing by the HAST due to resting SpO_2 values between 92–95% or PaO_2 < 9.3 kPa [26,27]. Based on findings from the HAST, 4 (19%) would have qualified for supplemental oxygen at altitude. At 2500 m, 3 (14%) patients (1 HAST-positive and 2 HAST-negative) actually experienced an ARAHE and thus received supplemental oxygen (Figure 4). Thus, the sensitivity of the HAST for experiencing an ARAHE at altitude was 33.3% in terms of SpO_2 - and PaO_2 -levels. The specificity of the SpO_2 - and PaO_2 -criteria of the HAST for ARAHE was 83.3% and 82.4%, respectively. The best predictive parameter assessed within these studies for an ARAHE at altitude was the baseline NYHA class with an AUC of 0.85 (Figure 5). Being in NYHA class 3 revealed a sensitivity for ARAHEs of 66.6% and a specificity of 88.8%.

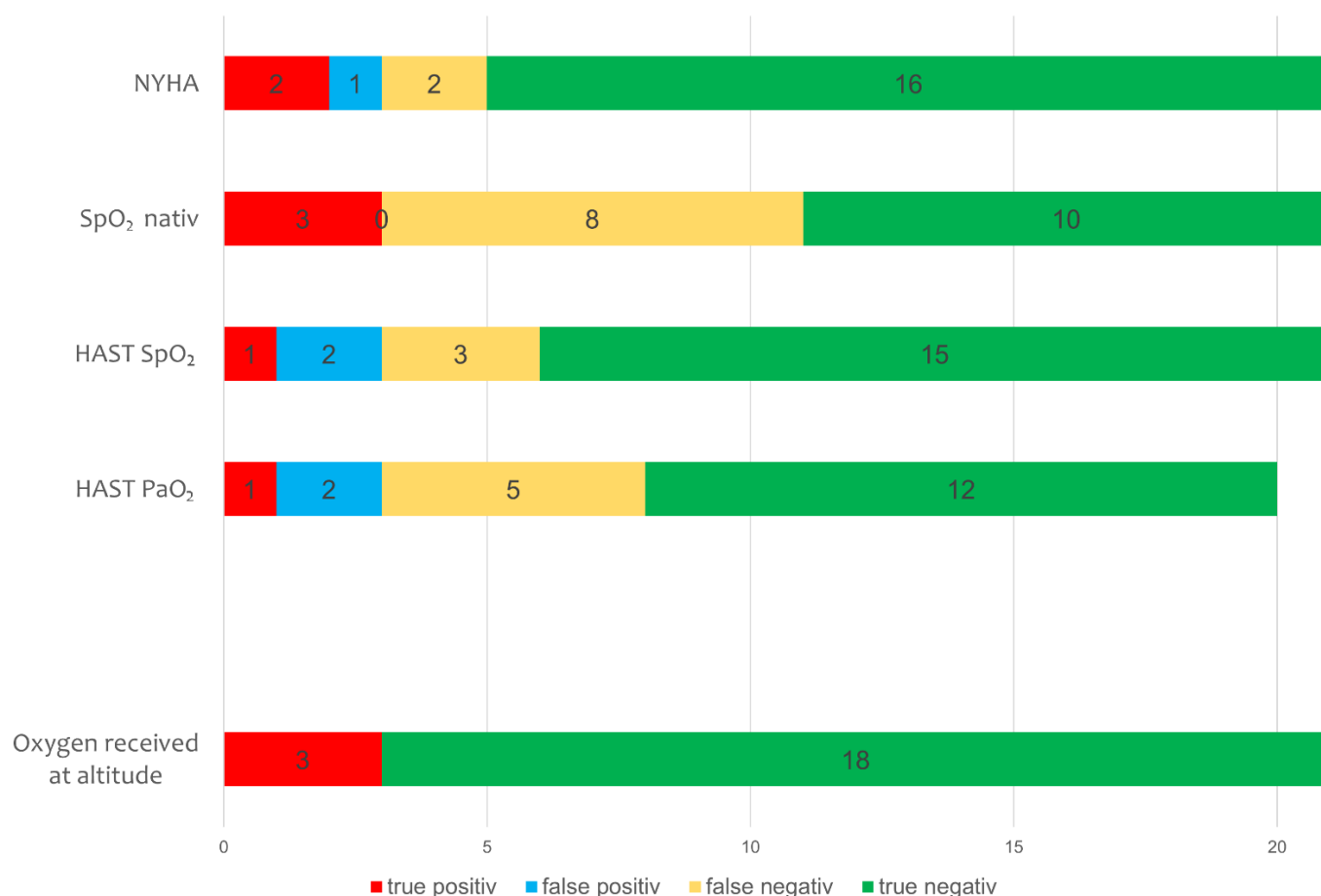


Figure 4. Predictions for oxygen at altitude. NYHA = New York Heart Association class, HAST = High altitude simulation test, numbers in bar represent absolute numbers. PaO_2 (n = 20).

