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# Effects of nocturnal periodic breathing on sympathetic nerve activity and ventilatory control at high altitude: a randomised, crossover study

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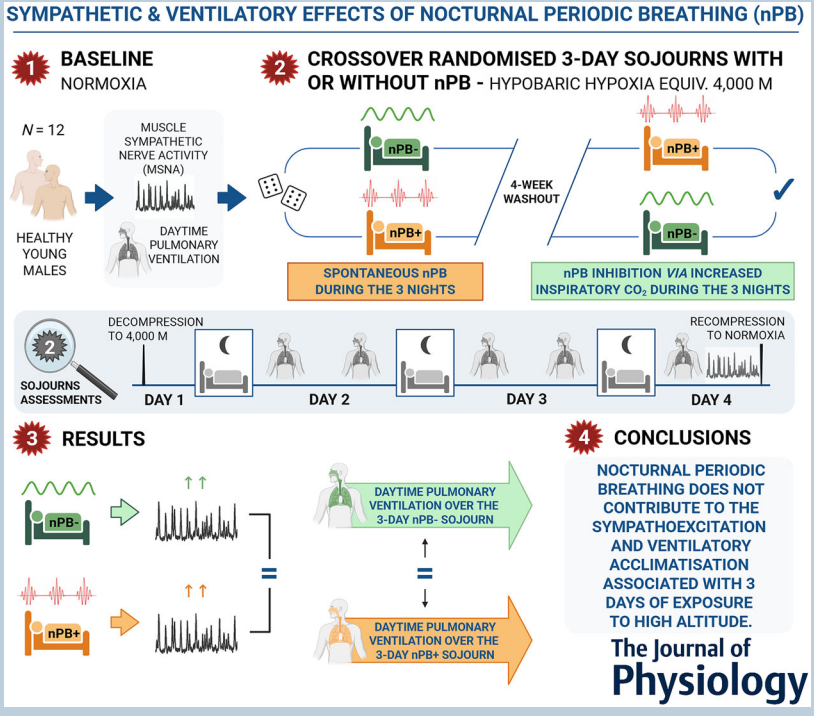


**Abstract figure legend** Schematic overview of the randomised crossover study investigating the effects of nocturnal periodic breathing (nPB) on sympathetic activity and ventilatory acclimatisation in hypobaric hypoxia equivalent to 4000 m altitude. Participants completed two 3-day sojourns where nPB was inhibited by increasing inspiratory $CO_2$ fraction during the nights of one (nPB−), but not the other sojourn (nPB+). The hypoxia-induced increases in sympathetic activity and ventilation were not different between the two sojourns, suggesting that nPB does not contribute to the sympathoexcitation and ventilatory acclimatisation associated with 3 days of exposure to high altitude.



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**Abstract** During acute exposure to the hypoxia of high altitude, activation of the peripheral chemoreflex increases sympathetic nerve activity (SNA) and pulmonary ventilation. If exposure extends over several days, SNA and ventilation further increase and we investigated whether nocturnal periodic breathing (nPB) – a form of sleep-disordered breathing that is common at high altitude – contributes to these further increases. In a randomised, placebo-controlled, cross-over protocol, twelve healthy men completed two 3-day sojourns in hypobaric hypoxia equivalent to 4000 m altitude. nPB was inhibited by increasing inspiratory $CO_2$ fraction during the nights of one (nPB−), but not the other sojourn (nPB+). Ventilation and plasma catecholamines were measured daily, while muscle SNA (MSNA) was assessed before and at the end of sojourns, without and with peripheral chemoreflex inhibition (transient hyperoxia). The hypoxia-induced increases in MSNA burst frequency (nPB−, +104%; nPB+, +94%; $P = 0.789$) and incidence (nPB−, +47%; nPB+, +50%; $P = 0.791$) were not different between sojourns. Catecholamine concentrations throughout the sojourns were also similar (sojourn: $P \geq 0.271$, time × sojourn: $P \geq 0.495$). Ventilatory variables were not different between sojourns (sojourn: all $P \geq 0.090$, time×sojourn: all $P \geq 0.062$) except for a slightly greater tidal volume throughout nPB+ (sojourn: $P = 0.047$, time × sojourn: $PP = 0.482$). Chemoreflex inhibition induced similar reductions in ventilation during both sojourns (all $P \geq 0.151$) and larger reductions in MSNA burst frequency (nPB−: $-7.3 \pm 2.7$ bursts min$^{-1}$, nPB+: $-4.4 \pm 5.1$ bursts min$^{-1}$, $P = 0.037$) and incidence after the nPB− ($-0.9 \pm 5.7$ bursts (100 heart beats (HB))$^{-1}$) than after the nPB+ sojourn ($+2.4 \pm 7.3$ bursts (100 HB)$^{-1}$, $P = 0.046$). We thus conclude that nPB does not contribute to the sympathoexcitation and hyperventilation associated with 3 days of exposure to high altitude.

