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Early View

Original article

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Pulmonary hemodynamic response to exercise in highlanders vs. lowlanders

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Take home message

Central Asian highlanders living between 2500-3600m assessed by stress echocardiography showed that chronic exposure to hypoxia leads to a steeper pressure-flow relation during exercise and worse right ventricular-arterial coupling compared to lowlanders.

Abstract

The question addressed by the study: To investigate the pulmonary hemodynamic response to exercise in Central Asian high- and lowlanders (HL&LL).

Patients and methods: Cross-sectional study in Central Asian HL (living >2500m) compared to LL (living <800m), assessing cardiac function, including tricuspid regurgitation pressure gradient (TRPG), cardiac index and tricuspid annular plane systolic excursion (TAPSE) by echocardiography combined with heart rate (HR) and SpO_2 during submaximal stepwise cycle exercise (10 W increase/3min) at their altitude of residence (at 760m/3250m, respectively).

Results: 52 HL (26 females; age 47.9±10.7years; BMI 26.7±4.6kg/m^2; HR 75±11bpm; SpO_2 91±5%;) and 22 LL (8 females; age 42.3±8.0years; BMI 26.9±4.1kg/m^2; HR 68±7bpm; SpO_2 96±1%) were studied. HL had a lower resting SpO_2 compared to LL but change during exercise was similar between groups (HL vs LL. -1.4±2.9% vs. -0.4±1.1%, p=0.133). HL had a significantly elevated TRPG and exercise induced increase was significantly higher (13.6±10.5mmHg vs. 6.1±4.8mmHg, difference 7.5 [2.8 to 12.2]mmHg, p=0.002), whereas cardiac index increase was slightly lower in HL (2.02±0.89l/min vs. 1.78±0.61l/min, difference 0.24 [-0.13 to 0.61]l/min, p=0.206) resulting in a significantly steeper pressure-flow ratio (ΔTRPG/Δcardiac index) in HL 9.4±11.4WU and LL 3.0±2.4WU (difference 6.4 [1.4 to 11.3]WU, p=0.012). Right ventricular-arterial coupling (TAPSE/TRPG) was significantly lower in HL but no significant difference in change with exercise in between groups was detected (-0.01 [-0.20 to 0.18] p=0.901).

The answer to the question: In highlanders, chronic exposure to hypoxia leads to higher pulmonary artery pressure and a steeper pressure-flow relation during exercise.

Keywords: Stressechocardiography, altitude, high altitude pulmonary hypertension

Abbreviations list

BL	Baseline
BMI	Body mass index
BPd	Blood pressure diastolic
BPs	Blood pressure systolic
CI	Cardiac index
CMS	Chronic mountain sickness
CW	Continuous- wave Doppler
FAC	Fractional area change
HL	Highlanders
HR	Heart rate
LL	Lowlanders
LV	Left ventricle
SD	Standard deviation
sPAP	Systolic pulmonary artery pressure
SpO_2	Oxygen saturation by pulsoximetry
TAPSE	Tricuspid annular plane systolic excursion
TRPG	Tricuspid regurgitation pressure gradient
TR Vmax	Maximal tricuspid regurgitation velocity
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PAP	Pulmonary artery pressure
RV	Right ventricle
RVEDA	Right ventricle end-diastolic area
RVESA	Right ventricle end-systolic area
SV	Stroke volume
SVI	Stroke volume index

Introduction

Millions of people worldwide are permanently living above 2500 m altitude raising interest in uncovering the pathophysiological adaption to high altitude. In Andean or Tibetan individuals living at altitudes between 3600 and 4350 m an elevated pulmonary artery pressure (PAP) at rest and during exercise has been reported compared to lowlanders [1, 2], with highest values in patients with chronic mountain sickness (CMS) [3]. Recently, we found a slightly but significantly elevated PAP at rest in a large cohort of Central Asian highlanders living at altitudes between 2500 and 3600 m compared to lowlanders along with distinct alterations in cardiac function [4]. However, albeit depending on the definition used, high altitude pulmonary hypertension (HAPH) according to resting pulmonary hemodynamics in high altitude dwellers appears to be rare [1, 4, 5]. An abnormal pulmonary hemodynamic response to exercise may cause dyspnea and may precede manifest resting pulmonary hypertension (PH) in subjects at risk including those permanently exposed to a hypoxic environment at altitude [6]. Exercise PH is characterized by a steeper increase in PAP in relation to the increase in pulmonary blood flow, measured as cardiac output during exercise [7]. Already in 1966 exercise right heart catheterization was performed in 35 highlanders at 4500 m and revealed a larger increase in mean PAP from 29 mmHg to 60 mmHg during moderate exercise compared to lowlanders (from 12 mmHg to 18 mmHg) along with a significant desaturation during exercise whereas the change in cardiac output was mainly driven by an increase in heart rate (HR) and was comparable to controls near sea level [8]. However, performing invasive right heart catheterizations in remote areas is technically challenging and nowadays often considered unethical as it is an invasive procedure in presumably healthy subjects. Echocardiography has been established as a useful non-invasive and reliable tool to assess right heart function during exercise [9, 10] and is thus especially suited for rural regions.

Exercise hemodynamics have not been assessed in Central Asian highlanders living at a moderate to high altitude between 2500 and 3600 m such as the Kyrgyz high altitude dwellers in the Tien Shan mountain range and have not been compared to lowlanders of the

same ethnicity. It is not known whether these subjects chronically exposed to a hypobaric hypoxic environment would reveal a pathological hemodynamic response to exercise as potential early sign of imminent HAPH.

Therefore, the aim of the current trial was to investigate changes of pulmonary hemodynamics and heart function during stepwise incremental exercise in highlanders living between 2500 and 3600 m free of manifest diseases including CMS compared to healthy lowlanders.

Methods

This cross-sectional study was conducted in the National Center for Cardiology and Internal Medicine, Bishkek (760 m) and in the Ak-Say region of the Tien Shan mountain range in Kyrgyzstan at an altitude of 3250 m from July to August 2017. Healthy lowlanders and highlanders (living between 2500-3600 m) without overt cardiopulmonary diseases including absence of CMS were invited to participate in this study. This study was part of a larger trial registered at clinicaltrials.gov NCT03165656.