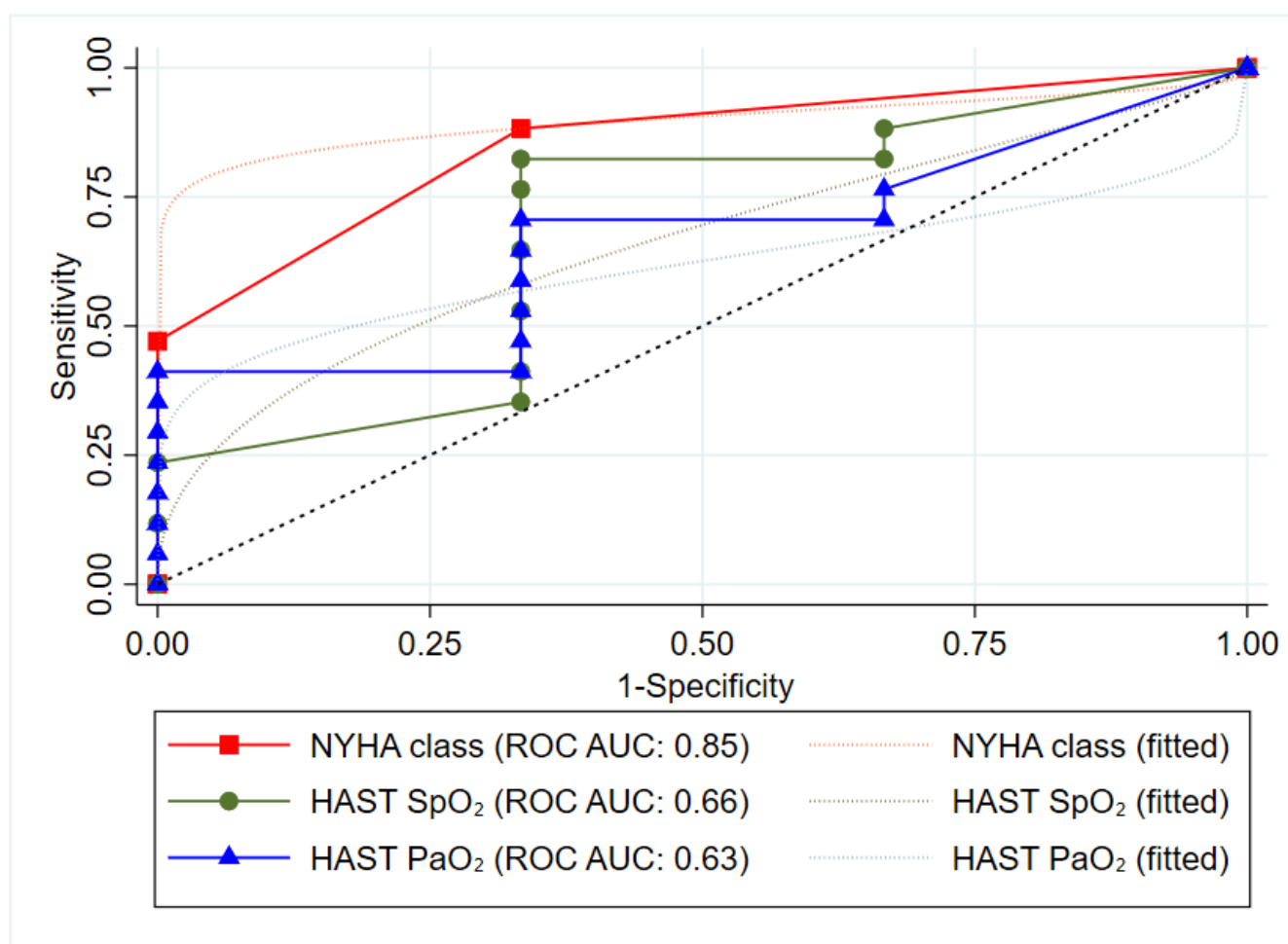


Figure 5. Receiver Operator Characteristic Curve for altitude related adverse health effects at 2500 m. HAST = High altitude simulation test including an exposure to normobaric hypoxia F_{iO_2} : 15%, NYHA = New York Heart Association class, ROC = Receiver Characteristic Operator Curve, AUC = Area under Curve.

4. Discussion

In this unique study, we compared hemodynamic and arterial blood gas changes in patients with pulmonary vascular disease during a comparable exposure time to NH at lowland (simulated altitude) and HH at altitude (2500 m). We found that HH decreased blood oxygenation to a significantly higher extent and resulted in a higher increase in PAP. The predictive value of low altitude baseline SpO_2 or the SpO_2 and PaO_2 at the end of a HAST to predict ARAHE was very low. Our results strongly indicate that physiological adaption during NH vs. HH differ and the value of the HAST to predict ARAHE is limited in patients with PH.

Several researchers made efforts to find predictors to assess fitness-to-fly for patients with respiratory diseases [11,14,15,30]. During commercial long-distance aircraft travelling, the minimal allowed P_{bar} is 752 hPa, equivalent to an altitude of around 2500 m. Several studies focused on fitness-to-fly but hardly any on fitness-for-altitude travel for patients with cardiorespiratory diseases. [31,32]

Similarities between NH and HH were first described in the Equivalent Air Altitude Model by Paul Bert (1878). This model explains identical physiological responses in both conditions on the human body provided that the P_{iO_2} remains unaltered. In other words, a reduced F_{iO_2} with low-altitude ambient P_{bar} was suggested to be comparable to a normal F_{iO_2} (20.9%) and a reduced P_{bar} as at altitude. However, this proposal resulted in numerous criticisms since the observed responses to NH often differed from HH [32–34].

In the current study, 3 out of 21 participants revealed severe hypoxemia during HH and had to receive oxygen therapy according to predefined safety criteria. The predictive value of the HAST was hereby very low, making this measure useless for predicting ARAHE [35].

Several previous studies, most of which had small sample sizes, focused on identifying patients with respiratory disease at risk for air travel or on predicting a low PaO_2 at altitude. Most of them assessed fitness-to-fly in patients with COPD, who later underwent air-travel with or without inflight oxygen. In line with our results, the majority of studies resulted in the conclusion that the prediction of HAST for ARAHE is limited [28,36,37]. In the absence of robust evidence, HAST is still commonly used to assess fitness-to-fly.