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## Key points

- Prolonged exposure to high altitude leads to progressive increases in sympathetic nerve activity and pulmonary ventilation.
- Nocturnal periodic breathing (nPB), a form of sleep-disordered breathing that is common at high altitude, may contribute to these progressive increases in sympathetic nerve activity and ventilation.
- In this randomised, placebo-controlled, crossover study, twelve healthy men completed two 3-day sojourns in hypobaric hypoxia where nPB was either inhibited or not.
- The hypoxia-induced increases in sympathetic nerve activity and ventilation were not different between the two sojourns.
- We conclude that nPB does not contribute to the sympathoexcitation and hyperventilation associated with 3 days of exposure to high altitude.

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## Introduction

During acute high altitude exposure, sympathetic nerve activity (SNA) and pulmonary ventilation increase in response to the decreased arterial oxygen tension ($P_{aO_2}$) (Saito et al., 1988). As the exposure extends, SNA and ventilation increase further despite partial restoration of $P_{aO_2}$ and it is unclear what drives these further increases (Hansen & Sander, 2003; Lundby et al., 2018; Schoene, 1997; Simpson et al., 2021). One candidate is nocturnal periodic breathing (nPB), which is common during sleep at high altitude (Ainslie et al., 2013; Kryger et al., 2021; Patrician et al., 2024) and consists of repeated central apnoea alternating with bursts of hyperventilation leading to oscillations in arterial oxygen saturation ($S_{aO_2}$) (Berssenbrugge et al., 1983; Burgess et al., 2004; Douglas & Haldane, 1909). If similar $S_{aO_2}$ oscillations are provoked at sea level by exposure to intermittent hypoxia (IH), they induce persistent sympathoexcitation (Narkiewicz et al., 1999; Tamisier et al., 2011), an increased hypoxic ventilatory response (Lusina et al., 2006; Pialoux et al., 2009; Tamisier et al., 2009), and reductions in end-tidal $CO_2$ partial pressure ($P_{ETCO_2}$) indicative of an increased ventilation (Pialoux et al., 2009; Tamisier et al., 2009). Accordingly, the main aim of this study was to investigate whether nPB increases SNA and ventilation at high altitude. In a randomised, placebo-controlled, cross-over design, 12 healthy lowlanders completed two 3-day sojourns in hypobaric hypoxia (HH). During one sojourn, nPB was inhibited (nPB− sojourn) by an increased inspiratory $CO_2$ fraction ($F_{ICO_2}$), whereas during the other sojourn nPB was not inhibited (nPB+ sojourn). We hypothesised that the nPB+ sojourn would facilitate more pronounced increases in SNA and ventilation than the nPB-sojourn.

This study also had secondary aims: The increases in SNA and hypoxic ventilatory response that IH induces at sea level are attributed to changes in peripheral chemoreflex function (Narkiewicz et al., 1999; Tamisier et al., 2011). Specifically, animal studies (Peng et al., 2003) and indirect evidence in humans (Tamisier et al., 2009; Vermeulen et al., 2020) support the hypothesis that IH facilitates sensitisation of the chemoreflex, along with a tonic activation that is referred to as sensory long-term facilitation. If nPB-induced $S_{aO_2}$ oscillations at high altitude have the same effects, they should evoke an increase in chemoreflex activity that persists during wakefulness. Our second aim was thus to test the hypothesis that chemoreflex inhibition would facilitate more pronounced decreases in SNA and ventilation during the nPB+ than the nPB− sojourn.

Finally, the high altitude-induced increases in SNA and ventilation persist for several days after return to sea level (Dempsey et al., 1979, 2014; Hansen & Sander, 2003), presumably reflecting persistent activation of the peripheral chemoreflex (Dempsey et al., 2014). nPB at high altitude could contribute to this persistent activation through sensory long-term facilitation. Our third aim was thus to test the hypothesis that SNA and ventilation after return to sea level pressure would be higher after the nPB+ than after the nPB−sojourn.

