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RESEARCH ARTICLE

One night at 1,900 m prompts ventilatory acclimatization without altering cardiac autonomic regulation at 3,000 m in males with coronary artery disease

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Abstract

Spending a single night at moderate altitude before ascending to high altitude may enhance ventilatory acclimatization but also exacerbate sympathetic activation, a response that should be carefully pondered in persons with coronary artery disease (CAD). Ten males with CAD participated in this randomized placebo-controlled crossover trial in a hypobaric chamber, where they slept either at simulated 1,900 m (intervention) or in control conditions (250 m, placebo) before being decompressed to 3,000 m the following morning. Respiratory polygraphy was performed each night. Peripheral oxygen saturation (Sp_{O_2}), end-tidal partial pressure of CO_2 ($P_{ET_{CO_2}}$), cerebral tissue oxygen saturation index (cTSI), baroreflex sensitivity (BRS), heart rate variability (HRV), and pulmonary artery systolic pressure (PASP) were recorded during wakeful rest each morning, both before the overnight stay (at 250 m) and after the simulated ascent to 3,000 m. The intervention night was associated with a greater number of apneas/hypopneas (33 [9, 51] h^{-1}) than placebo (6 [3, 13] h^{-1}, $P = 0.02$). At 3,000 m, Sp_{O_2} was higher after intervention (88 ± 2%) than placebo (87 ± 2%, $P = 0.03$), $P_{ET_{CO_2}}$ was lower after intervention (34 ± 3 mmHg) than placebo (36 ± 3 mmHg, $P = 0.002$), cTSI decrease was smaller after intervention (−3.6 ± 2.2%) than placebo (−6.5 ± 3.1%, $P = 0.02$), and PASP was higher after intervention (30 ± 8 mmHg) than after placebo (28 ± 7 mmHg, $P = 0.04$), whereas BRS and HRV indices showed no differences. We conclude that a single night at 1,900 m is sufficient to trigger measurable ventilatory acclimatization in persons with CAD without altering BRS and HRV at 3,000 m, but likely enhancing pulmonary hypoxic vasoconstriction.

NEW & NOTEWORTHY We found that a single night spent at simulated moderate altitude (1,900 m) prompts measurable ventilatory acclimatization when ascending to simulated high altitude (3,000 m) in males with coronary artery disease. We also found that, although sleeping at 1,900 m increases the occurrence of apneas and/or hypopneas, this did not modify heart rate variability and baroreflex sensitivity responses at 3,000 m.

blood pressure; central sleep apnea; hypobaric hypoxia; myocardial infarction; preacclimatization

INTRODUCTION

High altitude (HA) exposure [>2,500 m above sea level (asl)] can increase the risk of sudden cardiac death (SCD) (1, 2), particularly in people with prior myocardial infarction (MI) (3–5). Several factors contribute to this increased risk. First, hypoxia and physical activity are known to activate the sympathetic nervous system, both increasing myocardial oxygen demand and electrical instability (6, 7). Second, hypoxic pulmonary vasoconstriction (8, 9) can impair cardiac output (CO) (10) and lung diffusion capacity (11–13). Therefore, persons with coronary artery disease (CAD) are particularly prone to maladaptive responses to HA, such as myocardial oxygen supply-demand mismatch and atherosclerosis-induced paradoxical hypoxic vasoconstriction of coronary arteries (5, 14, 15), leading to a higher risk of ischemia. To reduce the risk of adverse cardiovascular events when sojourning to mountainous locations, appropriate pretravel physical assessment, review of medical treatment, regular physical activity, and gradual ascent not higher than 4,200 m asl are recommended for persons with CAD (15, 16). Nonetheless, it is known that approximately half of SCDs

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during mountain sports occur on the first day at altitude (17), which underscores the importance of preacclimatization before going to HA.

Sleeping at moderate altitude (MA, 1,500–2,500 m asl) has been proposed as an adequate form of preacclimatization to HA as it was reported to be linked to a lower risk of SCD during mountain leisure activities (18). Although the involved mechanisms are not completely understood, MA is thought to induce a ventilatory acclimatization that mitigates further hypoxemia at HA (19). However, sleeping at MA increases nighttime blood pressure and induces central apneas and hypopneas even in healthy adults (20), which, in turn, could increase sympathetic activity (21) and, thus, the risk of acute coronary events (22). In individuals with CAD, the trade-off between positive and negative effects of a night's sleep at MA before ascending to HA should be carefully considered.

The aim of this single-blind, placebo-controlled, crossover study was to investigate whether a single night spent at MA affects the physiological responses to a subsequent passive ascent to HA. We hypothesized that sleeping at MA (1,900 m asl, intervention) would trigger a measurable ventilatory acclimatization, leading to increased resting arterial oxygen saturation upon acute exposure to HA (3,000 m asl). Furthermore, we tested the hypothesis that staging one night at MA, potentially through central sleep apneas, would lead to different resting cardiovascular and pulmonary arterial responses to a subsequent HA exposure compared with a direct ascent from sea level (SL).

MATERIALS AND METHODS

Ethical Approval

The study protocol adhered to the guidelines of good clinical practice, was carried out in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the Autonomous Province of Bolzano (123-2020). The study was registered as a clinical trial on ClinicalTrials.gov (ID NCT04725539).