Participants

Kyrgyz lowlanders (born, raised and living < 800 m) and highlanders (born, raised and currently living > 2500 m) of both genders, aged ≥ 16 years, were recruited among outpatients of the National Center for Cardiology and Internal Medicine in Bishkek or in the Ak-Say region, respectively. Highlanders were excluded if they had excessive erythrocytosis as an indicator of CMS (defined as hemoglobin >19 g/dL in females and >21 g/dL in males) or other relevant cardiopulmonary diseases such as coronary heart disease, chronic obstructive pulmonary disease or heavy smoking (>20 cigarettes/day). This study was conducted in accordance with the Declaration of Helsinki, approved by the ethics committee in Kyrgyzstan (01-8/433). All participants gave written informed consent to participate in the study.

Assessments

Echocardiographic recordings were obtained with a real-time, phased array sector scanner (CX 50, Philips, Philips Respironics, Zofingen, Switzerland) with an integrated Color Doppler system and a transducer containing crystal sets for imaging (1-5 MHz) and for continuous-wave Doppler (CW). Recording and analysis were performed according to guidelines of the European Association of Echocardiography [11]. Measurements were performed at rest and during cycling exercises both in upright position on a cycle ergometer. Patients performed a stepwise incremental exercise test with increase of 10 W every 3 min. At each step echocardiographic measures as described below were performed and HR, blood pressure

and oxygen saturation by pulse oximetry (SpO_2) were measured. Tricuspid regurgitation pressure gradient (TRPG) was calculated from maximal tricuspid regurgitation velocity (TR Vmax) obtained with CW-Doppler using the modified Bernoulli equation: $\Delta P=4 \times Vmax^2$. As the right atrium pressure by echocardiography is estimated from the collapsibility of the cava vein at rest and cannot be assumed as constant during exercise[12], we provided the measured TRPG as surrogate for the PAP during exercise. For systolic PAP (sPAP)-estimates, we added the RAP of 5mmHg to the TRPG. Mean PAP (mPAP) was calculated from sPAP with the formula: $mPAP = sPAP * 0.61 + 2$ [13]. Systolic and end-diastolic areas of the right ventricle (RV) were manually traced. Fractional area change (FAC) of the RV was calculated (end-diastolic RV area – end-systolic RV area / end-diastolic RV area). Tricuspid annular plane systolic excursion (TAPSE) was measured in M-mode. Cardiac index (CI) was estimated by the Doppler velocity time integral method from the left ventricular (LV) outflow tract indexed with body surface area [14]. The TRPG/CI-ratio at every step was calculated as surrogate for total pulmonary resistance or pressure-flow ratio. The pressure-flow slope was calculated as change of TRPG/change of CI (ΔTRPG/ΔCI) with exercise (maximal value minus resting value), additionally, the mPAP/cardiac output slope was calculated from sPAP-estimates. RV- arterial coupling was estimated by TAPSE/TRPG [15].

Outcomes

The primary endpoint was the TRPG measured during exercise in highlanders compared to lowlanders expressed in relation to the increasing flow. Secondary endpoints were SpO_2, HR, CI and further parameters of the right ventricular function (FAC, TAPSE, TAPSE/TRPG) during exercise in highlanders compared to lowlanders.

Analysis and statistics

Outcomes were analyzed per protocol and values are presented as mean ± standard deviation (SD) and mean differences (95% confidence intervals [95%CI]). Patients were included in the analysis when they had at least two valid TRPG measures during exercise. Differences between lowlanders and highlanders were compared by T-tests at baseline and

end exercise as well as the difference of the change from baseline to end exercise. Highlanders were divided into 3 subgroups according to their resting measures for further explorative analysis: (a) mPAP < 20 mmHg: noHAPH, (b) mPAP 20-30 mmHg: borderline HAPH, (c) mPAP > 30 mmHg: HAPH. Differences between the subgroups were calculated with ANOVA. Linear mixed regression analysis was performed with pressure-flow slope as dependent variable and age, gender and mPAP subgroups as independent variables. Analysis was performed with STATA 15 and a p-value < 0.05 or 95%CI of differences not including zero were considered statistically significant.

Results

The study flow chart is shown in figure 1 and baseline characteristics in table 1. We included 52 highlanders (50% female, age 47.9 years, BMI 26.7 kg/m^2) and 22 lowlanders (36% female, age 42.3 years, BMI 26.9 kg/m^2), highlanders were on average 5.5 (0 to 11) years older, smaller with a smaller body surface area, but with the same BMI and had a higher HR, hemoglobin, hematocrit and lower blood oxygenation compared to lowlanders.

Highlanders had a higher TRPG with a significantly higher increase during exercise, which along with a similar CI-increase resulted in a significantly steeper pressure-flow slope in highlanders vs. lowlanders ((ΔTRPG/ΔCI: 9.4 ± 11.4 vs. 3.0 ± 2.4., p=0.012; mPAP/cardiac output: 3.3 ± 3.8 vs. 1.0 ± 0.8, p=0.007 table 2 and figure 2a and b). Table 3 shows physiological measurements at baseline and end-exercise as well as the change from rest to end-exercise and the between group differences. Highlander had a lower SpO_2 but a similar decrease with exercise compared to lowlanders. Highlanders achieved a higher HR at end-exercise vs. lowlanders, otherwise HR and stroke volume index (SVI) were mostly similar (table 3). However, highlanders were not able to increase their SVI as much as lowlanders and between group difference in change from baseline to end-exercise was 3.4 (0.0 to 6.8) p=0.052, whereas the increase in HR was similar (table 3).

TAPSE/TRPG was lower in highlanders compared to lowlanders at rest and end-exercise as sign of impaired RV-coupling, but the difference in change from baseline to end-exercise between groups was similar (table 3). In figure 3 results of the consecutive exercise steps (baseline, 3min, 6min, 9min and individual end-exercise) are shown.