## Methods

### Ethical approval

This study was approved by the Ethics Committee of the Bolzano Hospital, Italy (No 76–2021) and conducted in accordance with the *Declaration of Helsinki*, except for registration in a database. All recruited participants provided written informed consent to participate in the study. Note that an evaluation of our approach to inhibit nPB has already been published (Ibrahim et al., 2024) and that, for the reader's convenience, some of these results are repeated in the following Methods section (wherever this is the case, reference to the original article is made). Nevertheless, the results pertaining to the hypotheses of the current article have not been published.

Thirty-nine healthy, non-smoking, lowlanders (9 women) without history of high altitude illness were recruited. A specific inclusion criterion was susceptibility to hypoxia-induced nPB, which was evaluated during a screening night in HH. Throughout that night, respiration was monitored by polygraphy (Alice PDx, Philips Respironics, Amsterdam, The Netherlands) and analysed with a high altitude-specific scoring system (Tan et al., 2020). Susceptibility to hypoxia-induced nPB was defined as an apnoea-hypopnoea index (AHI) $\geq$30 events $h^{-1}$. Seventeen volunteers, including all women, did not surpass this AHI threshold and 9 participants withdrew consent after the screening night, leaving 13 male participants (27.6 $\pm$ 4.4 years, 1.8 $\pm$ 0.1 m, 71.3 $\pm$ 6.1 kg) who enrolled in the main study.

### Hypobaric hypoxia

All HH exposures included in our protocol took place in a hypobaric chamber (terraXcube, Eurac Research, Italy), where the barometric pressure was 462.3 mmHg, corresponding to an altitude of $\sim$ 4000 m. The temperature was 22°C during the day and reduced to 18–20°C at night. The relative humidity was 30%.

### Protocol

The study protocol is illustrated in Fig. 1. Four weeks after the screening night, baseline measurements were performed, where muscle SNA (MSNA) and cardio-respiratory variables were measured in normoxia (NX),

first before and then during peripheral chemoreflex inhibition. Participants then spent a familiarisation night in HH while instrumented for nPB inhibition (see below) and polysomnography.

After another 4 weeks, participants completed the nPB− and nPB+ sojourns in randomised order and with a 4-week washout between the onsets of the sojourns. Apart from the nPB inhibition, the sojourns had identical protocols: On the morning of the first day, participants entered the hypobaric chamber and underwent decompression corresponding to an ascent rate of 2 m $s^{-1}$. Throughout the sojourns, they were free to work or engage in recreational activities but did not perform any exercise and were in bed and equipped for nPB inhibition from 23.00 to 07.00 h. They were provided three meals per day and had *ad libitum* access to snacks and water. For breakfast, they were allowed one cup of tea or coffee, except on the last day, where MSNA was measured.

Venous blood was collected for analysis of circulating catecholamines in the morning before chamber entry and on every morning of the sojourns. Cardiorespiratory variables were recorded on the mornings of days 2, 3 and 4, as well as in the afternoons of days 2 and 3. On the last morning of the sojourns, MSNA and cardiorespiratory variables were recorded before and then during peripheral chemoreflex inhibition, and again 10 min after rapid recompression to NX.

**nPB inhibition and respiratory monitoring.** As indicated, a detailed description of the method for participant-blinded nPB inhibition via increased $F_{ICO_2}$ has been published (Ibrahim et al., 2024). Briefly, an air-tight canopy was placed over the participants' head to retain exhaled $CO_2$. The $CO_2$ fraction within the canopy, and thus in the participants' inspirate ($F_{ICO_2}$), was continuously measured and controlled by manual adjustment of fresh air inflow. Throughout the nights of the nPB-sojourn, an operator monitored participants' respiration and attempted to find and maintain the lowest $F_{ICO_2}$ that prevented nPB (median [25–75% IQR]: 1.76% [1.07–2.44], individual values ranging from 0.17% to 3.1%), whereas during the nPB+ sojourn $F_{ICO_2}$ was $\leq$ 0.2%.