Participants

Participants were recruited by public advertising and through physician referral. Inclusion criteria were age from 45 to 70 yr with known history of CAD, with or without prior MI. Exclusion criteria were residence >600 m asl, overnight stay >1,000 m asl during the 4 wk preceding any experimental session, regular smoking (>5 cigarettes per day), inability to perform moderate exercise, recent MI or revascularization (<6 mo prior to inclusion), unstable angina, ejection fraction <50%, life-threatening arrhythmias, symptomatic aortic outflow obstruction, uncontrolled systemic hypertension (>180/100 mmHg), pulmonary hypertension, drug abuse, and any other severe systemic noncardiac disease.

After reviewing the inclusion/exclusion criteria, 12 male subjects were enrolled. Although several applications were received from females, all either did not meet the inclusion criteria or met some exclusion criteria. After having received a detailed description of the study methods and experimental procedures and having been informed of their right to withdraw at any time without jeopardy, all participants gave their written informed consent before study enrollment. Then, they provided a health-related history and underwent a medical routine examination. Two participants did not complete the study for personal reasons. Overall, 10 participants [all male, nonsmokers, living below 500 m asl, aged 63 ± 8 yr old (range 46–70), BMI 27 ± 3 $kg \cdot m^{-2}$ (range 23–32)] completed the study. Nine of the participants were diagnosed with critical coronary stenosis (eight multivessel and three also with prior MI), whereas one had only a prior MI. Coronary revascularization procedure had been previously performed in eight (six percutaneous and two surgical bypass), whereas the remaining two received medical therapy only. One participant was diagnosed with obstructive sleep apnea. All participants were on lipid-lowering therapy, and three were taking renin-angiotensin system inhibitors (one in combination with amlodipine). Regarding chronotropic medications, five participants were taking β1-selective beta blockers and one diltiazem. Notably, one subject was affected by permanent atrial fibrillation and was excluded from the heart rate variability and baroreflex analyses. A week before each visit, subjects were reminded to carefully adhere to their chronic medication intake, which was also visually monitored in the mornings and evenings of each study day. The detailed subject characteristics are reported in Table 1.

Study Design

This was a single-blind placebo-controlled, randomized crossover trial. Tests and intervention were performed in a large (12 × 6 × 5 m), well-ventilated (inspired CO_2 fraction < 0.1%) hypobaric chamber (terraXcube, Bolzano, Italy, 250 m asl). Participants entered the chamber on three occasions: the first to familiarize themselves with the experimental protocol; the subsequent two for the experimental sojourns, each comprising measurements during the night (1,900 or 250 m), the preceding morning (250 m), and the following morning (3,000 m), as detailed in *Study Protocol*. The experimental sojourns were separated by 3–4 wk of washout.

Study Protocol

The experimental protocol is depicted in Fig. 1. Participants arrived at 0900 and underwent resting measurements near sea level (SL, 250 m asl); then, they returned to the chamber at 1900 for a standardized meal. At 2030, either a chamber decompression to reach 804.9 hPa [corresponding to 1,900 m asl (23), intervention] or a placebo decompression [cycles of decompression and recompression of ∼50 hPa for the same duration as previously proposed (24), placebo] was performed. Under both conditions, participants were instrumented for respiratory polygraphy and were allowed to sleep from 2230 to 0700. At 0800, after breakfast, the chamber was decompressed to 701.1 hPa [corresponding to 3,000 m asl (23), HA] at a rate of 3 $m \cdot s^{-1}$ (thus in 6 min from 1,900 m and 15 min from 250 m, mimicking an ascent by cable car). Once at HA, the resting measurements were repeated ∼30 min after reaching 3,000 m.

After a 3-wk washout period, according to the crossover design, the same participants returned to the chamber to repeat the experimental chamber sojourn. Those who previously slept at SL (placebo night) returned to sleep at 1,900 m asl (intervention night) and vice versa. All participants were

Table 1. *Participants' characteristics and medical history*

Age, yr	BMI, kg·m^{-2}	Critical Coronary Stenosis	Previous Myocardial Infarction	Revascularization Procedure	Heart Rate Control Medications	Medication Regime	Blood Pressure Control Medications
69	28.6	Yes	No	CABG	Diltiazem	30 mg twice a day	No
54	31.5	Yes	No	Not indicated	Bisoprolol	1.25 mg once daily	No
72	23.1	Yes	No	PCI (single stent)	No		No
72	26.9	Yes	No	PCI (single stent)	No		No
65	25.3	Yes	Yes	PCI (multiple stents)	No		Valsartan; Hydrochlorothiazide
71	28.0	Yes	No	PCI (multiple stents)	Metoprolol	100 mg twice a day	Ramipril
61	32.6	Yes	Yes	PCI (multiple stents)	No		Perindopril; indapamide; amlodipine
47	24.0	No	Yes	Not indicated	Bisoprolol	1.25 mg once daily	No
69	25.9	Yes	No	CABG	Metoprolol	50 mg twice a day	No
62	26.2	Yes	Yes	PCI (multiple stents)	Metoprolol	50 mg twice a day	No

BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

blinded to sleep altitude. Placebo and intervention nights were allocated in a randomized and balanced order so that half the participants started with the placebo and half the participants started with the intervention night.

Resting Measurements

During both chamber sojourns, resting measurements were taken in the morning, 1.5 h after breakfast, both at SL before the overnight stay and at 3,000 m asl (HA) after the overnight stay. First, ultrasound echocardiography (CX50, Philips, The Netherlands) was performed with participants lying in bed in thermoneutral conditions. Right ventricular outflow tract (RVOT) velocity time integral (VTI) was measured using a pulsed wave Doppler signal, and right ventricular stroke volume (RVSV) was estimated as $\pi \times (\text{RVOT radius})^2 \times \text{RVOT VTI}$. Cardiac output (CO) was calculated as the RVSV $\times$ heart rate (HR). Pulmonary artery systolic pressure (PASP) was derived from the maximum velocity of the tricuspid regurgitation jet (TRV_{peak}) (25). The peak systolic pressure gradient of the right ventricle to the right atrium was calculated according to the simplified Bernoulli equation [$4 \times (TRV_{peak})^2$]. PASP was then determined by adding the right atrial pressure, which was estimated by the inferior vena cava diameter and collapse during a sniff inspiration (25). Pulmonary vascular resistance (PVR) was calculated in Wood units as $10 \times TRV_{peak}/(\text{RVOT VTI}) + 0.16$ (26).

