Heart rate variability in pulmonary vascular disease at altitude: a randomised trial

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Shareable abstract (@ERSpublications)
Exposure of patients with pulmonary vascular disease to altitude leads to changes in heart rate variability in line with an increase in sympathetic activity, which is accompanied by a significant decrease in baroreflex sensitivity. https://bit.ly/4bYwlzH

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Abstract

Background Hypoxia is a trigger for sympathetic activation and autonomic cardiovascular dysfunction. Pulmonary vascular disease (PVD) is associated with hypoxaemia, which increases with altitude. The aim was to investigate how exposure of patients with PVD to hypobaric hypoxia at altitude affects autonomic cardiovascular regulation.

Methods In a randomised crossover study, patients with PVD were studied for 1 day and one night at an altitude of 2500 m (hypobaric hypoxia) and low altitude at 470 m in a random order. Outcomes were heart rate variability (HRV) in the time domain and in the frequency domain (low frequency (LF)/high frequency (HF) and LF/HF) and heart rate (HR) during day and night and baroreflex sensitivity (BRS).

Results In 25 patients with PVD (72% pulmonary arterial hypertension and 28% distal chronic thromboembolic pulmonary hypertension; mean±SD age 60.7±13.6 years), exposure to altitude resulted in significant increases in awake HR by 9.4 bpm (95% confidence interval (CI) 6.3–12.4, p<0.001) and nocturnal HR by 9.0 bpm (95% CI 6.6–11.4, p<0.001) and significant changes in awake and particularly nocturnal HRV indicating decreasing parasympathetic and increasing sympathetic activity (change in daytime LF/HF 1.7 (95% CI 0.6–2.8), p=0.004; nocturnal LF/HF 1.9 (95% CI 0.3–3.4), p=0.022) and a significant decrease in BRS (−2.4·mmHg^{-1} (95% CI −4.3– −0.4, p=0.024)).

Conclusion Exposure of PVD patients to altitude resulted in a significant change in HRV indicating an increase in sympathetic activity and a decrease in BRS. The relative change in HRV at altitude was more pronounced during sleep.

Introduction

Pulmonary arterial hypertension (PAH) and distal chronic thromboembolic pulmonary hypertension (CTEPH) are pre-capillary forms of pulmonary hypertension characterised by pulmonary vascular disease (PVD) [1]. PVD is characterised by a chronic increase in right ventricular afterload, which leads to right ventricular remodelling and finally right heart failure [2]. PVD often leads to hypoxaemia, especially due to an increased ventilation–perfusion mismatch, which aggravates especially under physical activity and exercise due to impaired haemodynamics and reduced cardiac output. Since patients with PVD can already be hypoxaemic in room air, staying at altitude and illnesses associated with an increase in hypoxaemia will lead to a significantly greater increase in hypoxaemia than in healthy individuals when the oxyhaemoglobin dissociation curve is taken into account. This is also significant when you consider the 80 million people in the world who live in hypobaric hypoxia above 2500 meters.

Cardiovascular disease is often associated with chronic sympathetic hyperactivity and autonomic cardiac nervous system dysfunction with decreased baroreflex sensitivity (BRS) and blunted HR variability

(HRV) [3, 4]. Autonomic cardiovascular dysregulation in PVD is less well described but PVD seems to be associated with increased sympathetic nervous activity [5]. Blunted HRV during wakefulness is considered a marker of cardiovascular autonomic impairment and low HRV has been shown to be associated with an adverse cardiovascular outcome [3].

Short-term HRV can be quantified in the time domain and in the frequency domain from 5-min segments of the ECG and provides information about the modulation of heart rate (HR), which is regulated by the interaction of the sympathetic and parasympathetic nervous system [6]. There are no validated standard values and there are differences in HRV based on different ECG lengths (5 min *versus* 24 h) and awake *versus* asleep and during different sleep stages, which must be considered when interpreting. Time domain values are calculated using RR intervals and the most important indices are SD of normal RR intervals (SDRR), root mean square of successive RR interval differences (RMSSD) and percentage of normal RR intervals that differ by >50 ms (pRR50) [6, 7]. These values provide quantitative information about the cardiovascular regulation by the autonomic nervous system and are suppressed by parasympathetic blockade [8]. Frequency domain measurements are divided into high frequency (HF; representing parasympathetic activity) and low frequency (LF; measuring sympathetic and parasympathetic activity with a dominance of sympathetic activity) and provide further information about autonomic nervous system modulation [8, 9]. During non-rapid-eye-movement (REM) sleep, an increase in vagal control usually results in an increase in the HF component accompanied by a decrease in the LF component [10]. Impaired autonomic nervous system modulation, as evidenced by changes in HRV indices, is a strong predictor of poor cardiovascular prognosis in patients with ischaemic and nonischaemic heart disease [7, 11–14]. Decreased BRS is a marker of impaired cardiovascular autonomic regulation [15]. PVD has been associated with increased sympathetic activity and a further increase in sympathetic activity may result in an increase in pulmonary vascular resistance [5]. A decrease in arterial partial pressure of oxygen (P_{aO_2}) usually results in sympathetic stimulation [16]. It is not known how cardiovascular autonomic control responds to hypobaric hypoxia (altitude) in patients with PVD. The aim of the study was to investigate the effect of altitude exposure on both daytime and nocturnal HRV and BRS in patients with PVD.