The exploratory subgroup analysis for highlanders (no HAPH vs HAPH borderline vs HAPH) is shown in the supplementary tables 1-3 and illustrated in figure 2b. Resting baseline measures of these subgroups revealed only a significant difference in systemic systolic blood pressure at rest. During exercise, TRPG was significantly different with a gradual increase from no HPAP to borderline to HAPH (end-exercise 31.0 ± 10.0 vs 37.9 ± 10.2 vs 54.7 ± 13.6 mmHg, p=0.002). The TAPSE/TRPG was significantly decreased from noHAPH to HAPH at

end-exercise (0.89 ± 0.33 vs 0.76 ± 0.33 vs 0.48 ± 0.22 mm/mmHg, p=0.039) along with a decreasing SpO_2 and with significant differences at end-exercise (89 ± 3 vs 90 ± 3 vs 85 ± 3 %, p=0.013) and increasing blood pressure. Figure 2b and supplementary table 2 show the pressure-flow relationship by subgroups and illustrates a significantly steeper (p<0.001) increase of the pressure-flow in the HAPH-group (24.5±4.0) compared to the no HAPH (5.4±3.7) and the borderline HAPH group (9.7±13.6).

Linear mixed regression analysis revealed that ΔTRPG/ΔCI depends on the resting mPAP group (noHAPH, borderline HAPH, HAPH) but is independent of age and gender (supplementary table 4).

Discussion

This is the first study investigating cardiac function and pulmonary hemodynamics by echocardiography during stepwise cycling exercise in Central Asian highlanders living between 2500-3600 m compared to lowlanders of the same ethnicity. Our main results show that highlanders reveal a significantly steeper pressure-flow slope during exercise due to a higher and more increasing PAP compared to lowlanders along with sings of an impaired right ventricular to arterial coupling at end exercise reflected by a lower TAPSE/TRPG. Within highlanders, the steeper pressure-flow slope on exercise was predicted by exploratory subgroups according to resting mPAP indicating borderline or manifest HAPH.

Previous studies investigating exercise hemodynamics in highlanders vs. lowlanders mainly focused on South-American men living at altitudes above 3600 m in the Andes. In these populations, a higher PAP-increase during exercise in highlanders compared to lowlanders was found in 35 healthy men aged 17-35 years who volunteered to undergo cycling exercise right heart catheterization with a workload of 300 kg-m/min/m^2 (50 W/m^2) near their living altitude at 4540 m in Bolivia, where the mean PAP increased from 29 to 60 mmHg and in lowlanders from 12 to 18 mmHg [8]. A meta-analysis summarized PAP during exercise echocardiography whilst subjects pedaled semi-supine with 50 W in 125 highlanders living in South America at altitudes between 3600-4350 m published between 2010-2016 [1]. The calculated average TRPG (reported as systolic PAP, i.e. TRPG plus estimated right atrial pressure) at maximal exercise was 36.3 mmHg and SpO_2 89.4 % in healthy highlanders and 48.3 mmHg and 82 % in patients with CMS and the increase of TRPG during exercise was 13 mmHg for healthy and 22 mmHg for patients with CMS [1]. In comparison, TRPG in the presently investigated Kyrgyz highlanders was 36.4 mmHg, the increase with exercise was 14 ± 11 mmHg and SpO_2 at end-exercise was 89%. Part of the difference in steepness in the pressure-flow of highlanders vs. lowlanders may be due to a higher hematocrit[16]. However, the hematocrit was in the normal range in both cohorts. Of note, patients with CMS have been excluded from the current study. In addition, the average cardiac output at exercise in the studies summarized by the meta-analysis was higher compared to the current trial (9.2 ±

0.9 l/min vs. 7.2 ± 1.4 l/min) [1]. But we assume that these were similarly restricted to men, as they were performed by the same teams in the same populations, whereas in our study, half of the highlanders investigated were female. However, the only study we found which differentially reported exercise hemodynamics by echocardiography in men and women revealed a similar pressure-flow slope as ours [17]. In the current trial we did not detect a significant difference of the pressure-flow in men and women. A different ethnicity with different genetic adaptation to altitude in the presently investigated Central Asian population compared to the Andean highlanders might lead to differently steep pressure-flow slopes However, we can only speculate, as to our knowledge there are no genetic factors known to date which may alter pulmonary hemodynamic response to exercise and this may be subject of future studies. Studies on the genetic adaptation up to now focused on the difference in Andean, Tibetan and Ethiopian high altitude dwellers but not on the response to exercise at altitude [18-20]. Patients assessed in the Andean region and summarized by Soria [1] were assessed semi-supine, whereas our protocol included upright cycling, which is usually associated with a lower mPAP and CI however resulting in an unchanged pressure-flow but higher pulmonary vascular resistance [21]. The cycling protocols used in the Andean studies were two steps at 25 W (3min) and 50 W, whereas we used a stepwise increase of 10 W every 3 min, which might have resulted in different cycling duration resulting in difficulties to compare the studies.

Reasons for the steeper increase of the PAP in highlanders compared to lowlanders are the chronic hypoxic pulmonary vasoconstriction and consecutive a reduced pulmonary vascular distensibility during exercise and hypervolemia, polycythemia and high blood viscosity [8]. The latter are more pronounced in patients with CMS [22]. However, resting arterial oxygen content was not different in the presently investigated highlanders compared to lowlanders, pointing towards an unchanged oxygen delivery to the tissue in regard of the slightly increased resting CI and similar changes of SpO_2 and CI during exercise [8]. A loss of vascular distensibility during exercise has been described as an early hemodynamic marker in patients with pulmonary vascular disease [23] and a steeper increase in pressure-flow

relationship during exercise is known to be a predictor of survival in patients with pulmonary hypertension [24]. The relationship of the TRPG/CI ratio decreases in lowlanders during exercise, whereas in highlanders with HAPH it increases in accordance with a much steeper pressure-flow slope (ΔTRPG/ΔCI), possibly indicating a worse distensibility or pulmonary arterial coupling. One other point might be that highlanders have a reduced pump function since heart rate increase is not significantly different but SVI increase was higher in lowlanders compared to highlanders during exercise albeit narrowly not significant (p=0.052). However, the pressure-flow slope in the presently investigated highlanders living between 2500-3500m was only slightly above the normal range and thus, the clinical relevance of this finding has to be further explored.