After echocardiography and instrumentation, the participants were asked to lie in supine position for 10 min and then to stand up and stay in an upright position for a further 10 min. During this time, arterial blood pressure profile was measured by finger plethysmography (Finapres NOVA, FMS, Amsterdam, The Netherlands), HR was measured by single-lead ECG (Bio Amp, ADInstruments, Dunedin, New Zealand), end-tidal CO_2 partial pressure ($P_{ET_{CO_2}}$) by nasal capnography (Cap10, Medlab, Stutensee, Germany), peripheral hemoglobin saturation for O_2 (Sp_{O_2}) was measured by fingertip probe (ML320/F Oximeter Pod, ADInstriments, Dunedin, New Zealand), and cerebral tissue oxygenation index (cTSI) was measured by near-infrared spectroscopy with an optode placed over the frontal cortex (O3 Regional Oximeter, Masimo, Irvine, CA). All devices were calibrated following the manufacturer's instructions. Data were sampled at 1 kHz (PowerLab 16/35 and LabChart software, ADInstriments, Dunedin, New Zealand), except for cTSI, which was sampled at 0.5 Hz and stored on a personal computer for subsequent analysis. Free of artifacts, steady-state

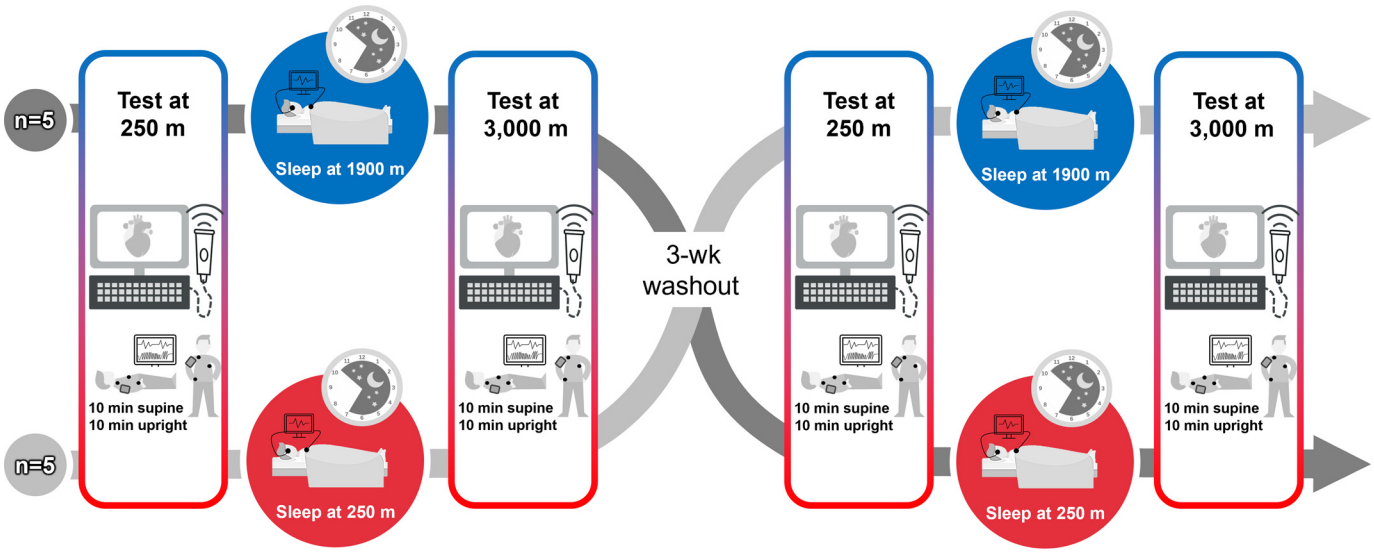

Figure 1. Experimental protocol.

time windows of 5 min length in the last part of the supine and upright resting periods were identified for the analysis. Arterial blood pressure profile, HR, and $P_{ET_{CO_2}}$ profile for respiratory rate were analyzed by means of CVRanalysis 1.0 software (27) to obtain resting baroreflex sensitivity (BRS) and heart rate variability (HRV) with time- and frequency-domain analysis. BRS was calculated by sequence method (28, 29) on relative changes in systolic blood pressure (SBP) and RR intervals. Sequence length was set between 3 and 6 beats, lag between SBP and RR response was set to 0, correlation coefficient of the regression line to validate a sequence was set >0.85, and the threshold values for SBP and R-R interval changes in a sequence were set at 1 mmHg and 1 ms, respectively. BRS was calculated on all retrieved sequences and on sequences characterized by increasing SBP and RR (up-sequences) or by decreasing SBP and RR (down-sequences) separately; since no differences were observed between up- and down-sequences in every investigated condition, only BRS calculated on all sequences is reported in RESULTS. According to guidelines (30), HRV was quantified in the time domain by the root mean square of the successive RR interval differences (RMSSDs), and in the frequency domain by the total power of the RR spectrum (Ptot), spectral power of the very low-frequency (VLF, 0.003–0.04 Hz), low-frequency (LF, 0.04–0.15 Hz), high-frequency (HF, 0.15–0.40 Hz) bands, and the LF/HF ratio. LF and HF were also expressed in normalized units (LFnu and HFnu), which represent their relative value in proportion to Ptot minus VLF (31).