Polysomnography (Morpheus, Micromed, Mogliano Veneto, Treviso, Italy) was used during the 1st and 3rd night, and polygraphy during the 2nd night, to monitor participants' respiration. The respiratory events were scored by a blinded, board-certified operator following both the recommendations of the American Academy of Sleep Medicine (Berry et al., 2020) and a high altitude-specific scoring system (Tan et al., 2020). For both scorings, reductions in breathing amplitude $\geq$30%, of a duration $\geq$10 s, with arterial $O_2$ desaturation $\geq$3% and/or associated arousal were scored as hypopnea, and reductions in breathing amplitude $\geq$90% of a duration $\geq$10 s were scored as apnoea (Berry et al., 2020). For the high altitude-specific scoring, reductions in breathing amplitude $\geq$ 50% of a duration $\geq$5 s were also scored as hypopnoea/apnoea if they occurred as part of a periodic breathing pattern with at least three consecutive cycles (Tan et al., 2020).

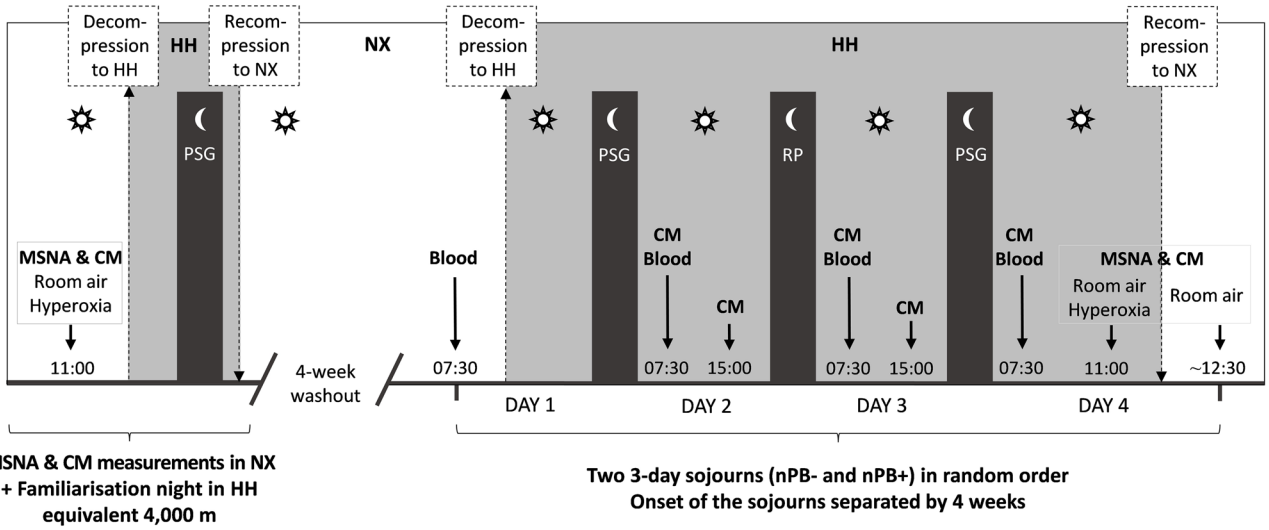


**Figure 1. Overview of the study measurements**
NX, normoxia; HH, hypobaric hypoxia equivalent to 4000 m altitude; nPB−, sojourn where nPB was inhibited by increased inspiratory $CO_2$; nPB+, sojourn where nPB was not inhibited; MSNA, muscle sympathetic nerve activity; CM, measurement of cardiorespiratory variables; hyperoxia, MSNA and CM measurements during peripheral chemoreflex inhibition by pure $O_2$ breathing, blood; measurement of plasma catecholamines; PSG, polysomnography; RP, respiratory polygraphy. White area indicates time in NX, grey shaded areas indicate time in HH equivalent 4000 m, dark areas indicate nighttime.