Study design and methods

Study design and randomisation

In a randomised controlled crossover study, patients with PVD were examined over 30 h (nocturnal and daytime assessments) in a random order once at low altitude (Zurich, 470 m) and once at high altitude (Mount Saentis, 2500 m). Four-block randomisation was performed with Stata (version 16, StataCorp). The study was conducted in accordance with national ethical principles and the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the Ethics Committee of the Canton of Zurich (KEK 2021-00243) and the study was registered at ClicalTrials.gov (NCT05107700). All participants provided written informed consent to participate in the study.

Patient population

Adult patients from the Pulmonary Hypertension Centre of the University Hospital Zurich with a diagnosis of PAH or CTEPH were eligible for inclusion if they lived below 1000 m, had been in a stable condition for the last 4 weeks and had a P_{aO_2}>8 kPa at 470 m on room air. Exclusion criteria were altitude exposure >1000 m for ⩾3 days in the last 4 weeks, pregnancy, other significant medical conditions (*e.g.* renal failure or hepatic dysfunction), mental illness and abuse of illicit drugs or alcohol as well as chronotropic drugs.

Assessments

HR and HRV were assessed during the night and while awake at low altitude at 470 m and during a 30 h stay at altitude at 2500 m (after a rapid ascent by cable car) in a random order. In addition, BRS was assessed in the morning. Spontaneous BRS was assessed by analysing the relation of blood pressure and HR variations using beat-to-beat blood pressure measurement by Finapres® NOVA (Finapres Medical Systems, Enschede, the Netherlands) for more than 15 min at rest in the morning [17, 18]. This noninvasive continuous measurement of finger arterial pressure by a servo-plethysmo-manometer with infrared transmission provides accurate assessments of short-term changes of blood pressure [18]. BRS was automatically quantified with a dedicated software (BeatScope easy version 1.1a, ADInstruments, Dunedin, New Zealand) [17]. Patients wore a three-lead ECG (sampling rate 100 Hz) continuously and underwent cardiorespiratory polygraphy (Alice 5, Philips Respironics, Murrysville, PA, USA) during the night. In addition, they received arterial blood gas analysis.

Outcomes

The main outcomes of interest were the difference between low and high altitude in HRV parameters in the time (RMSSD and pRR50) and frequency (LF, HF and LF/HF) domains during the daytime and at

night [6]. ECGs were imported into LabChart version 8.1.19 (LabChart Software, ADInstruments Ltd., Sydney, Australia) and analysed with the HRV Module for LabChart. They were calculated using the mean of two out of three best reproducible measurements from nonoverlapping 5-min ECG segments. Other outcomes of interest were the difference between low and high altitude in morning BRS, resting HR, other measures of HRV (SD of RR intervals (SDRR) and coefficient of variation of RR intervals CVRR)) and beat-to-beat blood pressure variability (BPV) expressed as the coefficient of variation. For the resting measurement in the awake state, all patients were at rest in the supine position for at least 30 min. For HRV analysis during the night, 5-min segments between 00:00 and 04:00 were used. Only 5-min intervals with at least 150 normal sinus rhythm beats were included in the analysis. BRS and beat-to-beat BPV were measured at rest in the morning for at least 15 min. The association of changes in HRV at altitude with relevant outcome parameters such as 6-min walking distance (6MWD) and pulmonary vascular resistance (PVR) was an explorative outcome.

Statistics

Data are expressed as mean±SD and mean differences are reported along with 95% confidence interval (CI). Differences between low altitude (470 m) and high altitude (2500 m) were tested using a mixed-model analysis, following the CONSORT recommendation for crossover trials [19]. The linear mixed model was fitted to the data with intervention (2500 m *versus* 470 m), period and intervention–period interaction as fixed effects and subject as a random intercept, thus controlling for carry-over (treatment–period interaction) effects and period effects according to the standards of crossover trials. We tested whether the intervention–period interaction could be removed from the model. Model assumptions were tested by visual inspection of the homogeneity and normality of the residuals and random effects. Linear regression models were used to test the association between altitude-induced changes in HRV and baseline characteristics. A p-value <0.05 with a corresponding 95% CI that did not contain the null effect was considered as evidence of statistical significance. Based on data on the effects of normobaric hypoxia on RMSSD in patients with PVD, a total of 23 patients had to be included into this crossover study to detect a hypoxia-induced difference in RMSSD with a power of 80% at a two-sided 0.05 significance level if the true difference between conditions is 24 ms with an SD of 39 ms [20]. For this study assessing physiological outcomes, a per-protocol analysis was performed. RStudio version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses and GraphPad Prism version 9.5.1 for Windows (GraphPad Software, Boston, MA, USA) was used for figures.

Results

Patient population

All 27 of the included patients completed the study per-protocol and complete and artefact-free data were available from 24 and 25 patients for HRV and BRS analysis, respectively (figure 1). A total of 25 patients with PVD (72% with PAH, 28% with CTEPH; 44% women) with a mean age±SD of 60.7±13.6 years, a PVR of 6.1±2.6 WU and a P_{aO_2} at low altitude on room air of 10.0±1.6 kPa were included in the per-protocol analysis. Baseline characteristics are listed in table 1.