Overnight Respiratory Polygraphy

Whole night respiratory polygraphy was performed with a portable device (Embletta MPR, Natus, Middleton, WI) according to the current American Academy of Sleep Medicine guidelines (32). The recorded channels included *1*) single-lead electrocardiography, *2*) nasal pressure cannula for the measure of airflow, *3*) pulse oximetry (Nonin Medical, Plymouth, MN) for fingertip Sp_{O_2}, *4*) thoracic and abdominal inductance plethysmography for the measure of respiratory efforts, and *5*) and body position.

Nocturnal recordings were analyzed by a blinded, trained physician (C.L.), and only traces comprising at least 4 h of recorded interpretable data were retained. Following current guidelines (32), apnea was defined as a ≥90% reduction in airflow for at least 10 s, associated with the presence of respiratory effort for obstructive apnea or associated with absent respiratory effort during one portion of the event and the presence of inspiratory effort in another portion for mixed apnea. Central apnea was defined as a ≥90% reduction in airflow for at least 10 s with absent inspiratory effort throughout the entire event. Hypopnea was defined as a ≥30% reduction in airflow for at least 10 s associated with a ≥3% fall in oxygen saturation.

The obstructive apnea, central apnea, mixed apnea, and hypopnea indices, the apnea-hypopnea index (AHI, also computed for supine and nonsupine positions) and the oxygen desaturation ≥3% index (ODI; events/h), were computed. Mean Sp_{O_2}, minimum Sp_{O_2}, time spent <90% and <80% of Sp_{O_2}, and median HR were reported. All indices and parameters were calculated in time in bed (TIB, h).

Statistics

Sample size was calculated according to a previous study (33), which found significant increases in Sp_{O_2} (89.6 ± 1.1% to 91.0 ± 1.1%) after an overnight stay at 2,000 m. According to this study, a sample size of $n = 9$ would be adequate to detect increases in resting Sp_{O_2} after the overnight stay with a statistical power of 0.90 and level of significance of $P < 0.05$. Normal distribution of the data was assessed by means of the Shapiro–Wilk test and normal QQ plots. Data are reported as means ± SD, if normally distributed, or median [interquartile range] otherwise. Paired-sample two-tailed *t* tests were used for normally distributed data, and Wilcoxon signed-rank tests otherwise, to investigate *1*) differences between intervention and placebo nights in PSG and subsequent morning HA data (main outcome) and *2*) differences in prenight SL data, both between the preintervention and preplacebo visits (comparability of baselines) and between the chronologically first and second visits (practice effect). Reliability between preintervention and preplacebo SL visits was also computed via Cronbach's alpha (34) and typical error (35) on normally distributed data. Cardiovascular data were analyzed separately for supine and upright position, whereas Sp_{O_2}, $P_{ET_{CO_2}}$, and cTSI data were averaged on the entire resting period. Absolute changes from SL to HA within the same session (ΔHA − SL) were also computed. Due to possible differences in sensor positioning between sessions, cTSI was evaluated only as ΔHA − SL (ΔcTSI). Statistical significance was set at $P < 0.05$. The software R 4.4.1 was used.

RESULTS

No statistical differences were identified at SL neither before the placebo and before the intervention nights (Table 2) except for supine diastolic blood pressure (DBP) (before placebo 78 ± 11 mmHg, before intervention 82 ± 10 mmHg, $P = 0.0294$) nor between the first and the second SL session ($P \geq 0.0665$). At SL, the between-visit reliability analysis showed a good to excellent internal consistency of normally distributed data: Cronbach's alpha was 0.90 for supine SBP, 0.89 for upright SBP, 0.93 for supine DBP, 0.93 for upright DBP, 0.94 for supine MBP, 0.94 for upright MBP, 0.98 for supine HR, 0.96 for upright HR, 0.91 for PASP, 0.98 for PVR, 0.97 for RVSV, 0.83 for CO, 0.88 for Sp_{O_2}, and 0.94 for $P_{ET_{CO_2}}$.

Nocturnal respiratory data are reported in Table 3. During the intervention night, AHI, ODI, and time at $Sp_{O_2} < 90\%$ were higher, and mean Sp_{O_2} was lower compared with the placebo night.

Resting data obtained at HA after the placebo and the intervention nights as well as their delta changes from SL are reported in Table 2 and in Figs. 2 and 3. No differences were found between placebo and intervention regarding blood pressure, HR, BRS, or HRV indices (Table 2). Regarding respiratory parameters (Fig. 2), at HA, Sp_{O_2} was higher after the intervention night (88 ± 2%) than after the placebo night (87 ± 2%, $P = 0.0279$). Moreover, at HA, $P_{ET_{CO_2}}$ was lower after the intervention night (34 ± 3 mmHg) than after the placebo night (36 ± 3 mmHg, $P = 0.0022$) with an average decrease from corresponding SL values of −1.5 ± 1.4 mmHg after the placebo night and −2.7 ± 1.6 mmHg after the intervention night.