An explanation for the inability of the HAST to predict changes during HH might be that NH is not an experimental set-up directly comparable to HH and that the setting of breathing hypoxic gas mixtures through tubes results in different changes compared to spontaneous breathing at HH. In our study, we exposed patients with pulmonary vascular disease to NH (F_iO_2 : 15%) and HH (2500 m) during a similar exposure time in a randomized-cross-over design and indeed found several significant differences between the associated changes in estimated PAP and oxygenation. We observed a significant lower SpO_2 , PaO_2 , and PaCO_2 as well as more pronounced respiratory alkalosis at altitude compared to NH (Table 2, Figure 2). This lower blood oxygenation despite more pronounced hyperventilation and thus higher respiratory drive as indicated by the lower PaCO_2 at altitude, was associated with a significantly higher PAP under HH at altitude compared to equivalent NH. In addition, we found hints for reduced ventriculo-arterial coupling as indicated by the lower TAPSE/SPAP ratio.

Current literature contains plenty of criticism of the Equivalent Air Altitude model, since acute mountain sickness (AMS) and other physiological parameters differed between the same hypoxic inspired oxygen partial pressure (P_iO_2) at different barometric pressures [32].

In 1982, Grover et al. reported that a reduction in P_{bar} alone, without a change in P_iO_2 , may reduce peripheral chemoreceptor sensitivity, but a plausible mechanism was not described [38]. Savourey, Tucker and Loeppky observed a decrease in ventilation at HH versus NH with a lower tidal volume and higher respiration rate (fast but shallow). Loeppky raised the notion that the lower gas density at altitude is responsible for a smaller CO_2 production, which could reduce the ventilation and would also reduce the work of breathing and therefore the alveolar dead space [32]. However, in our study population, PaCO_2 was lower at altitude, indicating an increased ventilation mainly due to a higher respiratory rate (tendency towards a higher breathing rate compared to NH with a borderline significance-level ($p = 0.056$)). However, minute ventilation was not measured in our study.

Data from 9 trained healthy men reported by Loeppky et al. revealed no difference in SpO_2 between NH and HH up to 10 h, whereas the study by Savourey et al. including 18 healthy men revealed a lower blood oxygenation during 40 min at HH vs. NH in line with our results in PH-patients [32,39]. Part of the difference between these studies and our results may be explained due to the fact that we exposed PH patients to HH at real altitude after ascent by cable car, a setting different to experimental hypobaric chamber conditions and that our subjects were significantly older, half were females and all suffered from chronic pulmonary vascular disease.

Another potential mechanism potentially explaining a difference between NH and HH as found in our PH-patients may be the difference in N_2 -movements resulting in lower PaO_2 and PaCO_2 in HH as previously postulated [32].

The lower blood oxygenation during HH vs. NH in our study was associated with an elevated PAP, presumably due to enhanced hypoxic pulmonary vasoconstriction [8,40]. Driven by the increased PAP at altitude, the TAPSE/SPAP was reduced, which may indicate a slightly more impaired ventricular-arterial coupling at 2500 m vs. NH. However, we believe that the exposure time was too short to influence right-heart stiffness [23].

Limitations

The sample size was rather small. However, the cross-over design allows a high statistical power with a low sample size, and this study demonstrated a significant difference in the main outcomes of interest, PaO₂ and TRPG, with high statistical power (99%). As we investigated HH at real altitude, the setting at altitude was different and participants had to travel by cable car with a short break during ascent on 1300 m while waiting for the gondola, thus the exposure time to HH might have been slightly less acute/slower. However, this reflects reality for any altitude stay or air-travel and this real-life setting strengthens the conclusions from our findings at HH.

5. Conclusions

Hypobaric hypoxia exposure at real altitude results in a significantly lower blood oxygenation and higher PAP compared to simulated altitude using HAST during comparable exposure time and at comparable P_iO₂ at real and simulated altitudes.

The value of the HAST protocol to predict ARAHE was very weak, and thus its use to counsel patients in regard to risk of ARAHE during air travel or altitude stays is questionable.

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Data Availability Statement: Data available on request due to restrictions e.g., privacy or ethical. The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to reasons of sensitivity of human data.

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CHAPTER 3 Discussion

3.1. Overall

This PhD thesis addresses the uncertainty about the potential adverse health-effects faced by an increasing number of stable and active PH patients whilst travelling at high altitudes or by aeroplane.