Highlanders have not only higher HR and systemic blood pressures but also a higher TRPG, CI and an enlarged right ventricle compared to lowlanders at rest, albeit the reported values of right ventricular area are within the limits of normal according to the guidelines [25]. However, whether these normative values are applicable for Kyrgyz ethnicity remains unclear. Whether the enlarged right ventricle in highlanders vs. lowlanders may reflect chronic strain, especially during exercise, relates to the slightly steeper pressure-flow relationship and would be associated with an exercise-induced increase in right atrial pressure remains to be determined.

RV-arterial coupling expressed as TAPSE/sPAP has been studied in patients with PH and heart failure and TAPSE/sPAP at rest was an independent predictor of invasively assessed coupling [15, 26-28]. In these studies poor prognosis was defined by a cutoff value below 0.36mm/mmHg [29] and 0.31mm/mmHg [15]. In our study, TAPSE/TRPG and also TAPSE/sPAP at rest were 0.9 ± 0.1 resp. 0.8 ± 0.3 mm/mmHg and thus significantly worse compared to lowlanders and lower compared to previously published healthy European cohorts revealing a TAPSE/sPAP of 1.26 ± 0.5 [30]. TAPSE/TRPG resp. TAPSE/sPAP at end-exercise remained lower in highlanders compared to lowlanders, but interestingly there

we found no worsening of the RV-coupling during exercise as it has been shown by D'Alto et al., which may indicate a preserved contractile reserve of the right heart in highlanders potentially reflecting adaption to high altitude [31]. In contrast to the presently investigated highlander collective without CMS, Andean highlanders with CMS, where the capacity for altitude adaption is lost, present with right ventricular hypertrophy and dilatation and pulmonary vascular plexiform lesions [32]. The subgroup of highlanders with a resting mPAP >30mmHg which can be diagnosed as HAPH presented with a reduced RV-arterial coupling reflected by a significantly lower TAPSE/TRPG at end-exercise albeit still within the normal-range.

The proportion of highlanders with HAPH depends on the definition used and many of which fulfilling certain definitions are clinically oligosymptomatic and the natural course of PAP increase at altitude is insufficiently known. Thus, it is not known which cutoff of PAP or PVR at rest is associated with right heart failure and premature death and whether a steeper pressure-flow slope during exercise would be predictive for worse outcome in this population, such it has been shown in lowlanders with pulmonary arterial or chronic thromboembolic pulmonary hypertension [24] and in patients with systemic sclerosis with exercise induced pulmonary hypertension [33]. Whether the increase in pressure-flow relationship or worsening of right ventricular pulmonary arterial coupling are of prognostic relevance in highlanders has not been studied so far and remains to be elucidated. Furthermore, genetic factors might play a role as has been previously postulated [34].

Limitations

Pulmonary hemodynamics were assessed by echocardiography at rest and during exercise, as the golden standard, right heart catheterization, was not possible for logistical and ethical reasons. However, stress echocardiography has been shown to be sufficiently accurate, but potentially less precise [9]. Subjects with elevated hemoglobin >19 g/dL in females and >21 g/dL in males, were not included in the current trial aiming to exclude patients possibly suffering from CMS. Therefore, we cannot present hemodynamic changes with exercise for

these patients, as most published studies on stress echocardiography at altitude focused on the difference between highlanders with and without CMS [1]. This trial focused on the comparison of highlanders without CMS compared to lowlanders. The results of the current trial may include a selection bias as patients without two valid TRPG measures during exercise were not included in the analysis, presumably excluding patients with very low PAP in highlanders, but also lowlanders.

In conclusion, the present study is the first to investigate a large collective of Central Asian highlanders living at moderate to high altitude between 2500-3500m by stress echocardiography compared to lowlanders. The main results are that highlanders reveal a significantly higher PAP over all exercise steps together with a similar CI resulting in a steeper pressure-flow slope, as indicator of an increased pulmonary resistance and potential sign of early pulmonary hypertension, which was most pronounced in highlanders with an elevated PAP already at rest thus qualifying as HAPH, intermediate in patients with borderline resting PAP increase and lowest in patients with normal resting hemodynamics. Whether the steeper pressure-flow increase with exercise predicts worse outcome in these highlanders remains to be studied.

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Figure legends

Figure 1: Patient flow.

Figure 2: Pressure-flow relationship displayed as tricuspid regurgitation pressure gradient (TRPG) in relation to the cardiac index from baseline to end-exercise, reflecting the pressure/flow relationship for a) highlanders and lowlanders and b) all groups: lowlanders, no HAPH (resting mean pulmonary artery pressure mPAP < 20mmHg), borderline HAPH (resting mPAP 20-30 mmHg) and HAPH (resting mPAP > 30 mmHg).

Figure 3: Vital signs of the lowlanders and highlanders during exercise (baseline, 3min, 6min, 9min and individual end exercise). TAPSE: tricuspid annular plane systolic excursion, TRPG: tricuspid regurgitation pressure gradient.

Table 1: Baseline characteristics

	Lowlanders n=22	Highlanders n=52	p-value
Gender, male/female	14/8	26/26	
Age, years	42.3±8.0	47.9±10.7	0.033
Height, cm	168.5±10.4	162.2±9.4	0.014
Weight, kg	75.9±10.4	70.2±13.4	0.078
BMI, kg/m^2	26.9±4.1	26.7±4.6	0.845
Body surface area, m^2	1.89±0.16	1.75±0.19	0.017
Heart rate, bpm	68±7	75±11	0.010
Blood pressure systolic, mmHg	121±15	127±23	0.274
Blood pressure diastolic, mmHg	82±10	85±12	0.348
New York Heart Association functional class I/II/III	18/3/1	30/18/4	0.379
Workload achieved, Watt	48±11	45±14	0.344
SpO_2, %	96±1	91±5	<0.001
Hemoglobin concentration, g/dL	14.4±1.7	16.0±2.3	0.008
Hematocrit, %	39.1±5.0	46.8±7.6	<0.001
PaO_2, mmHg	79.3±10.9	56.2±6.2	<0.001
$PaCO_2$, mmHg	38.9±2.9	32.5±2.8	<0.001
Oxygen content, mL O_2/dL	18.3±2.4	18.9±2.8	0.447
Pack years	1.9±5.2	3.7±6.2	0.227

Values are presented as mean ± SD. *Abbreviations*: BMI: Body mass index; SpO_2: oxygen saturation by pulseoximetry; PaO_2: Partial pressure of arterial oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide.