**Table 1. Main respiratory parameters during the nights of the nPB− and nPB+ sojourns**

| | | nPB− sojourn | | | nPB+ sojourn | | |
|---|---|---|---|---|---|---|---|
| | | Night 1 | Night 2[a] | Night 3 | Night 1 | Night 2[a] | Night 3 |
| AHI, ev $h^{-1}$ | AASM | 14.4 [9.9–20.3] | 8.9 [6.9–15.5] | 15.0 [7.2–16.1] | 68.3 [53.2–116.9] | 30.0 [22.2–42.9] | 49.4 [31.1–64.2] |
| | High Altitude | 17.8 [13.5–23.7] | 31.8 [26.4–36.4] | 16.3 [10.2–18.8] | 81.9 [54.2–122.7] | 63.6 [51.6–78.5] | 56.5 [36.5–84.9] |
| ODI 3%, ev $h^{-1}$ | | 14.9 [9.5–19.1] | 9.8 [7.4–18.6] | 12.4 [8.1–16.8] | 77.7 [59.0–108.2] | 35.2 [25.9–53.7] | 49.1 [34.4–78.5] |
| Mean $S_{pO_2}$, % | | 77.8 [76.0–80.9] | 79.0 [76.8–81.8] | 81.2 [80.3-82.8] | 76.0 [74.5-79.5] | 79.0 [75.0-79.5] | 79.4 [75.5-81.4] |
| Mean $P_{ETCO_2}$, mmHg | | 31.4 [30.3–34.5] | 31.0 [28.7–34.1] | 29.9 [28.9–32.1] | 29.9 [28.2–31.7] | 28.7 [27.5–29.6] | 28.5 [27.6–29.2] |

Values are median [25%–75% IQR]. AHI, apnoea-hypopnoea index; AASM, American Academy of Sleep Medicine; ODI 3%, oxygen desaturation ≥ 3% index; $S_{pO_2}$, Peripheral $O_2$ saturation; $P_{ETCO_2}$, end-tidal $CO_2$ partial pressure.
[a]Respiratory parameters for night 2 were acquired by respiratory polygraphy and therefore calculated over time in bed. Those for nights 1 and 3 were acquired by polysomnography and therefore calculated over total sleep time. Part of the data displayed is reproduced from Ibrahim et al. (2024).

As reported (Ibrahim et al., 2024), the increased $F_{ICO_2}$ during nPB− induced a marked and highly significant reduction in nPB and the most important respiratory parameters are repeated in Table 1. All information regarding sleep architecture, nocturnal ventilation and statistical analysis can be found in Ibrahim et al (2024).

## Cardiorespiratory variables

Cardiorespiratory variables were always measured over a duration of 5 min (except during chemoreflex inhibition, see below) and following at least 5 min of supine rest. Tidal volume ($V_T$) and breathing frequency ($f_B$) were measured by spirometry (ADInstruments, Sydney, Australia), and $P_{ETCO_2}$ by a capnograph (CAP10 Medlab GmbH, Stutensee bei Karlsruhe, Germany). Minute ventilation ($\dot{V}_E$) was computed as $V_T \times f_B$. Heart rate (HR) was measured using a lead II electrocardiogram (Bio Amp, ADInstruments), continuous arterial blood pressure by finger photoplethysmography (NOVA, Finapres Medical System, Enschede, The Netherlands), and peripheral oxygen saturation ($S_{pO_2}$) by pulse oximetry (MLT321 $S_pO_2$ Finger Clip Transducer, ML320 Oximeter Pod, ADInstruments). Systolic (SBP) and diastolic blood pressures (DBP) and mean arterial pressure (MAP) were obtained from the arterial pressure waveform. Cardiorespiratory variables were sampled at a rate of 10 kHz (Powerlab 16/35 and LabChart Pro software, ADInstruments).

## MSNA

MSNA was recorded in the peroneal nerve by microneurography (Neuro AMP EX amplifier, ADInstruments), always by the same operator (CS) and following recent guidelines (Macefield, 2021). Recordings always took place at 11.00 h, after at least 3 h of fasting, and participants refrained from exercise, caffeine, and alcohol throughout the 24 h preceding the measurements. They were placed semi-recumbent with the leg stabilised by a vacuum pillow. A sterile microelectrode (FHC, Bowdoin, ME, USA) was inserted percutaneously near the fibular head and advanced into a fascicle of the peroneal nerve innervating a muscle of the lower leg, using intraneural electrical stimulation for guidance (Stimulus Isolator, ADInstruments). A reference microelectrode was inserted nearby into the subcutaneous tissue. Correct needle placement was confirmed by observing increased activity during an end-expiratory breath-hold or Valsalva manoeuvre, with no responses to unexpected loud noises or skin stroking. Once the needles were in position, 10 min were provided for signal stabilisation before data acquisition. MSNA measurements were always performed over a duration of 5 min, except during chemoreflex inhibition (see below), with a sampling rate of 10 kHz (Powerlab 16/35 and LabChart Pro software, ADInstruments). The raw signal was amplified, filtered (300 Hz low pass, 50 Hz notch), rectified and integrated to obtain a mean MSNA voltage. MSNA bursts were identified by an experienced, blinded researcher not involved in data collection (JPF) using the Spike 2 scoring script (Cambridge Electronic Design, Cambridge, UK). Acceptable recordings exhibited a pulse-synchronous bursting pattern and had a signal-to-noise ratio greater than 3:1 (Hart et al., 2017; Macefield, 2013). MSNA was always expressed as burst frequency (bursts $min^{-1}$) and incidence (bursts $(100\ HB)^{-1}$).