Table 2. *Cardiovascular data obtained before (SL, at 250 m asl) and after (HA, at 3,000 m asl) the placebo (250 m asl) or the intervention (1,900 m asl) night*

	Night	Supine	Upright
SBP, mmHg			
SL before	Placebo	135 ± 10	145 ± 14
	Intervention	135 ± 11	145 ± 16
HA after	Placebo	131 ± 11	138 ± 14
	Intervention	132 ± 13	136 ± 9
ΔHA − SL	Placebo	−4 ± 7	−7 ± 16
	Intervention	−4 ± 12	−9 ± 13
DBP, mmHg			
SL before	Placebo	78 ± 11	90 ± 14
	Intervention	82 ± 10*	94 ± 15
HA after	Placebo	78 ± 8	85 ± 12
	Intervention	81 ± 6	89 ± 8
ΔHA − SL	Placebo	−0 ± 5	−5 ± 14
	Intervention	−2 ± 8	−5 ± 11
MBP, mmHg			
SL before	Placebo	101 ± 10	112 ± 14
	Intervention	104 ± 9	114 ± 16
HA after	Placebo	100 ± 9	105 ± 12
	Intervention	101 ± 7	107 ± 7
ΔHA − SL	Placebo	−1 ± 5	−7 ± 14
	Intervention	−2 ± 9	−7 ± 12
HR, beats/min			
SL before	Placebo	54 ± 9	60 ± 9
	Intervention	55 ± 9	62 ± 11
HA after	Placebo	58 ± 10	65 ± 10
	Intervention	61 ± 12	68 ± 14
ΔHA − SL	Placebo	4 ± 3	5 ± 5
	Intervention	6 ± 4	6 ± 4
BRS, ms·mmHg^{-1}			
SL before	Placebo	8.2 [6.8, 10.5]	6.1 [4.6, 7.5]
	Intervention	7.7 [6.5, 9.4]	4.8 [3.9, 6.3]
HA after	Placebo	6.2 [4.8, 8.8]	4.9 [3.2, 8.0]
	Intervention	6.1 [5.4, 8.2]	5.0 [3.2, 7.9]
ΔHA − SL	Placebo	−1.8 [−4.4, 0.8]	−1.8 [−2.1, 0.4]
	Intervention	−1.6 [−2.5, 0.1]	0.5 [−0.6, 1.6]
RMSSD, ms			
SL before	Placebo	33 [26, 64]	23 [20, 34]
	Intervention	35 [25, 47]	23 [19, 29]
HA after	Placebo	32 [23, 45]	18 [13, 23]
	Intervention	29 [24, 35]	17 [14, 23]
ΔHA − SL	Placebo	−3 [−16, 8]	−5 [−14, −1]
	Intervention	−8 [−10, 2]	−5 [−8, −4]
Ptot, ms^2			
SL before	Placebo	2,799 [1,372; 3,447]	1,431 [1,008; 2,286]
	Intervention	1,363 [1,179; 2,727]	1,490 [856, 2,164]
HA after	Placebo	1,732 [999, 3,090]	1,109 [821, 1,843]
	Intervention	2,147 [1,090; 2,828]	1,238 [754, 1,900]
ΔHA − SL	Placebo	92 [−1,127, 1,709]	−249 [−891, 9]
	Intervention	−4 [−309, 1,062]	−500 [−802, −80]
VLF, ms^2			
SL before	Placebo	746 [613, 1,120]	708 [517, 994]
	Intervention	719 [551, 1,056]	733 [549, 1,119]
HA after	Placebo	997 [621, 1,732]	610 [465, 929]
	Intervention	904 [490, 1,198]	626 [323, 953]
ΔHA − SL	Placebo	440 [−344, 1,179]	−170 [−275, 347]
	Intervention	131 [−766, 577]	−304 [−592, −92]
LF, ms^2			
SL before	Placebo	1,391 [192, 1,553]	277 [148, 1,258]
	Intervention	481 [345, 989]	444 [229, 766]
HA after	Placebo	437 [324, 834]	385 [199, 801]
	Intervention	638 [350, 1,160]	561 [256, 714]
ΔHA − SL	Placebo	85 [−958, 166]	59 [−7, 153]
	Intervention	−14 [−77, 251]	−66 [−119, 43]
HF, ms^2			
SL before	Placebo	238 [152, 711]	110 [90, 306]
	Intervention	289 [165, 572]	126 [85, 239]
HA after	Placebo	197 [109, 402]	87 [40, 212]
	Intervention	191 [103, 254]	89 [57, 133]
ΔHA − SL	Placebo	−41 [−199, 222]	−34 [−103, 2]
	Intervention	−59 [−168, 59]	−39 [−118, −19]
LF, nu			
SL before	Placebo	60.7 [53.8, 72.3]	60.4 [49.0, 66.9]
	Intervention	59.7 [55.7, 61.3]	68.5 [64.0, 70.8]
HA after	Placebo	61.9 [54.0, 67.4]	74.4 [71.7, 79.7]
	Intervention	60.4 [53.8, 69.1]	77.0 [72.4, 78.6]
ΔHA − SL	Placebo	−8.9 [−10.9, 5.8]	17.6 [4.8, 25.1]
	Intervention	5.0 [1.2, 12.6]	7.3 [−1.2, 15.2]
HF, nu			
SL before	Placebo	30.0 [18.9, 37.1]	25.2 [21.1, 30.8]
	Intervention	34.4 [31.2, 37.5]	19.6 [17.6, 25.2]
HA after	Placebo	28.5 [19.3, 32.1]	15.6 [13.4, 20.7]
	Intervention	23.7 [13.4, 33.1]	13.7 [10.5, 19.0]
ΔHA − SL	Placebo	4.8 [−5.0, 8.8]	−4.4 [−14.9, −0.3]
	Intervention	−8.5 [−15.2, 1.9]	−6.3 [−12.2, 1.0]
LF/HF			
SL before	Placebo	2.1 [1.3, 3.7]	2.3 [1.6, 3.5]
	Intervention	1.7 [1.5, 2.0]	3.5 [2.5, 4.2]
HA after	Placebo	2.1 [1.7, 3.5]	4.9 [3.4, 6.4]
	Intervention	2.7 [1.7, 5.5]	5.9 [4.1, 6.9]
ΔHA − SL	Placebo	−0.6 [−1.8, 0.7]	2.4 [0.1, 3.7]
	Intervention	0.5 [0.2, 1.5]	2.3 [−0.3, 3.6]