Table 2: Between group differences of the pressure / flow slope.

	Lowlanders N=22			Highlanders N=52			Between group differences	p-value
ΔTRPG/ΔCI, WU	3.0	±	2.4	9.4	±	11.4	6.4 (1.4 to 11.3)	0.012
ΔmPAP/ΔCO, WU	1.0	±	0.8	3.3	±	3.8	2.3 (0.6 to 3.9)	0.007

Values are presented as mean ± SD and mean differences with 95% confidence interval.

Abbreviations: TRPG: tricuspid regurgitation pressure gradient; CI: cardiac index; mPAP: mean pulmonary artery pressure; CO: cardiac output.

Table 3: Assessment during stepwise exercise

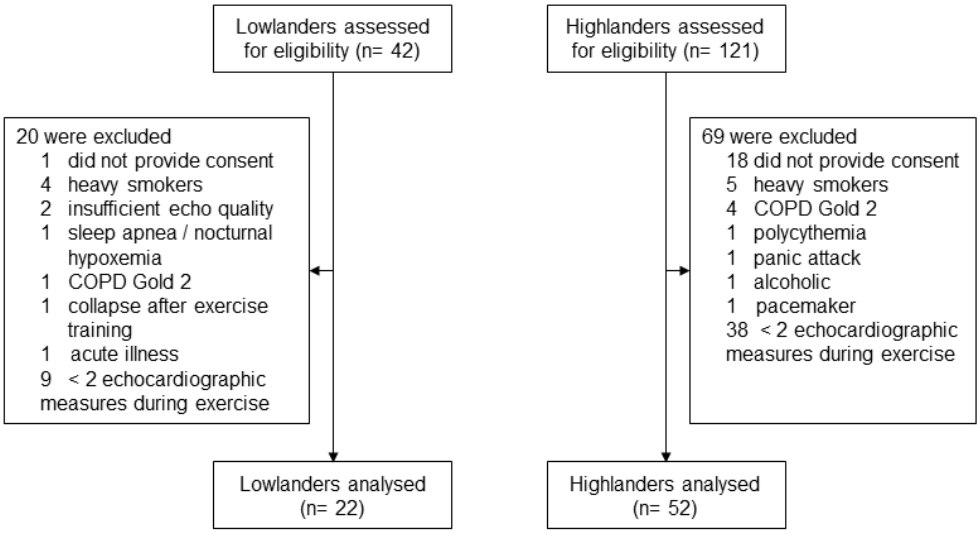
	Lowlanders n=22			Highlanders n=52			Between group differences 95% confidence interval	p-value
SpO_2, % BL	96	±	2	91	±	3	-5 (-6 to -4)	<0.001
SpO_2, % end-exercise	95	±	1	89	±	3	-6 (-8 to -5)	<0.001
SpO_2 end-exercise - BL	-0.4	±	1.1	-1.4	±	2.9	-1.0 (-2.2 to 0.3)	0.133
HR, bpm BL	77	±	13	82	±	12	5 (-2 to 11)	0.137
HR, bpm end-exercise	101	±	15	110	±	14	9 (2 to 16)	0.012
HR end-exercise - BL	24	±	15	28	±	13	-4 (-2 to 11)	0.185
TRPG, mmHg BL	13.9	±	4.2	22.8	±	5.5	8.9 (6.3 to 11.5)	<0.001
TRPG, mmHg end-exercise	20.0	±	7.4	36.4	±	12.2	16.4 (10.8 to 21.9)	<0.001
TRPG end-exercise - BL	6.1	±	4.8	13.6	±	10.5	7.5 (2.8 to 12.2)	0.002
CI l/min/m^2 BL	1.98	±	0.47	2.36	±	0.58	-0.38 (-0.66 to -0.09)	0.011
CI l/min/m^2 end-exercise	4.00	±	1.17	4.14	±	0.78	-0.14 (-0.62 to 0.34)	0.566
CI end-exercise - BL	2.02	±	0.89	1.78	±	0.61	0.24 (-0.13 to 0.61)	0.206
SVI, l/min/m^2 BL	26.0	±	5.4	29.2	±	6.8	-3.3 (-6.6 to	0.055

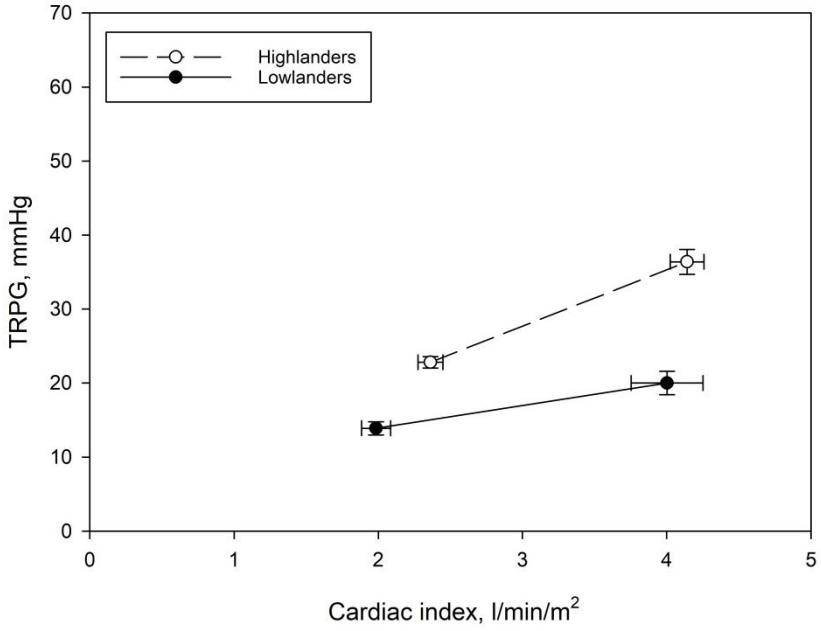
							0.1)	
SVI, l/min/m^2 end-exercise	38.6	±	6.6	37.8	±	6.3	0.8 (-2.5 to 4.1)	0.634
SVI end-exercise - BL	12.6	±	3.7	9.3	±	7.5	3.4 (0.0 to 6.8)	0.052
TAPSE, cm BL	2.1	±	0.3	1.9	±	0.4	-0.1 (-0.3 to 0.1)	0.153
TAPSE, cm end-exercise	2.7	±	0.4	2.5	±	0.5	-0.2 (-0.4 to 0.1)	0.163
TAPSE end-exercise - BL	0.6	±	0.4	0.6	±	0.4	0.0 (-0.2 to 0.2)	0.739
FAC. % BL	42.7	±	5.5	41.7	±	8.1	1.0 (-6.3 to 4.2)	0.691
FAC. % end-exercise	50.0	±	7.0	44.0	±	7.7	-6.0 (-11.3 to 0.8)	0.024
FAC end-exercise-BL	7.8	±	7.5	3.9	±	12.0	-3.9 (-12.7 to 5.0)	0.380
RVEDA, cm^2 BL	13.4	±	2.2	18.1	±	3.7	4.7 (2.4 to 7.1)	<0.001
RVEDA, cm^2 end-exercise	17.6	±	2.7	19.5	±	3.4	1.8 (-0.4 to 4.1)	0.112
RVEDA, end-exercise - BL	3.5	±	1.8	1.8	±	4.3	-1.7 (-4.7 to 1.4)	0.275
RVESA, cm^2 BL	7.7	±	18	10.6	±	2.9	2.9 (1.0 to 4.8)	0.003
RVESA, cm^2 end-exercise	8.9	±	2.5	10.9	±	2.2	2.0 (0.4 to 3.6)	0.014
RVESA, end-exercise - BL	0.6	±	1.3	0.2	±	3.1	-0.4 (-2.6 to 1.8)	0.707
TAPSE/TRPG,	1.6	±	0.5	0.9	±	0.1	-0.7 (-0.9 to -	<0.001