The focus was an investigation of the physiological changes that occur at rest and during exercise in hypoxic conditions, with the obtained results intended to allow evidence-based counselling of PH patients.

The results of the three projects included in this thesis are discussed below in detail and are put in perspective to facilitate future research projects and to close the gaps in the scientific knowledge.

3.1.1. Project I

In the first randomised, placebo/sham-controlled trial, we investigated 28 patients with PH under NH with a fraction of inspired oxygen (FiO_2) of 15% and ambient air (placebo) in a safe environment at the University Hospital Zurich. Participants were exposed to either ambient air or NH for approximately 2 hours and given a constant loaded work-rate cycle exercise test (CWRET) at the end. The main finding was that exercise performance was significantly reduced with NH compared to placebo. We observed increased blood hypoxemia but unaltered hemodynamics, cardiac output (CO), and perceived dyspnoea at end-exercise. We interpreted that the reduced exercise performance was due to the reduced oxygen content of the blood and the increased ventilatory work. NH was tolerated well. Occasional headaches were found with NH and placebo air and may be partially explained by the tightly fitting facemask around the patient's head.

At the end of the exercise, hypoxic conditions showed a significantly higher lactate compared to ambient air, which can be explained by a premature anaerobic muscle metabolism, as observed in previous studies.^[1]

Interestingly, the patients stopped cycling, with similar hemodynamics and patient self-reported symptoms. This indicates that the circulatory limitation arose earlier under hypoxia due to the reduced arterial oxygen content, which would have led to a further increase in CO, which was not possible because of the pulmonary vascular disease.^[2, 3]

3.1.2. Project II

With the second project (a randomised-sequence, crossover trial), we investigated 28 patients during a daytrip to a high-altitude environment in Switzerland – Mount Säntis, which is at 2500m.

The majority of patients tolerated the hypoxic environment well. As in the Zurich trial that used NH versus placebo, exercise performance was reduced, though with high inter-individual variability. The echocardiographic measurements revealed significantly higher PAP and elevated CO, compared to LA.

At altitude, three of the 28 patients were treated with supplemental oxygen due to peripheral hypoxemia within the first 3 hours and could therefore not undergo exercise testing. The criteria for supplemental oxygen were predefined, with a SpO₂ of <80% for >30 minutes. These criteria have been employed multiple times in studies of patients with chronic obstructive pulmonary disease (COPD) since no comparable studies for PH were available at that time.^[4]

^{5]} Exposure to high altitudes was generally well-tolerated, and even those treated with supplemental oxygen felt well after the application.

CWRET time was significantly reduced by 22.9% at HA compared to LA, and this was to a greater extent than in the first project with NH, albeit with large inter-individual variability. Compared to previously published data on COPD, there was a smaller decrease in exercise test time, which may be due to the shorter exposure time, compared to the COPD cohort.

As expected, we observed a significantly lower SpO₂ at HA compared to LA at rest – and even at end-exercise, despite the reduced exercise time.

In contrast to our findings under NH, we observed a significantly higher PAP at rest and at end-exercise, which may be explained by the longer exposure time at altitude of >3h, compared to 30 minutes under NH. The most plausible reason for the increased PAP is the effect of HPV, which occurs when the alveolar oxygen partial pressure is low and also in the presence of a low mixed venous oxygen saturation, leading to a complex feedback mechanism to vasoconstriction of the pulmonary arteries to optimise perfusion in the lungs. Consequently, PVR and PAP increase. In line with the higher PVR, right-heart afterload increases, which – in the context of the course of the disease – is linked with worse survival.^[6]

Additionally, we measured muscle and cerebral tissue oxygenation by near-infrared spectroscopy. Neither value differed between LA and HA. We assume that adaptive mechanisms protected the skeletal muscle and the brain from deoxygenation. This assumption is supported by the unchanged oxygen delivery, together with the higher heart rate and higher CO and a potential redistribution of blood flow to the muscles and brain.^[7, 8]

3.1.3. Project III

The third project was dedicated to the question of whether NH at LA corresponded to the findings at real HA. We therefore analysed data from the 21 participants who took part in both trials. We found that NH could not accurately predict ARAHEs at real HA and thus concluded that hypoxia-altitude simulating testing was of limited help for counselling patients going into HA environments.