## Peripheral chemoreflex inhibition

To inhibit the peripheral chemoreflex and thus quantify the tonic levels of SNA and respiratory drive elicited by the peripheral chemoreflex, five 1-min exposures to 100% inspiratory $O_2$ were provided, each separated by 3 min of room air breathing (Prasad et al., 2020). MSNA, HR

and respiratory pre-hyperoxia values were determined as the average of the 30 s preceding each hyperoxic bout, averaged over the 5 bouts. Variables during chemoreflex inhibition were derived as follows: For $V_T$, $f_B$ and $\dot{V}_E$, individual single-breath nadirs were identified during the last 45 s of the hyperoxic bouts (thus providing 15 s for the chemoreceptors to be silenced). For MSNA and HR, the respective nadir 15-s averages were determined from the 15–30, 30–45 and 45–60 s intervals of the hyperoxic bouts. For all variables, the nadir values derived from all five hyperoxic bouts were then averaged (Prasad et al., 2020).

### Catecholamines

Six millilitres of blood was collected into a lithium heparinised Vacutainer from an antecubital vein using a 21-gauge butterfly needle at 07.30 h, always under fasting condition and following >15 min of supine rest. Plasma was immediately separated by centrifugation, and then frozen at −80°C. Plasma adrenaline and noradrenaline concentrations were subsequently measured by blinded investigators using ultra-high-pressure liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) (van Faassen et al., 2020) with slight modifications (Rodriguez et al., 2022). During the nPB-sojourn, one adrenaline value was below the detection threshold (0.01 nM) and thus estimated as half that threshold.

### Statistical analyses

Cardiorespiratory variables measured throughout the sojourns, and plasma catecholamines concentrations collected immediately before and throughout the sojourns, were compared between sojourns by mixed model for repeated measurements (MMRM) with fixed factors of order of sojourns (nPB− → nPB+ *vs.* nPB+ → nPB−), sojourn (nPB− *vs.* nPB+), and measurement time points, and with random effect of participant. MSNA values are expressed as changes (Δ) from baseline measurements in NX to end of sojourns. Δ MSNA, as well as MSNA and cardiorespiratory values measured during peripheral chemoreflex inhibition (expressed as pre-hyperoxia, hyperoxia nadir and as Δ from pre-hyperoxia to nadir) and following recompression were compared between sojourns by mixed models with fixed factors of order of sojourns and sojourn and with random effect of participant. For data collected during peripheral chemoreflex inhibition, values from baseline NX measurements were entered as co-factors. Data distribution was assessed by visual inspection. We did not impute missing values, as MMRM analysis controls type I error and minimises bias. For ΔMSNA and data collected during peripheral chemoreflex inhibition and following recompression, effect sizes were computed using Cohen's *d*. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and data are presented as mean ± standard deviation unless otherwise stated. *P* values < 0.05 were considered statistically significant.

## Results

One participant withdrew from the study for personal reasons after completing the nPB− sojourn only. His data were included in the statistical analyses and written results, whereas in the figures they are presented as individual data points but not included in average values.

### Cardiorespiratory variables

Cardiorespiratory variables measured during wakefulness are illustrated in Figs 2 and 3. For logistical reasons, cardiorespiratory variables could not be assessed in two participants in the afternoon of Day 2 of the nPB− sojourn, and in one participant in the afternoon of Day 3 of the nPB+ sojourn. $f_B$, $V_T$ and $\dot{V}_E$ did not change (time: all $P \geq 0.143$, Fig. 2*A*–*C*) over the course of the sojourns, while $P_{ETCO_2}$ and $S_{pO_2}$ decreased and increased, respectively (time: both $P \leq 0.003$, Fig. 2*D* and *E*). $V_T$ was slightly higher throughout the nPB+ than the nBP− sojourn (sojourn: $P = 0.047$) but no time × sojourn interaction was found ($P = 0.482$). Conversely, $f_B$, $\dot{V}_E$, $P_{ETCO_2}$ and $S_{pO_2}$ were not different between the sojourns (sojourn: all $P \geq 0.090$, time × sojourn: all $P \geq 0.062$).