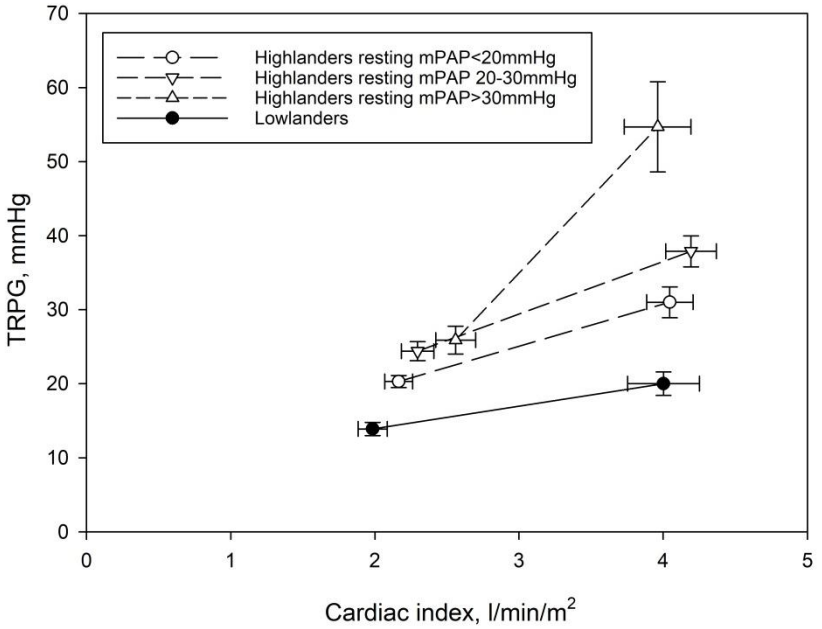
mm/mmHg BL							0.4)	
TAPSE/TRPG, mm/mmHg endex	1.6	±	0.8	0.8	±	0.3	-0.8 (-1.0 to -0.5)	<0.001
TAPSE/TRPG, endex - BL	-0.1	±	0.4	-0.1	±	0.3	-0.01 (-0.20 to 0.18)	0.901
TAPSE/sPAP, mm/mmHg BL	1.1	±	0.3	0.7	±	0.2	-0.39 (-0.52 to -0.26)	<0.001
TAPSE/sPAP, mm/mmHg end-exercise	1.2	±	0.5	0.7	±	0.3	-0.50 (-0.67 to -0.34)	<0.001
TAPSE/sPAP, end-exercise - BL	-0.01	±	0.26	-0.06	±	0.23	-0.04 (-0.17 to 0.09)	0.515
BPs, mmHg BL	104	±	19	112	±	15	7 (-1 to 15)	0.094
BPs, mmHg end-exercise	123	±	20	133	±	23	9 (-2 to 20)	0.010
BPs end-exercise - BL	19	±	12	21	±	17	2 (-6 to 10)	0.579
BPd, mmHg BL	70	±	11	77	±	10	7 (1 to 12)	0.015
BPd, mmHg end-exercise	68	±	14	78	±	13	10 (3 to 17)	0.004
BPd end-exercise - BL	-2	±	8	2	±	12	4 (-2 to 9)	0.191