Difference in daytime HRV parameters, awake HR and S_{pO_2} between low (470 m) and high altitude (2500 m, hypobaric hypoxia)

When analysing changes in HRV parameters of 5-min ECG segments, a significantly lower time domain HRV was found in response to exposure of PVD patients to hypobaric hypoxia (table 2, figure 2). In addition, significantly lower LF and HF but significantly higher LF/HF values were found (table 2, figure 2).

Awake HR significantly increased in patients with PVD at high altitude compared with low altitude. Mean oxygen saturation was significantly lower at high altitude (table 3).

Difference in nocturnal HRV parameters, nocturnal HR and nocturnal S_{pO_2} between low altitude (470 m) and high altitude (2500 m)

Nocturnal time domain HRV parameters tended to be lower at high altitude compared with low altitude (table 4). The nocturnal LF/HF ratio was significantly higher at high altitude compared with low altitude (table 4). In addition, nocturnal HR was significantly higher (table 4). The changes in nocturnal HRV and HR during altitude exposure were similar to the changes in the waking state, but more accentuated in percentage change compared with low altitude at night (especially the frequency domain parameters).

Difference in BRS and in BPV between low (470 m) and high altitude (2500 m, hypobaric hypoxia)

Exposure of patients with PVD to hypobaric hypoxia led to a significant decrease in BRS (-2.4 ms·mmHg^{-1} (95% CI, -4.3– -0.4, p=0.024; table 2, figure 2).

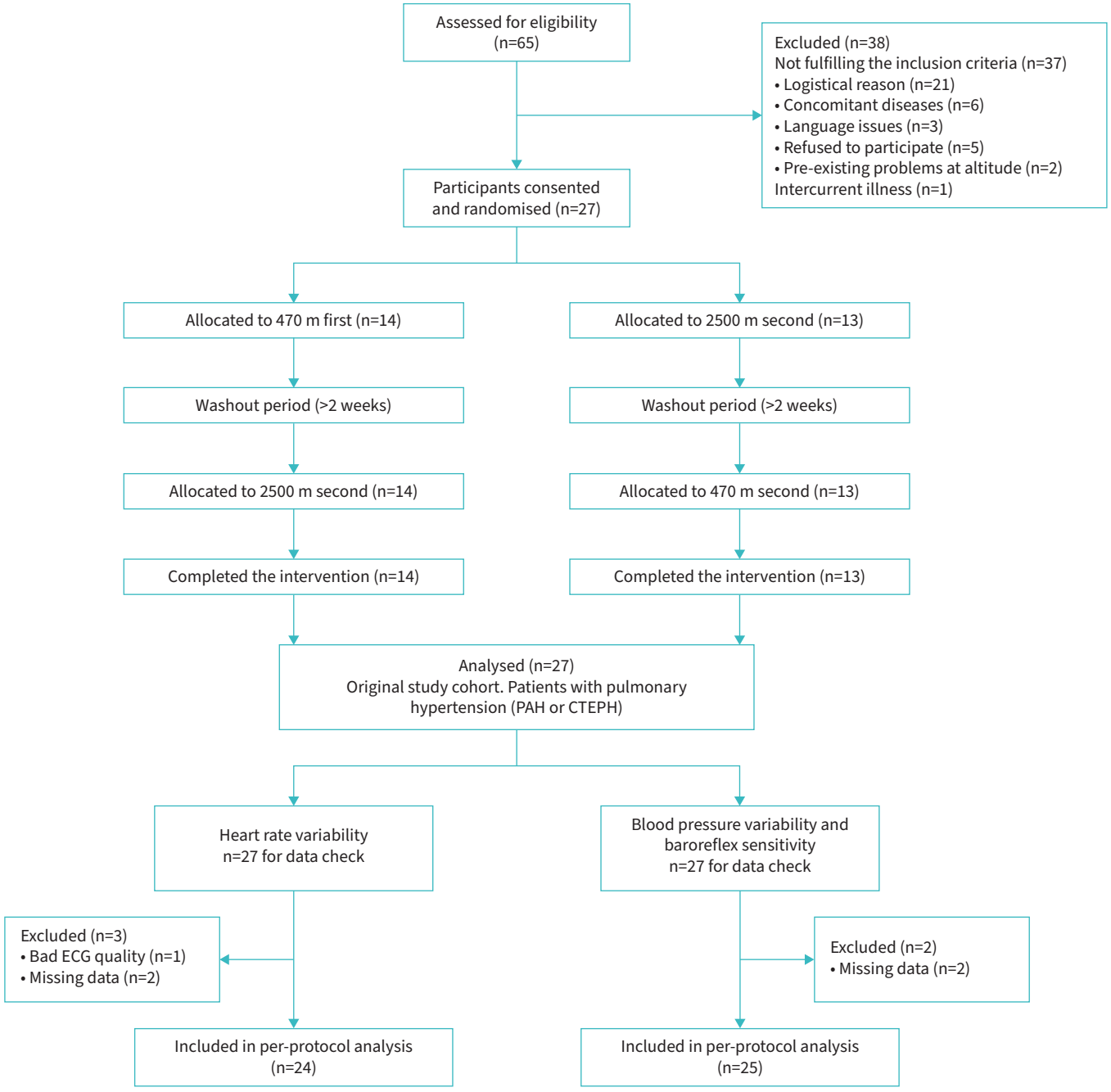

FIGURE 1 Flow diagram of study patients. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.