Absolute changes from SL to HA (ΔHA − SL) are also provided. For systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR) data are reported as means ± SD and $n = 10$; other data are reported as median [interquartile range] and $n = 8$. asl, above sea level; BRS, baroreflex sensitivity; HA, high altitude; HF, absolute (ms^2) and relative (nu) power of the high-frequency band (0.15–0.4 Hz); LF, absolute (ms^2) and relative (nu) power of the low-frequency band (0.04–0.15 Hz); Ptot, total absolute power; RMSSD, root mean square of successive RR interval differences; SL, sea level; VLF, absolute power of the very-low-frequency band (0.003–0.04 Hz). *$P < 0.05$ vs. corresponding placebo session (paired t test).

Finally, ΔcTSI was smaller after the intervention night (−3.6 ± 2.2%) than after the placebo night (−6.5 ± 3.1%, $P = 0.0192$).

PASP was higher after the intervention night (30 ± 8 mmHg) than after the placebo night (28 ± 7 mmHg, $P = 0.0413$), and PVR was higher after the intervention night (1.59 ± 0.26 Wood units) than after the placebo night (1.51 ± 0.23 Wood units, $P = 0.0137$) (Fig. 3). Measured RVSV was 81 ± 14 mL after the intervention night and 82 ± 14 mL after the placebo night ($P = 0.3785$). Measured CO was not significantly different between the two conditions (4.8 ± 0.9 L·min^{-1} after the intervention night vs. 4.6 ± 0.8 L·min^{-1} after the placebo night, $P = 0.1773$).

DISCUSSION

In this study, we showed that sleeping at MA (1,900 m asl) induced sleep-disordered breathing in males with CAD and that one night at MA was sufficient to trigger a measurable, though relatively modest, ventilatory acclimatization upon acute exposure to HA (3,000 m asl) in this population. In particular, Sp_{O_2} and ΔcTSI were higher, and $P_{ET_{CO_2}}$ was lower at 3,000 m asl after the intervention compared with the placebo night. In addition, although sleeping at MA increased the occurrence of apneas and hypopneas, this was not associated with significant changes in HRV and BRS at HA. Finally, the night spent at 1,900 m induced a higher PASP and PVR at 3,000 m compared with a night near SL.

Nocturnal Breathing at MA

The intervention night at MA was associated with a higher frequency of apneas and hypopneas, a lower mean Sp_{O_2}, and a

Table 3. *Nocturnal respiratory data (median [interquartile range]) during the placebo (250 m asl) and the intervention (1,900 m asl) night*

	Placebo Night 250 m asl		Intervention Night 1,900 m asl		Wilcoxon *P* Value
AHI, h^{-1}	5.8	[2.7, 13.4]	32.6	[8.8, 51.4]	0.0216
AHI supine, h^{-1}	12.7	[6.6, 22.7]	44.8	[29.4, 60.0]	0.0188
AHI nonsupine, h^{-1}	1.6	[0.4, 3.2]	13.4	[4.7, 20.4]	0.0093
Apnea index, h^{-1}	1.6	[0.1, 7.0]	6.7	[0.3, 50.3]	0.1564
Obstructive apnea index, h^{-1}	0.1	[0.0, 6.0]	0	[0, 0]	0.1193
Central apnea index, h^{-1}	0.1	[0.0, 1.2]	6.6	[0.3, 50.3]	0.0825
Mixed apnea index, h^{-1}	0	[0, 0]	0	[0, 0]	0.5403
Hypopnea index, h^{-1}	3.1	[2.7, 7.6]	3.9	[2.1, 17.0]	0.5361
Mean Sp_{O_2}, %	93	[93, 94]	87	[87, 88]	0.0002
Minimum Sp_{O_2}, %	86	[83, 87]	78	[76, 80]	0.0149
ODI, h^{-1}	9.8	[4.1, 15.4]	39.7	[13.1, 62.9]	0.0078
Time at Sp_{O_2} < 90%, %	2.4	[0.6, 4.4]	86.8	[77.6, 91.8]	0.0020
Time at Sp_{O_2} < 80%, %	0	[0, 0]	0.1	[0.0, 0.6]	0.0869
Median HR, beats/min	56	[50, 60]	59	[58, 62]	0.2161

AHI, apnea-hypopnea index; asl, above sea level; HA, high altitude; HR, heart rate; ODI, oxygen desaturation index; SL, sea level; Sp_{O_2}, peripheral oxygen saturation.

longer time spent at Sp_{O_2} < 90% (see Table 3) than during the placebo night. Similar results were obtained in healthy individuals acutely exposed to 2,035 m asl (20) and it is known that there is a dose-response effect of altitude on ventilation (36, 37). Regarding the obstructive apnea index, no effect of MA was observed. The only person diagnosed with obstructive sleep apnea showed a lower obstructive apnea index at MA ($0.0 \cdot h^{-1}$) than at SL ($6.0 \cdot h^{-1}$), supporting the idea that HA might switch obstructive to central sleep apneas due to an increase in respiratory rate and upper airway tone, as previously shown (38). Regarding the central apnea index, although statistical significance was not reached, 6 out of 10 participants exhibited a higher apnea index and none presented a lower index during the intervention than during the placebo night. This is in agreement with previous literature on healthy individuals and on patients with chronic obstructive pulmonary disease or obstructive sleep apnea syndrome (39).