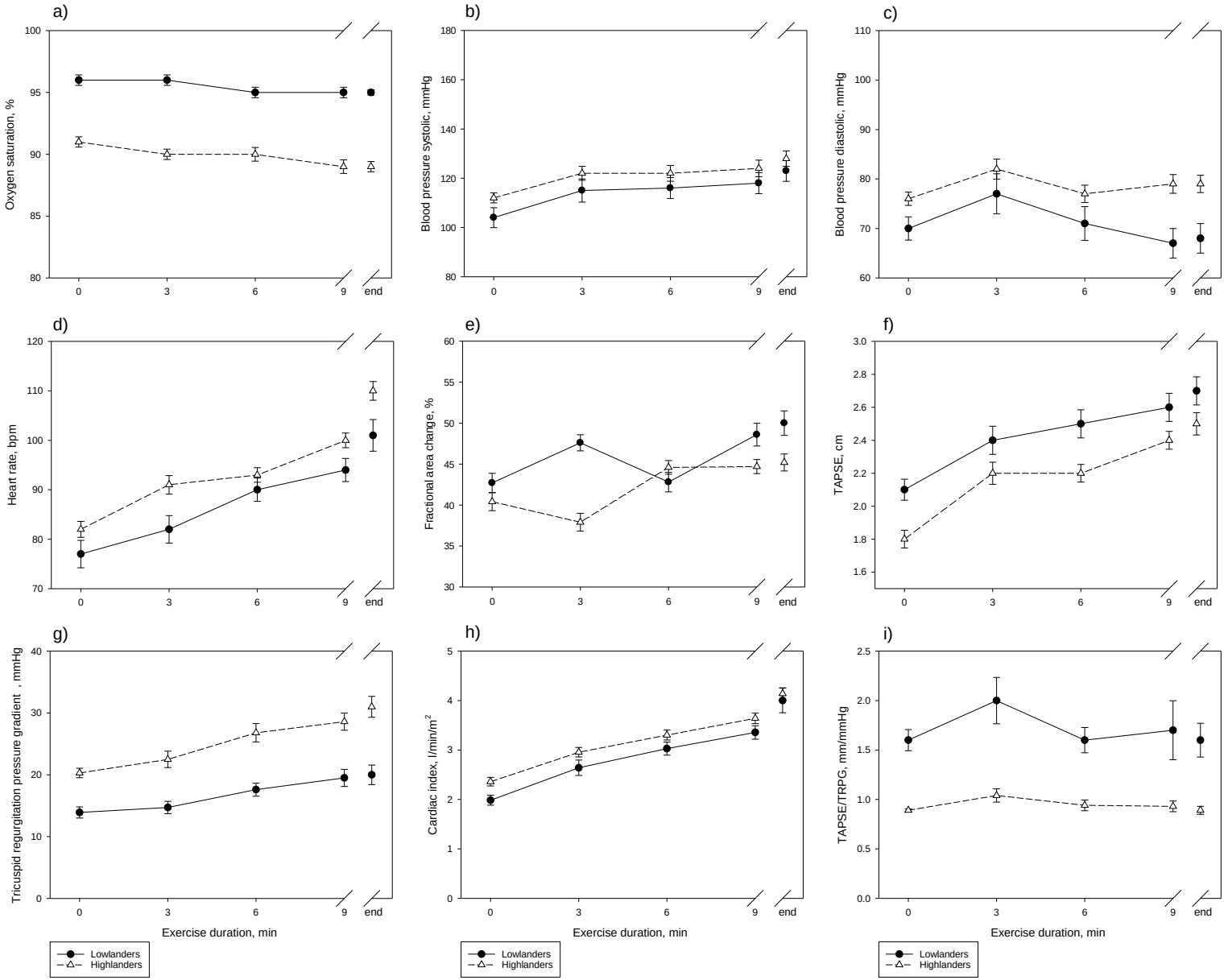
Values are presented as mean ± SD and mean differences with 95% confidence interval.

Abbreviations: BL: baseline upright on cycle ergometer; end-exercise: values at end exercise; end-exercise-BL: difference between end exercise and baseline; SpO_2: oxygen saturation; HR: heart rate; TRPG: tricuspid regurgitation pressure gradient; CO: cardiac output; SVI: stroke volume index; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area change; RVEDA: right ventricle end-diastolic area; RVESA: right ventricle end-systolic area; BPs: blood pressure systolic; BPd: blood pressure diastolic.


Lowlanders assessed for eligibility (n= 42)
20 were excluded
1 did not provide consent
4 heavy smokers
2 insufficient echo quality
1 sleep apnea / nocturnal hypoxemia
1 COPD Gold 2
1 collapse after exercise training
1 acute illness
9 < 2 echocardiographic measures during exercise
Lowlanders analysed (n= 22)
Highlanders assessed for eligibility (n= 121)
69 were excluded
18 did not provide consent
5 heavy smokers
4 COPD Gold 2
1 polycythemia
1 panic attack
1 alcoholic
1 pacemaker
38 < 2 echocardiographic measures during exercise
Highlanders analysed (n= 52)


Highlanders
Lowlanders
TRPG, mmHg
Cardiac index, l/min/m2
0
10
20
30
40
50
60
70
0
1
2
3
4
5


Highlanders resting mPAP<20mmHg
Highlanders resting mPAP 20-30mmHg
Highlanders resting mPAP>30mmHg
Lowlanders
TRPG, mmHg
Cardiac index, l/min/m2
0
10
20
30
40
50
60
70
0
1
2
3
4
5


a)
Oxygen saturation, %
b)
Blood pressure systolic, mmHg
c)
Blood pressure diastolic, mmHg
d)
Heart rate, bpm
e)
Fractional area change, %
f)
TAPSE, cm
g)
Tricuspid regurgitation pressure gradient , mmHg
h)
Cardiac index, l/min/m2
i)
TAPSE/TRPG, mm/mmHg
0
3
6
9
end
Exercise duration, min
Lowlanders
Highlanders

Pulmonary hemodynamic response to exercise in highlanders vs. lowlanders

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Supplementary tables

Supplementary table 1: Baseline characteristics by exploratory subgroups of highlanders according their resting mean pulmonary artery pressure

	Highlanders mPAP<20mmHg, n=23	Highlanders mPAP 20-30mmHg, n=24	Highlanders mPAP >30mmHg, n=5
Gender, male/female	13/10	11/13	2/3
Age, years	45.9±9.3	47.8±10.6	57.4±14.1
Height, cm	162.8±10.9	162.3±7.8	158.8±9.9
Weight, kg	68.8±12.4	70.4±15.2	75.8±8.1
BMI, kg/m^2	26.0±3.8	26.6±5.3	30.2±4.1
Body surface area, m^2	1.73±0.19	1.75±0.20	1.78±0.14
Heart rate, bpm	72±10	76±11	78±12
Blood pressure systolic, mmHg	123±21	126±21	152±26*
Blood pressure diastolic, mmHg	94±11	84±13	90±8
New York Heart Association functional class I/II/III	12/8/2	11/11/2	3/1/1
Max. workload, W	48±13	44±14	34±17
SpO_2, %	91±5	91±4	90±2
Hemoglobin concentration, g/dL	16.4±2.1	15.4±2.5	16.6±1.5
Hematocrit, %	47.8±8.9	45.7±6.6	48.0±4.6
PaO_2, mmHg	56.9±5.2	56.5±7.1	52.2±4.9
$PaCO_2$, mmHg	32.5±2.7	32.5±3.1	32.8±3.0
Oxygen content, mL O_2/dL	19.7±2.8	18.2±3.0	19.3±1.5
Pack years	3.1±5.5	4.6±7.1	2.8±4.4