There was no statistically significant change in morning beat-to-beat BPV or blood pressure upon altitude exposure (table 5, figure 3).

Association of change in HRV with prognostic outcome parameters

There was no independent association between the change in RMSSD and LF/HF ratio with altitude exposure or RMSSD and LF/HF ratio at altitude with prognostic parameters such as 6MWD at low altitude, mean pulmonary arterial pressure, PVR or maximal oxygen uptake.

Discussion

An increase in hypoxaemia can occur in patients with PVD during worsening of right heart failure or in acute illnesses, but also during air travel and stays at high altitude (*e.g.* ski resorts or mountain huts).

TABLE 1 Baseline characteristics at low altitude

Characteristic	LA first (n=13)	HA first (n=12)	Total (n=25)
Female	6 (46)	5 (31)	11 (44)
Pulmonary arterial hypertension	9 (69)	9 (75)	18 (72)
Idiopathic pulmonary arterial hypertension	6 (46)	5 (42)	11 (44)
Associated with connective tissue disease	3 (23)	4 (33)	7 (28)
Chronic thromboembolic pulmonary hypertension	4 (31)	3 (25)	7 (28)
Inoperable	1 (8)	0 (0)	1 (4)
Persistent after pulmonary endarterectomy	3 (23)	3 (25)	6 (24)
Age, years	63±12	58±15	61±14
WHO functional class I, II, III	5 (39), 8 (62), 0 (0)	2 (13), 9 (56), 1 (6)	7 (28), 17 (68), 1 (4)
Body mass index, $kg \cdot m^{-2}$	24±2	26±5	25±4
6-min walk distance, m	606±72	569±94	589±82
Peak oxygen uptake, $mL \cdot kg^{-1} \cdot min^{-1}$	19±4	18±6	19±5
V'_E/V'_{CO_2}	39±7	39±9	39±9
Most recent right heart catheter			
Mean pulmonary artery pressure, mmHg	41±12	44±14	42±13
Pulmonary vascular resistance, WU	6.0±2.6	6.1±2.7	6.1±2.6
PH-targeted therapy	13 (100)	10 (83)	23 (92)
Endothelin receptor antagonist	11 (85)	8 (75)	19 (76)
Phosphodiesterase-5-inhibitor	4 (31)	5 (42)	9 (36)
Soluble guanylate cyclase stimulator	4 (31)	2 (17)	6 (24)
Parenteral prostanoid	1 (8)	2 (17)	3 (12)
Combination therapy	8 (62)	6 (50)	14 (56)
Calcium channel blockers	2 (15)	2 (17)	4 (16)
Arterial blood gas analysis at low altitude			
pH	7.44±0.18	7.43±0.04	7.44±0.03
P_{aCO_2}, kPa	4.5±0.5	4.7±0.4	4.6±0.4
HCO_3^-, $mmol \cdot L^{-1}$	24.2±1.6	24.3±2.5	24.2±2.1
BE, $mmol \cdot L^{-1}$	−0.81±2.51	−0.65±8.97	−0.77±2.84
P_{aO_2}, kPa	9.8±1.7	10.2±1.5	10.0±1.6
S_{aO_2}, %	95.3±1.8	95.4±3.2	95.4±2.6
Pulmonary function testing			
FEV_1 % predicted, %	89±18	87±2	88±15
FVC % predicted, %	94±15	91±13	92±14
FEV_1/FVC	74±10	76±5	75±7
D_{LCO} % predicted, %	59±21	63±9	61±14

Data are presented as mean±SD or number (%). LA: low altitude; HA: high altitude; WHO: World Health Organization; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; PH: pulmonary hypertension; P_{aCO_2}: arterial partial pressure of carbon dioxide; HCO_3^-: calculated bicarbonate; BE: base excess; P_{aO_2}: arterial partial pressure of oxygen; S_{aO_2}: oxygen saturation; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity for carbon monoxide.

Air travel and journeys to regions >2500 m have become normal for both healthy subjects and patients with cardiovascular disease or PVD. How autonomic cardiovascular regulation changes while subjects are awake and during the night was investigated for the first time in patients with PVD when they are exposed to hypobaric hypoxia for more than 1 day. Investigating the effect of hypoxaemia on cardiovascular autonomic regulation in patients with PVD is particularly important, as they may be less susceptible due to pre-existing hypoxaemia but are particularly vulnerable due to already impaired haemodynamics.