During a comparable exposure time of 20–30 minutes, we found that HH decreased blood oxygenation and resulted in a significantly higher increase in PAP.

Based on our data, LA blood oxygenations measured at baseline and after 20–30 minutes under NH were not predictive of ARAHE. These data indicate that physiological adaptation during NH versus real altitude (HH) differ, and the HAST has limited value as a predictor of the need for supplemental oxygen.

In 1878, Paul Bert described similarities between NH and HH in the equivalent air altitude model. The model assumes that, unless the inspired partial pressure of O₂ remains unaltered, the physiological effects on the human body should be identical. The idea is that a reduced P_{bar}, as present at HA, in combination with an unchanged FiO₂, has identical effects on the human body as a LA P_{bar} and a reduced FiO₂.^[9] However, within the last century, this model has earned numerous criticisms, with data from patients with COPD showing that the correlation between NH and HH is weak and the predictive value of the HAST needs further investigation.^[10, 11]

There is a body of evidence to suggest that the equivalent air altitude model is not accurate. Grover et al. (1982) stated that a reduced P_{bar} alone, without a change in inspired partial pressure of O₂ might reduce chemoreceptor sensitivity. This would mean that the physiological response at altitude, in combination with oxygen, would still show a reduced chemoreceptor sensitivity. Another finding was a decrease in ventilation at HH versus NH, with a lower tidal volume and higher respiration rate.^[12] One explanation for this could be that the reduced gas density at altitude results in lower CO₂ production, which might reduce ventilation and the work of breathing.^[10]

We also observed, in combination with reduced blood oxygenation, an increased PAP, which may be explained by the enhanced HPV, as described previously.^[6]

The HAST is still frequently used in clinical settings, despite its predictive value for fitness-to-fly or fitness-for-altitude being questionable. This is probably because no better predictors are yet available.

Altogether, the novel findings of the three trials represent long-awaited data that could enhance evidence-based recommendations for stable non-hypoxemic patients with PH. They suggest that altitude exposure during a day-trip of up to 2500m is safe but will probably lead

to a reduced exercise performance, which is in line with findings in healthy subjects. These data can thus be applied to help counsel PH patients for air travel or altitude exposure. The two randomized-controlled trials have been included in the recently published guidelines for diagnosis and treatment of PH, which are used worldwide as a standard for therapy in PH.^[13]

3.2. Strengths and limitations

3.2.1. Project I

To reach a conclusion on the effect of NH, a maximal exposure time of 2 hours may be considered short. However, the HAST, which is widely used for the evaluation of fitness-to-fly, is defined as 15–20 minutes or until the SpO₂ is levelling out and is thus even shorter. With the exposure time of the present study, we could define significant changes with NH versus placebo.

3.2.2. Projects I and II

We chose a randomised single-blinded crossover study design. Crossover designs are particularly beneficial with rare diseases such as PH because each patient is its own control. This allows the sample size to be considerably reduced. However, depending on the intervention, the potential for a carry-over effect should be considered. Our first project had a washout period of >2 hours. A review of the literature and clinical experience suggested that this would be sufficient time to avoid carry-over effects after different inspiratory oxygen fractions. Statistical testing supported this, revealing no indication of an order effect.

Another problem with crossover designs is the potential for dropouts in between the two study phases. We did not report any dropouts after randomisation, thus there was no need to impute missing data.