Values are presented as mean ± SD. *Abbreviations*: BMI: Body mass index; SpO_2: oxygen saturation; PaO_2: Partial pressure of arterial oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide. *: significant difference in ANOVA $p<0.05$

Supplementary table 2: Between subgroups differences of the pressure / flow slope by exploratory subgroups of highlanders according their resting mean pulmonary artery pressure

	Highlanders mPAP<20mmHg, n=17	Highlanders mPAP 20-30mmHg, n=24	Highlanders mPAP >30mmHg, n=4	ANOVA
ΔTRPG/ΔCardiac index, WU	5.4±3.7	9.7±13.6	24.5±4.0	<0.001
ΔmPAP/ΔCO	1.9±1.3	3.4±4.4	8.6±1.9	<0.001

Values are presented as mean ± SD*. Abbreviations:* TRPG: tricuspid regurgitation pressure gradient.

Supplementary table 3: Measures during step-wise cycle exercise by exploratory subgroups of highlanders according their resting mean pulmonary artery pressure

	Highlanders mPAP<20mmHg, n=23	Highlanders mPAP 20-30mmHg, n=24	Highlanders mPAP >30mmHg, n=5	ANOVA
SpO_2, % BL	91±3	91±2	88±2	0.139
SpO_2, % end exercise	89±3	90±3	85±3	0.017
SpO_2 end exercise - BL	-1.7±3.1	-0.8±2.5	-3.0±2.7	0.611
HR, bpm BL	80±13	82±11	87±13	0.556
HR, bpm end exercise	103±18	110±11	112±6	0.914
HR end exercise - BL	29±15	28±10	25±11	0.127
TRPG, mmHg BL	20.3±3.9	24.4±6.2	25.9±4.2	0.018
TRPG, mmHg end exercise	31.0±10.0	37.9±10.2	54.7±13.6	<0.001
TRPG end exercise -BL	10.7±8.6	13.5±8.5	27.8±16.9	0.097
CI l/min/m^2 BL	2.36±0.69	2.33±0.55	2.56±0.28	0.216
CI l/min/m^2 end exercise	4.16±0.72	4.16±0.88	3.96±0.46	0.367
CI endex - BL	1.80±0.49	1.83±0.68	1.40±0.64	0.410
SVI, l/min BL	29.9±6.6	28.2±7.0	31.5±7.4	0.948
SVI, l/min end exercise	38.2±6.3	37.6±6.8	37.6±4.4	0.661
SVI end exercise - BL	8.2±5.0	10.7±8.8	6.1±9.1	0.079
TAPSE, cm BL	1.8±0.3	2.1±0.4	2.0±0.7	0.030

TAPSE, cm end exercise	2.5±0.4	2.6±0.5	2.4±0.6	0.741
TAPSE end exercise - BL	0.7±0.4	0.6±0.3	0.3±0.4	0.496
FAC. % BL	40.4±8.8	42.9±11.9	40.7±14.3	0.649
FAC. % end exercise	45.2±12.2	43.2±12.0	42.6±12.5	0.636
FAC end exercise - BL	5.9±15.3	2.4±9.2	6.2±12.8	0.379
RVEDA, cm^2 BL	17.2±3.6	17.6±3.2	23.1±2.0	0.656
RVEDA, cm^2 end exercise	18.9±3.0	19.2±3.4	22.1±4.5	0.542
RVEDA end exercise - BL	2.9±4.5	1.1±4.2	0.8±4.6	0.977
RVESA, cm^2 BL	10.4±3.3	10.1±2.3	13.7±2.9	0.585
RVESA, cm^2 end exercise	10.5±2.2	10.9±2.2	12.5±2.0	0.963
RVESA end exercise - BL	0.6±3.5	0.1±2.2	-1.0±5.4	0.180
TAPSE/TRPG, mm/mmHg BL	0.89±0.25	0.96±0.48	0.79±0.24	0.623
TAPSE/TRPG, mm/mmHg end exercise	0.89±0.33	0.76±0.33	0.48±0.22	0.039
TAPSE/TRPG end exercise - BL	-0.01±0.34	-0.19±0.35	-0.32±0.20	0.098
TAPSE/sPAP, mm/mmHg BL	0.71±0.17	0.77±0.30	0.66±0.20	0.039
TAPSE/sPAP, mm/mmHg end-	0.74±0.25	0.66±0.25	0.43±0.18	0.726

exercise				
TAPSE/sPAP, end-exercise - BL	0.03±0.25	-0.10±0.20	0.23±0.15	0.441
BPs, mmHg BL	112±13	109±16	122±21	0.195
BPs, mmHg end exercise	128±22	133±21	156±25	0.034
BPs end exercise - BL	15±18	24±15	34±18	0.573
BPd, mmHg BL	76±9	76±11	87±8	0.058
BPd, mmHg end exercise	79±9	74±13	97±18	0.008
BPd end exercise - BL	3±11	-2±13	10±12	0.782

Values are presented as mean ± SD*. Abbreviations:* BL: baseline on cycle ergometer; SpO_2: oxygen saturation; HR: heart rate; TRPG: tricuspid regurgitation pressure gradient; CI cardiac index; SVI: stroke volume index; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area change; RVEDA: right ventricle end-diastolic area; RVESA: right ventricle end-systolic area; BPs: blood pressure systolic; BPd: blood pressure diastolic.

Supplementary table 4: Linear mixed regression analysis with pressure-flow slope (Δ tricuspid regurgitation pressure gradient / Δ cardiac index) as dependent variable.

	Coefficient	95% confidence interval	p-value
Age	0.16	-0.04 to 0.37	0.122
Female vs. male	2.09	-1.87 to 6.04	0.302
Borderline HAPH	4.73	0.52 to 8.93	0.028
HAPH	18.06	9.10 to 27.02	<0.001
Intercept	-4.24	-14.18 to 5.70	0.403

Abbreviations: HAPH: high altitude pulmonary hypertension.