In this randomised controlled crossover study, we investigated the effect of hypobaric hypoxia (2500 m) in patients with PVD (PAH or distal CTEPH) on autonomic cardiovascular control using measures such as HRV, BRS and BPV. We found a blunted HRV and changes in the HRV frequency domain pattern, reflecting autonomic disturbance and sympathetic dominance. The effect was independent of drug therapy for PVD and consistent in all treatment groups (monotherapy, combination therapy, triple therapy and calcium antagonists). HRV changes were more pronounced during the night when hypoxaemia further aggravates (the per cent change at high altitude compared with low altitude was higher at night). In line with an increase in sympathetic activity, we found a significant increase in resting and nocturnal HR by 9 bpm in response to hypobaric hypoxia.

TABLE 2 Difference in awake heart rate variability parameters and BRS between low altitude (470 m) and hypoxia at high altitude (2500 m)

Variable	Low altitude (470 m, Zurich)	High altitude (2500 m, Saentis)	Altitude effect (HA – LA)	p-value
Time domain (n=24)				
RMSSD, ms	24.2±13.6	18.1±9.9	−7.0 (95% CI −10.9– −3.2)	<0.001
pRR50, %	8.5±11.1	3.1±5.5	−5.4 (95% CI −8.9– −2.0)	0.004
Frequency domain (n=24)				
LF, ms^2	352.5±274.8	236.2±239.1	−116.3 (95% CI −198.6– −34.0)	0.008
HF, ms^2	248.7±252.6	139.2±150.6	−109.5 (95% CI −206.8– −12.2)	0.029
LF/HF	2.1±1.8	3.8±3.4	1.7 (95% CI 0.6–2.8)	0.004
BRS (n=25)				
BRS, $ms{\cdot}mmHg^{-1}$	10.5±5.6	8.2±3.6	−2.4 (95% CI −4.3– −0.4)	0.024

Data are presented as mean±SD and the altitude effect along with its 95% confidence interval (CI). HA: high altitude; LA: low altitude; RMSSD: square root of the sum of all differences between successive RR intervals; pRR50: percentage of differences higher than 50 ms in RR intervals; LF: low-frequency band; HF: high-frequency band; LF/HF: ratio of LF/HF; BRS: baroreflex sensitivity.

HRV analysis is a simple method to assess autonomic cardiovascular changes and predict cardiovascular risk and mortality [3, 7]. HRV analysis is divided into time and frequency domains; in the time domain, the RMSSD value represents parasympathetic activity and is the easiest to assess because of its stability [9]. RMSSD was significantly reduced upon altitude exposure. The LF domain represents the efferent activity of the parasympathetic and sympathetic nervous systems, whereas the HF represents only the efferent parasympathetic activity [21]. An increase in the LF/HF ratio reflects a shift to "sympathetic dominance" [22]. Such a shift was observed at altitude both during daytime and during the night, and although absolute values were higher during daytime, the increase compared with low altitude (in per cent change) was more pronounced during the night. This could be explained by the trigger of more-pronounced nocturnal hypoxaemia and seems particularly important, since a reduction in sympathetic activity during sleep with a reduction in HR and blood pressure is particularly relevant for prognosis [23].

Only a few studies have investigated changes in HRV in PAH. A reduced HRV in the time and frequency domain has been described in PAH compared with the healthy population [24–27]. Our patients were all in the low-risk category for pulmonary hypertension and there was no difference in HRV change with altitude exposure between patients on monotherapy or combination therapy. The influence of altitude exposure on HRV has only been investigated in healthy volunteers (not in PVD) in several studies, and these studies found increased sympathetic activity or decreased parasympathetic activity. Under resting conditions, HR increases significantly at high altitude [28]. Studies found that the HF domain decreased and the LF/HF ratio increased when examining healthy patients at altitudes of 3700 m, 3180 m and 2700 m [28–30]. In the time domain, a blunted HRV (reduction in RMSSD and pRR50) was described [28, 30]. In line with our population with PVD, blunting of HRV was also found in healthy subjects, with a decrease in the time and frequency domain and an increase in LF/HF ratio. This is consistent with both decreased parasympathetic and increased sympathetic activation. The changes in HRV during altitude exposure seem to be comparable in healthy and in PVD patients. There is also a reduction in the time and frequency domain and an increase in the LF/HF ratio and HR in PVD patients, which represents a decreased parasympathetic activity and an increased sympathetic activity. In the study by Meszaros *et al.* [20], PVD patients were exposed to acute (30–70 min) normobaric hypoxia. In contrast to this study of longer exposure to hypobaric hypoxia, the study of short exposure to simulated hypoxia showed increased HRV. Why the effect of normobaric hypoxia differs from hypobaric hypoxia remains unclear. A possible explanation could be that in PVD, the autonomic nervous system reacts slower to hypoxia due to chronic sympathetic activation and, therefore, in our study, sympathetic activation resulted from prolonged exposure to high altitude. In contrast to the study by Mezaros *et al.* [20], a recent study in healthy volunteers showed that acute normobaric hypoxia leads to a decrease in HRV and parasympathetic tone and an increase in sympathetic activity [31]. In a study by Tanner *et al.* [32], the difference between a 24-h exposure to normobaric and hypobaric hypoxia was investigated in 41 healthy subjects. No significant difference was found in HRV between hypobaric and normobaric hypoxia. However, a decrease in the time and frequency domain as well as an increase in the LF/HF ratio was found at comparable exposure duration at altitude as in our study [32]. Exposure to 4970 m led to an acute activation of the