Although we did our best to minimise the technical limitations by testing all materials, the setting, and the installation with healthy subjects – as well as conducting plausibility checking with repeated measurements – some minor limitations are intrinsic to all test arrangements. The gas mixture was applied via a sealed facemask, fixed around the head. Despite the care taken to attach the mask as loosely as possible, whilst keeping it airtight, it may have caused headaches to some of the patients. As we assessed acute mountain sickness at the end of the intervention, and headaches are an essential parameter of this, a potential confounding factor was inevitable.

Caution must be taken when applying our study results to patients with more advanced disease or who are in less-fit conditions not corresponding to the study inclusion criteria, as

the patients included in these studies were all in good physical condition, with a 6-minute walk distance beyond the average for PH patients and primarily in WHO FC 1 and 2.

For safety reasons – and because data on exercise under hypoxia in PH are scarce – we chose a CWRET load at 60% of the patient's maximal workload in an incremental ramp protocol and not, for example, 75%, as we did in a previous study with COPD patients.^[14] The finding that many patients could maintain cycling for >20 minutes suggests that the threshold may have been too low for the relatively fit PH patients in our studies.

An often-criticised evaluation tool is the echocardiography, as intra-observer variability can be high. Our measures were performed by experienced echocardiographers, who were each taught about the parameters prior to the beginning of the projects. As echocardiography is less complex to perform than right-heart catheterisation, as well as being mobile and non-invasive, it is an indispensable examination, especially for field studies of PH patients.

3.2.3. Project III

Despite Project III has relatively small sample size (21 PH patients), which was due to the crossover design, as this allowed a reduction in sample size, we were able to achieve high statistical power for the main parameters of interest (PaO₂ and tricuspid pressure gradient).

This analysis compared identical exposure times under NH and HH at real altitude at equivalent levels. As we investigated patients at an elevation of 2500m, we had to consider the time needed to travel, including a short stopover at 1300m, where the patients waited for the gondola. Thus, exposure time at altitude may have been slightly longer than at HA. However, this reflects potential real-life experience at any altitude – or even during air travel – which strengthens the value of the findings of this scientific work.

3.3. Future research

Activities in mountain areas in all seasons have become increasingly popular in recent decades. Long-distance flights have also become more affordable, which has resulted in large numbers of people exposing themselves to hypoxic environments at altitude. For patients with cardiopulmonary diseases such as PH, a journey to these environments is often accompanied by fears and concerns about their health. This PhD thesis could provide valuable information necessary to counsel patients with PH who are travelling to hypoxic environments. However, future research is needed.

Our data show, when exposed to NH for up to 2 hours and to HH at high altitudes during a day-trip, stable PH patients tolerated this hypoxic environment equivalent to an altitude of 2500m well. To confirm and strengthen these results, data for longer exposure times, including overnight stays, is required. As observed frequently in healthy patients and in patients with COPD, the onset of ARAHE most frequently occurs during the first night and in the morning of the second day. This would reflect a representative real-life experience of a weekend journey to a touristic mountain resort. We conducted an altitude research study in 2021/2022 with similarly stable PH patients, also at 2500m, including an overnight stay. We are currently analysing these data, with a particular focus on the effect of altitude during the first night and second day.

To confirm our findings, further studies with larger sample sizes are needed.

As reflected by the Zurich PH cohort and the Swiss PH register, Swiss patients with PH have, on average, higher 6-minute walk distances and are thus fitter than those on other registries.^{[15,}

^{16]} Therefore, our data may not apply to patients with poor exercise performance. To identify the risks for a broader collective of PH patients, multi-centre studies would be desirable for examining different fitness and altitude levels. However, exposure to different elevations under real-life conditions in multiple research centres around the world would be costly and thus may not be feasible. Prospective, non-randomised registries or pooled meta-analyses of smaller studies would be another option.

A widespread notion that supplemental oxygen at altitude counteracts altitude effects on LA conditions was not confirmed in PH patients. In our recent trial with patients who stayed at altitude for up to 30 hours, we allowed them to continue with the study procedure with supplemental oxygen for as long as it was tolerable for them.