HR changed over the course of the sojourns (time: $P = 0.034$, Fig. 3*A*), whereas MAP, SBP and DBP remained unchanged (time: all $P \geq 0.229$, Fig. 3*B*–*D*). However, there were no differences in any of these variables between the sojourns (sojourn: all $P \geq 0.502$, time × sojourn: all $P \geq 0.647$). We found order effects for SBP and HR, which were both larger during the first sojourn (both $P \leq 0.029$). No order effects were observed for the remaining cardiorespiratory variables (all $P \geq 0.066$).

### Sympathetic nerve activity

**Muscle sympathetic nerve activity.** At the end of the nPB− and nPB+ sojourns, MSNA burst frequency was 104% [19–192] and 94% [49–174], and burst incidence 47% [−5–95] and 50% [18–101] higher than in NX, respectively. These hypoxia-induced increases in burst frequency and incidence were not different between the sojourns ($P \geq 0.789$, $d \leq 0.068$ for both, Fig. 4). Unexpectedly low MSNA values were recorded in one participant after the nPB− sojourn, and in another one after the nPB+ sojourn, potentially as a consequence of a poor signal quality during acquisition. These two data

points are shown in brackets in Fig. 4. It should be noted that excluding these two data points from the analysis does not alter the outcome ($P \geq 0.322$, $d \leq 0.176$ for both). No effect of sojourn order was detected ($P \geq 0.186$).

**Catecholamines.** Throughout both sojourns, circulating noradrenaline increased progressively from the values measured in NX (time: $P < 0.001$, Fig. 5*A*), while adrenaline did not change (time: $P = 0.485$, Fig. 5*B*). However, no differences for either noradrenaline (sojourn: $P = 0.271$, time × sojourn: $P = 0.731$) or adrenaline (sojourn: $P = 0.461$, time × sojourn: $P = 0.495$) were observed between the sojourns and no order effect was detected ($P \geq 0.382$). Note that the increase in noradrenaline persists when adjusted for plasma volume contraction (data not shown).

## Peripheral chemoreflex inhibition

The effect of peripheral chemoreflex inhibition by hyperoxia on MSNA, HR and respiratory variables is presented in Table 2. The hyperoxia-induced changes in burst