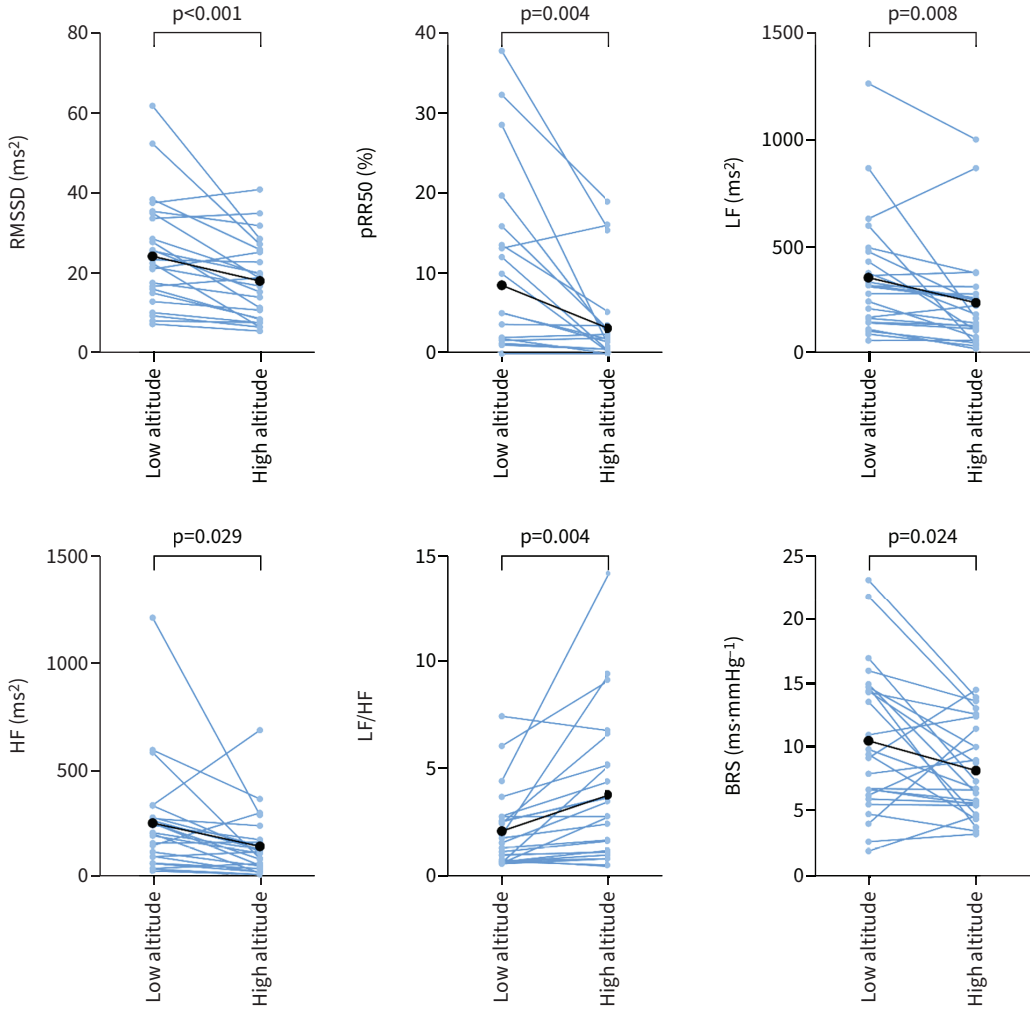

FIGURE 2 Difference in awake heart rate variability and BRS between low altitude and high altitude. The blue dots and lines show individual patients, the black dots and the corresponding line show the mean value. RMSSD: square root of the sum of all differences between successive RR intervals; pRR50: percentage of differences higher than 50 ms in RR intervals; LF: low-frequency band; HF: high-frequency band; LF/HF: ratio of LF/HF; BRS: baroreflex sensitivity.

TABLE 3 Difference in other heart rate variability parameters between ambient air (470 m) and hypoxia (2500 m)

Variable, n=24	Low altitude (470 m, Zurich)	High altitude (2500 m, Saentis)	Altitude effect (HA – LA)	p-value
Average RR, ms	882.3±119.6	774.4±88.5	−108.0 (95% CI −146.3– −69.6)	<0.001
SDRR, ms	34.5±11.5	29.6±11.0	−4.9 (95% CI −10.5–0.6)	0.079
CVRR, ms	0.039±0.012	0.039±0.014	−0.001 (95% CI −0.006–0.007)	0.817
Average HR, bpm	69.4±10.1	78.8±9.6	9.4 (95% CI 6.3–12.4)	<0.001
SDHR, bmp	3.0±1.1	3.2±1.2	0.2 (95% CI −0.4–0.8)	0.527
Oxygen saturation, %	93.2±2.3	86.4±3.8	−6.8 (95% CI −8.4– −5.1)	<0.001

Data are presented as mean±SD and the altitude effect along with its 95% confidence interval (CI). HA: high altitude; LA: low altitude; SDRR: SD in RR intervals; CVRR: coefficient of variation in RR intervals; HR: heart rate; bpm: beats per minute; SDHR: SD in heart rate.