Although chronic intermittent hypoxia due to sleep apnea is usually regarded as detrimental, because it increases daytime arterial blood pressure and sympathetic activity (40), our results showed that a single night spent at 1,900 m asl did not significantly increase blood pressure and HR nor did it alter BRS and HRV indices at 3,000 m asl with respect to a placebo night (see Table 2). However, we could speculate that intermittent hypoxia during the night might have had a role in ventilatory acclimatization as outlined in the next section.

Effects of MA Sleeping on Cardiorespiratory Responses to Acute Passive HA Exposure

MA exposure is known to stimulate ventilatory acclimatization (19); however, a measurable effect of MA on ventilation is usually observed in healthy persons and with a MA exposure of several days above 2,200 m asl (41, 42). In the present investigation, we showed that even a single night spent at 1,900 m asl dampened the HA fall in central and peripheral oxygenation, as witnessed by a higher Sp_{O_2} and ΔcTSI after the intervention night (see Fig. 2) than after the placebo night. Nonetheless, the differences at 3,000 m were quite small, in particular the +1% for Sp_{O_2} (1.3 times the typical error measured at SL). Such a small, yet significant, change might be due to the fact that at 3,000 m, the hemoglobin saturation curve is still relatively flat compared with studies conducted at higher altitudes (41), thus we expect greater the changes the higher the altitude. Future studies are needed to confirm this hypothesis.

The overnight hypoxia at 1,900 m, enhanced by the greater number of sleep apneas and hypopneas, might lead to partial ventilatory acclimatization (43). The putative mechanisms underlying this response are several; intermittent hypoxia and

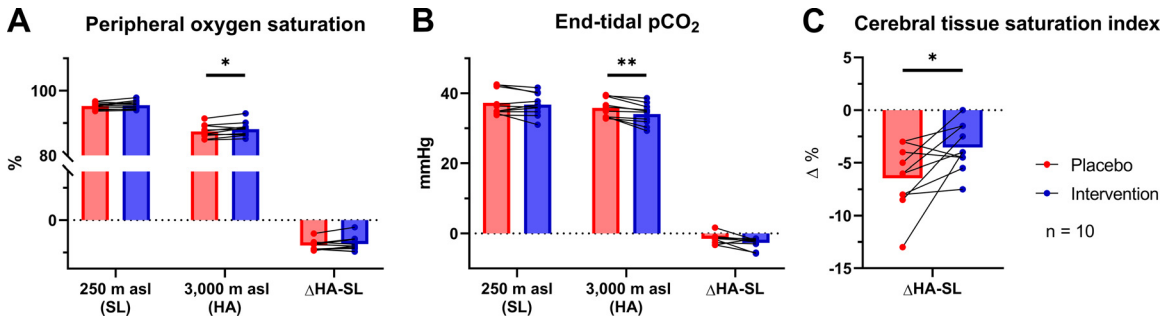

Figure 2. Resting peripheral oxygen saturation (*A*), end-tidal partial pressure of CO_2 (*B*), and delta cerebral tissue oxygen saturation index (*C*) recorded before (at 250 m asl, SL) and after (at 3,000 m asl, HA) the placebo (red data) or the intervention (blue data) night. *A* and *B* also report absolute changes from SL to HA (ΔHA − SL). Statistically significant differences between placebo and intervention are indicated *$P < 0.05$; **$P < 0.01$. asl, above sea level; HA, high altitude; SL, sea level.

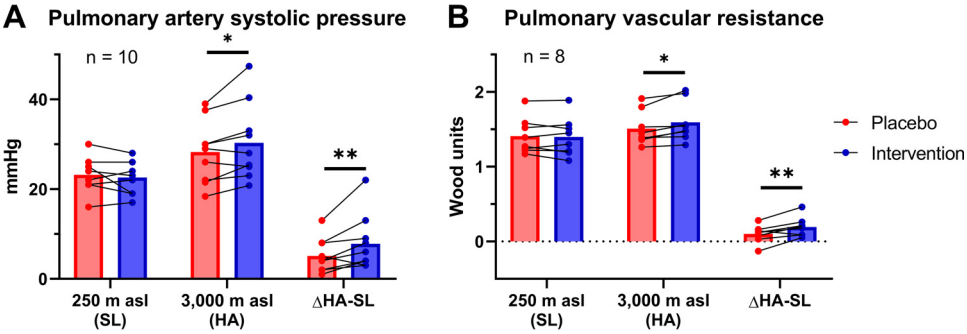

Figure 3. Resting pulmonary artery systolic pressure (*A*) and pulmonary vascular resistance (*B*) recorded before (at 250 m asl, SL) and after (at 3,000 m asl, HA) the placebo (red data) or the intervention (blue data) night. Absolute changes from SL to HA (ΔHA − SL) are also reported. Statistically significant differences between placebo and intervention are indicated $*P < 0.05$; $**P < 0.01$. asl, above sea level; HA, high altitude; SL, sea level.