These data will provide valuable information on whether patients with PH can travel to high altitudes and, in case of ARAHE, whether supplemental oxygen would prevent any additional risk.

Another question was whether repeated altitude exposure would change risk profiles. Re-exposure to altitude in healthy lowlander subjects showed a mitigation of altitude-induced deoxygenation.^[17] Future investigations could explore whether such an effect can be observed in PH patients and whether altitude tolerability can be learned.

3.4. Conclusion

Worldwide every year, millions of people expose themselves to HH when travelling to touristic mountain areas or by aeroplane. Operating aircrafts have pressurised cabins equivalent to an altitude of approximately 2500m.

Among these recreational and business travellers are many patients with cardiopulmonary diseases such as PH. Thanks to recent progress in available therapies, these patients are often less handicapped and more able to live almost normal lives at LA, but they remain at risk for ARAHE in hypoxic environments. In our daily practice at the PH clinic at the University Hospital Zurich, we regularly experience uncertainties and a demand for counselling regarding altitude exposure and air travel. Counselling for these activities remains expert-based, as there is a lack of scientific knowledge. Our series of randomised, crossover studies can help to fill some of these knowledge gaps by providing a physiological basis on which to counsel patients about day-trips to high altitudes – an activity not currently recommended in general by the guidelines. We have showed that hypoxic air breathing is generally well-tolerated to a similar extent with NH and HH – notwithstanding occasional reports of headaches and three patients (11%) needing oxygen during a day-trip to high altitudes, due to predefined safety criteria. The vast majority of these stable PH patients tolerated the altitude well, which will be reassuring for patients wishing to join their family and friends for short trips to alpine regions.

Like many studies of patients with COPD, our third study showed that exposure to NH for up to 20 minutes, as done frequently in the HAST, remains of questionable predictive value, as the values of blood oxygenation and other physiological measures differed significantly between NH and HH, with significant lower blood oxygenation and a higher PAP at HH.

We are currently about to analyse data from a study of a longer overnight trip to a high-altitude environment, and we hope that future studies will provide data on PH patients and longer altitude-exposures times, including overnight stays and potential prophylactic measures.

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CHAPTER 4 Author contribution

Project I

SR Schneider, working with S. Ulrich, substantially contributed to the conception and design of the project. SR Schneider organised the entire study logistics, including obtaining ethical approval, teaching and supervising the study team, and conducting the recruitment phase. He had primary responsibility for data acquisition and analysis. He drafted the manuscript, including the tables and figures. The authors worked together to revise the manuscript critically for important intellectual content.

Project II

SR Schneider contributed to the conception and design of the project. He was responsible for the entire conduct of the study, including logistics, recruitment, teaching and supervision, coordination, and acquisition. SR Schneider substantially contributed to data integrity and the analysis and drafting of the manuscript, including figures and tables. All the authors have read and agreed to the published version of the manuscript.

Project III

SR Schneider substantially contributed to conceptualisation, data curation, and analysis, and he contributed to the visualisation. He drafted the manuscript, and all the authors have read and agreed to the published version.

Stéphanie Saxer, who is listed as a co-author on these publications graduated from the University of Lucerne with a PhD. Prof. Dr Stucki and Prof. Dr Ulrich were also supervisors for her dissertation. The two dissertations have been created completely autonomous of each other and neither Stéphanie Saxer nor one of the supervisors have anything to disclose which may have influenced the present work in any kind.

CHAPTER 5 Supplementary material

Image S1: Examinations under normobaric hypoxia applied with the Altitrainer. SMTEC SA, Nyon)



The persons on the pictures gave their consent to present this picture in scientific content.

Altitrainer, SMTEC SA, Nyon [Online image]. Retrieved October 05, 2022 from <https://www.smttec.net/en/products/altitrainer/>

Image S2: Examination at the mount Säntis 2500m, Switzerland



Examinations at 2500m: Patients on the pictures gave their consent to present these pictures in scientific content.