TABLE 4 Difference in nocturnal HRV parameters between low altitude (470 m) and high altitude (2500 m)

Variable, n=24	Low altitude night (470 m, Zurich)	High altitude night (2500 m, Saentis)	Altitude effect (HA – LA)	p-value
Time domain				
RMSSD, ms	28.3±14.8	20.1±13.8	−8.2 (95% CI −14.0– −2.5)	0.007
pRR50, %	7.4±9.4	3.7±5.8	−3.6 (95% CI −7.7–0.5)	0.079
Frequency domain				
LF, ms^2	475.9±534.7	234.2±345.7	−241.6 (95% CI −394.5– −88.8)	0.003
HF, ms^2	450.3±645.7	218.7±342.8	−231.6 (95% CI −500.1–36.9)	0.088
LF/HF	1.6±1.3	3.4±4.7	1.9 (95% CI 0.3–3.4)	0.022
Other HRV parameters and HR				
Average RR, ms	933.6±120.4	840.7±97.8	−92.9 (95% CI −150.6– −35.3)	0.003
SDRR, ms	35.2±15.7	28.5±13.8	−6.7 (95% CI −13.4– −0.1)	0.047
CVRR, ms	0.04±0.02	0.03±0.02	−0.01 (95% CI −0.01–0.00)	0.220
Average HR, bpm	63.6±7.0	72.6±8.0	9.0 (95% CI 6.6–11.4)	<0.001
SDHR, bpm	2.4±1.1	2.6±1.5	0.2 (95% CI −0.3–0.8)	0.443

Data are presented as mean±SD and the altitude effect along with its 95% confidence interval (CI). HA: high altitude; LA: low altitude; RMSSD: square root of the sum of all differences between successive RR intervals; pRR50: percentage of differences higher than 50 ms in RR intervals; LF: low-frequency band; HF: high-frequency band; LF/HF: ratio of LF/HF; HRV: heart rate variability; HR: heart rate; SDRR: SD in RR intervals; CVRR: coefficient of variation in RR intervals; bpm: beats per minute; SDHR: SD in heart rate.

sympathetic nervous system in healthy volunteers, which persisted even after 1 week. In contrast, blood pressure returned to the baseline value at sea level after 1 week of exposure [33].

RMSSD values were higher during sleep compared with awake at both altitudes reflecting an increased parasympathetic activity during the night. Parasympathetic dominance during non-REM sleep is physiological [34]. In general, sleep-disordered breathing resulting in intermittent hypoxaemia and/or sleep fragmentation are well-known causes of nocturnal activation of the sympathetic nervous system [35–37]. Whether PVD patients are less or more sensitive to hypoxia than healthy subjects cannot be concluded from this randomised controlled trial in PVD or from data comparisons with the literature on healthy people due to different duration of exposure and levels of hypoxia. High-altitude exposure could theoretically be dangerous for patients with PVD because of hypoxic pulmonary vasoconstriction and the associated increase in PVR. However, right heart catheterisation studies have shown that hypoxic pulmonary vasoconstriction seems to be attenuated under short-term normobaric hypoxia [38]. There are limited data on the cardiovascular effects and their long-term risks in PVD during a stay at high altitude. In this study, significantly blunted HRV values and changes corresponding to autonomic disturbance with sympathetic dominance were found, which could correspond to increased cardiovascular risk. This is important considering that millions of people live at high altitudes, including patients with pulmonary hypertension, as well as situations in which patients with PVD are exposed to increased hypoxemia, *e.g.* during respiratory infections or pulmonary oedema. The next step would be to investigate how autonomic cardiovascular control and sympathetic activity change during prolonged exposure to altitude and how correction of hypoxaemia by oxygen supplementation affects HRV at altitude.

TABLE 5 Difference in blood pressure and BPV between low altitude (470 m) and high altitude (2500 m)

Variable, n=25	Low altitude (470 m, Zurich)	High altitude (2500 m, Saentis)	Altitude effect (HA – LA)	p-value
Systolic blood pressure, coefficient of variation, %	6.4±3.8	7.4±5.8	1.0 (95% CI −1.3–3.3)	0.382
Diastolic blood pressure, coefficient of variation, %	6.2±2.6	7.0±4.6	0.8 (95% CI −0.8–2.5)	0.306
Systolic blood pressure, mmHg	115.8±15.5	109.3±11.8	−6.5 (95% CI −13.7–0.8)	0.081
Diastolic blood pressure, mmHg	67.0±14.8	69.4±9.0	2.4 (95% CI −4.1–8.9)	0.459
Oxygen saturation during BPV assessment, %	92.1±3.0	89.0±4.4	−3.1 (95% CI −5.1– −1.2)	0.002
Respiratory rate, $breaths \cdot min^{-1}$	22.2±4.7	20.2±3.2	−2.0 (95% CI −4.6–0.6)	0.265

Data are presented as mean±SD and the altitude effect along with its 95% confidence interval (CI). Oxygen saturation and respiratory rate during beat-to-beat blood pressure measurement are reported. HA: high altitude; LA: low altitude; BPV: blood pressure variability.