sleep apnea have been shown to downregulate circulating soluble erythropoietin receptors (44), increase reactive oxygen species generation within the carotid body (45), decrease nitric oxide production (46), and modulate expression of hypoxia-inducible factor subtypes (47), all ultimately heading to an increase in peripheral chemoreflex sensitivity (48). With respect to the placebo night, the greater nocturnal desaturation observed at 1,900 m was followed by a 2 mmHg lower average $P_{ET_{CO_2}}$ at 3,000 m (corresponding to 1.5 times the typical error measured at SL). Notably, some degree of desaturation was recorded during the night at 250 m, a response consistent with previous studies in patients with CAD (49) and predictable, given the characteristics of the participants (50), which may have dampened the difference between intervention and placebo at 3,000 m. Although the effects of a single night at 1,900 m on ventilatory acclimatization might appear small, their clinical impact should be further investigated. In fact, persons with CAD are at higher risk of maladaptive responses to HA (15) and of SCD during the first hours of exposure to HA (17), possibly due to an unfavorable combination of hypoxia and an incomplete ventilatory acclimatization. In this context, even partial ventilatory acclimatization before HA arrival may infer protection against SCD.

Previous studies on healthy males involving longer acclimatization sojourns (7 days at 2,200 m) and higher tested altitude (4,300 m) showed that the improvement in Sp_{O_2} (+3%) was coupled to a dampened increase of HR, CO, and PASP compared with direct ascent (41). Contrarily to these observations, our results showed similar HR and CO after placebo and intervention night (see Table 2). We speculate that this might be due to the small effect observed on Sp_{O_2}, but we cannot rule out any role played by the cardioactive medications that some of our participants were taking at the time of the study. Further studies are needed to better clarify the interplay between MA ventilatory acclimatization and beta blockers on the HR and CO response at HA. Regarding PASP, we found that it was higher at HA after a night spent at MA than after the placebo night (see Fig. 3), showing an average difference of +2 mmHg (2.0 times the typical error measured at SL). A similar result was observed for PVR, which was 0.08 Wood units higher after the intervention than after placebo (1.9 times the typical error measured at SL). These results are not of straightforward interpretation as they contrast with the literature on healthy participants at higher altitudes (41) and with the observation that hyperventilation dampens the hypoxic pulmonary vasoconstriction (51, 52). However, it is also known that 8 h of sustained hypoxia increase the pulmonary vascular reactivity to a subsequent hypoxic reexposure (53), a phenomenon that could have happened during the night spent at MA and therefore overridden the effect of the small improvement in oxygenation on PVR. Moreover, it is known that hypoxic pulmonary vasoconstriction is enhanced by beta blockers' administration in young healthy participants (54) and is exaggerated in older men (~55 yr old) compared with younger (~20 yr old), when exposed to the same hypoxic stimulus (55); two observations that might limit the interpretation of the pathophysiological responses of our participants. Of note, no differences in PASP or PVR responses were observed between participants taking beta blockers and those who do not (data not shown), although this comparison is limited by the small sample size. Nonetheless, we are confident that our findings set the basis for future investigations concerning the PASP response to MA and HA and its clinical interpretation in this population.

Methodological Considerations

This study investigated the effects of a single night spent at MA before HA exposure, which can be easily performed where accommodation facilities are abundant, as in Europe. Although the choice was ecologically driven, we opted for the use of a hypobaric chamber. This experimental setting allowed us to perform a safer exposure and blinded intervention, as well as to avoid confounders, such as weather conditions, distance to be covered, and type of route to reach MA, variability factors that typically affect field studies. Our choice is strengthened by the high between-visit reliability of our measurements. Moreover, as PASP measurement in acute hypoxia is extremely time sensitive (56, 57), we meticulously matched its measurement timing in the two conditions. Despite these strengths, this study has some limitations, the main being the small number of participants. This was partly due to the application of several exclusion criteria to limit the impact of confounding factors. For instance, the age-range criterion limited the possibility of recruiting female participants, who typically develop CAD at older ages or in association with comorbidities that constituted exclusion criteria, such as heavy smoking or morbid obesity. Thus, caution should be exercised when extrapolating these results to females or older persons with CAD. Other possible limitations include the heterogeneous clinical histories and medications of the participants, as well as the absence of an age-matched healthy control group. Nonetheless, thanks to careful control of possible confounding factors owing to the crossover design, subject blinding, and the use of a tightly controlled environmental chamber, the present results should represent a solid base for further investigations.

Conclusions

A single night at moderate altitude (1,900 m asl) is sufficient to trigger measurable ventilatory acclimatization upon subsequent exposure to high altitude (3,000 m asl) in males with coronary artery disease. Although the occurrence of sleep-disordered breathing was higher during the moderate altitude night, this did not further affect heart rate variability and baroreflex sensitivity at high altitude compared with direct ascent from sea level. However, markers of hypoxic pulmonary vasoconstriction at high altitude were higher after a night's sleep at moderate altitude compared with direct ascent from sea level. Further studies are required to better elucidate the safety of such a staged altitude exposure model, in particular, the effects on the pulmonary vasculature.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

H.G. conceived and designed research; A.T., M.M., J.R., R.T., G.V., and H.G. performed experiments; A.T., C.L., G.V., and H.G. analyzed data; A.T., C.L., M.M., J.R., R.T., G.B., G.P., G.S., G.V., and H.G. interpreted results of experiments; A.T., R.T., and G.V. prepared figures; A.T., G.V., and H.G. drafted manuscript; A.T., C.L., M.M., J.R., R.T., G.B., G.P., G.S., G.V., and H.G. edited and revised manuscript; A.T., C.L., M.M., J.R., R.T., G.B., G.P., G.S., G.V., and H.G. approved final version of manuscript.

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