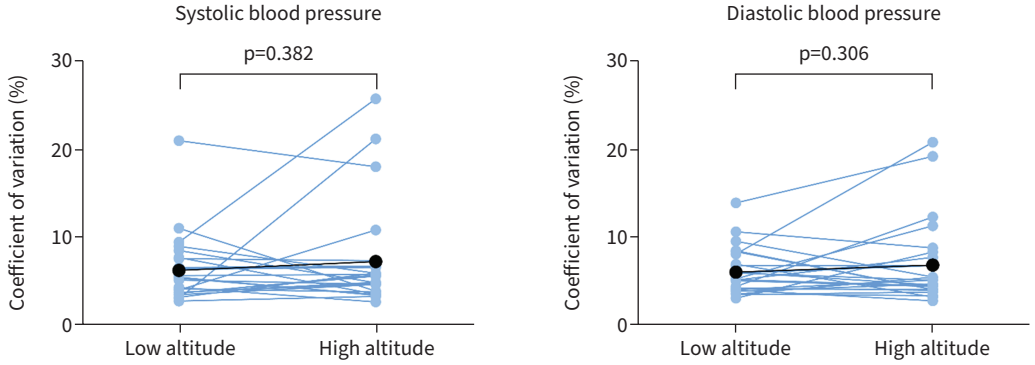

FIGURE 3 Difference in coefficient of variation for systolic and diastolic blood pressure between low altitude and high altitude. The blue dots and lines show individual patients, the black dots and the corresponding line show the mean value.

This study also investigated BRS in PVD patients exposed to altitude. In PVD patients, abnormal control of the sinus node by the autonomic efferent nervous system is common, which can lead to clinical worsening, increased risk of arrhythmias and increased mortality [24, 25, 39, 40]. The autonomic nervous system is influenced by afferent information from arterial baroreceptors and arterial chemoreceptors. Only a few studies have investigated the BRS and its influence on RR intervals in PAH patients and have found lower BRS in PAH patients compared with healthy subjects (5.8±0.6 *versus* 13.9±1.2 ms·mmHg^{-1} and 5.89±3.43 *versus* 8.55±5.76 ms·mmHg^{-1}) although patients with PAH are commonly female and younger [24, 41]. Our study in patients with PVD also found a reduction in resting BRS under hypobaric hypoxia.

A limitation is the duration of the stay at altitude, which does not allow a statement about a possible adaptation over a longer period of time. Nevertheless, this study does allow conclusions on HRV changes both during wakefulness and during the night during an overnight stay at altitude. The study population had good physical fitness for the age and severity of pulmonary hypertension, so the results could be different in less-fit patients. An analysis of the Swiss Registry for Pulmonary Hypertension shows an increase in the average 6MWD in recent years, which can be attributed to optimised therapy, including combination and triple-drug therapy as well as best-supportive therapy [42]. In addition, there is a selection bias for fitter patients who voluntarily participate in a higher study. Cardiorespiratory polygraphy and not polysomnography was performed in this study, so the results cannot be discussed in the context of sleep stages. To avoid the influence of REM sleep on nocturnal HRV, three independent 5-min segments of the ECG were always analysed and the mean value of the two least deviating from each other was used.

Conclusions

Exposure to hypoxia at high altitude results in blunted HRV and BRS in patients with PVD, representing autonomic cardiovascular dysfunction in the form of sympathetic overactivity. Changes in HRV are more pronounced during the night than during wakefulness, consistent with exposure to more severe hypoxaemia. Oxygen supplementation could possibly counteract these altitude-induced autonomic changes, which will be investigated as a next step.

Provenance: Submitted article, peer reviewed.

Data availability: The data presented in this study are available on reasonable request from the corresponding author.

This study is registered at www.clinicaltrials.gov with identifier number NCT05107700.

Ethics statement: The study protocol was approved by the Ethics Committee of the Canton of Zurich (KEK 2021-00243).

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Conflict of interest: S. Ulrich reports grants or contracts from Swiss National Science Foundation, Zurich, and Swiss Lung League; unrestricted grants from Orpha Swiss and MSD, outside the submitted work; consulting fees from Orpha Swiss, MSD SA and Janssen SA, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events for Orpha Swiss, MSD SA, Janssen SA and Novartis SA, outside the submitted work; support for attending meetings and/or travel from Orpha Swiss, MSD SA, Janssen SA and Novartis SA, outside the submitted work; participation on a data safety monitoring or advisory board for Orpha Swiss, MSD SA and Janssen SA, outside the submitted work; leadership or fiduciary roles for the Swiss Society of Pulmonology, European Respiratory Society and Swiss Society of Pulmonary Hypertension, outside the submitted work. M. Lichtblau reports receiving payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from MSD SA, outside the submitted work; support for attending meetings and/or travel from Orpha Swiss, Janssen and MSD, outside the submitted work; and participation on a data safety monitoring or advisory board for MSD SA, outside the submitted work. E.I. Schwarz reports receiving lecture fees from ResMed outside the submitted work and is Secretary of Assembly 4 of the European Respiratory Society (unpaid) outside the submitted work. The remaining authors have nothing to disclose.

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