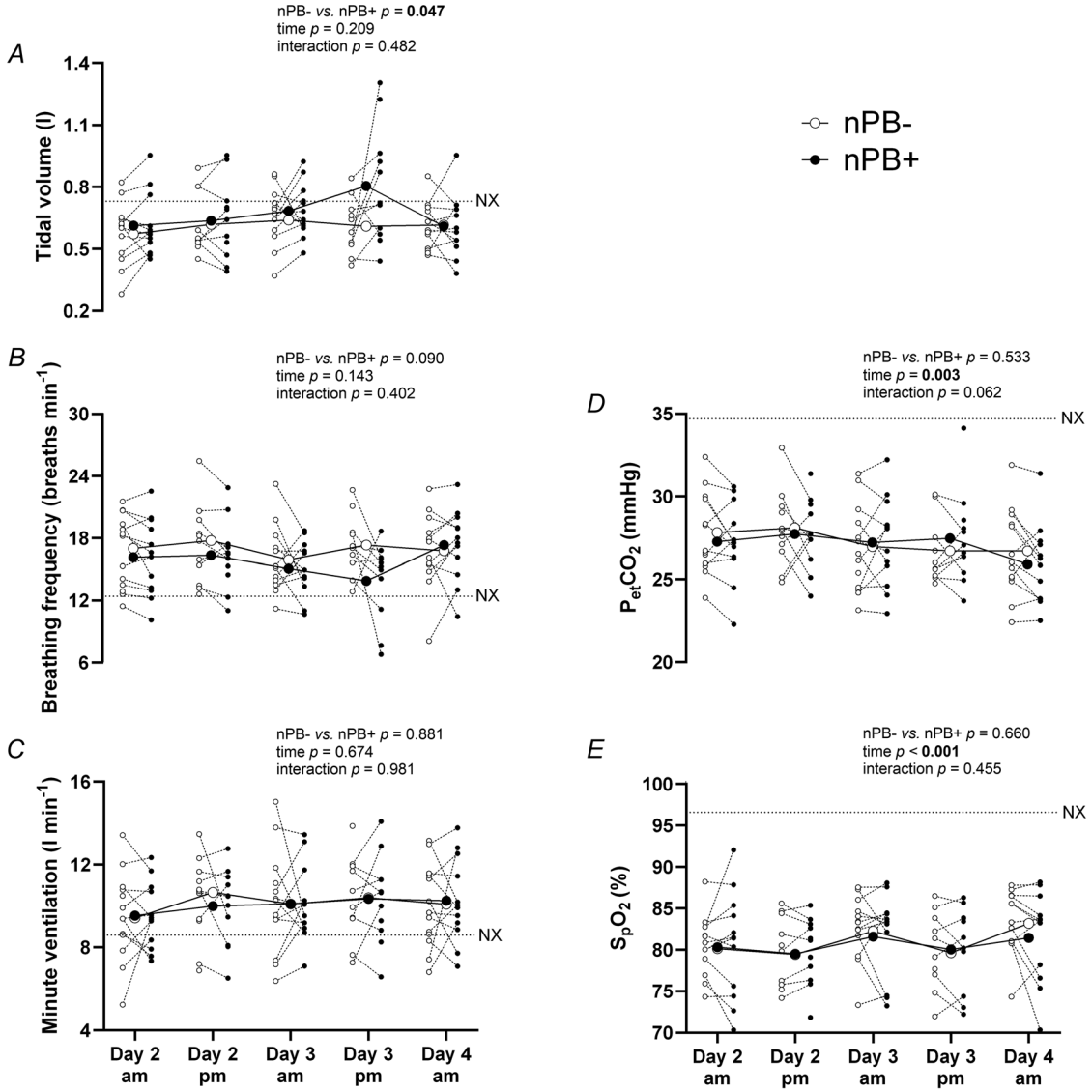


**Figure 2. Respiratory variables throughout the sojourns**
*A*, tidal volume; *B*, breathing frequency; *C*, minute ventilation; *D*, $P_{ETCO_2}$; *E*, $S_{pO_2}$. $P_{ETCO_2}$, end-tidal $CO_2$ partial pressure; $S_{pO_2}$, peripheral oxygen saturation. Large circles represent means and small circles individual values. As values measured in normoxia (NX) were collected 4 and 8 weeks prior to the sojourns, they were not included in the statistical analysis and are provided as average values (dotted lines) for visual reference only. $n$ = 13; 3 values (2 for nPB−, 1 for nPB+) are missing on Day 2 pm and Day 3 pm. Mixed models for repeated measurements were used for statistical analysis.

frequency ($P = 0.037$, $d = 0.711$), and burst incidence ($P = 0.046$, $d = 0.504$) were greater during the nPB− than the nPB+ sojourn. None of the hyperoxia-induced changes in respiratory variables differed between the nPB− and nPB+ sojourn (all $P \geq 0.151$, all $d \leq 0.353$). Hyperoxia-induced reductions in HR were not different between the sojourns ($P = 0.950$, $d = 0.000$), but an order effect indicated that the effect of hyperoxia on HR was greater during the first than the second sojourn ($P = 0.008$). No other order effects were detected (all $P \geq 0.050$).

### Recompression to normoxia

Following recompression to NX, none of the assessed variables differed between the nPB− and nPB+ sojourns (all $P \geq 0.085$, all $d \leq 0.835$, Table 3). An order effect was found where $P_{ETCO_2}$ was greater following recompression after the second sojourn ($P = 0.035$). No other order effect was detected (all $P \geq 0.088$).

## Discussion

We investigated whether nPB contributes to the increases in SNA and ventilation resulting from a 3-day exposure to HH. We further assessed whether nPB increases peripheral chemoreflex activity in HH and whether nPB explains the persistent elevation in SNA and ventilation following return to NX. In contrast to our hypotheses, we observed no differences in SNA and ventilation between the sojourns, whereas peripheral chemoreflex inhibition even elicited a slightly larger reduction in MSNA after the nPB− than after the nPB+ sojourn. Moreover, MSNA and ventilation following recompression to NX did not differ between the sojourns. These findings do not support the hypothesis that nPB contributes to the progressive sympathoexcitation, increase in ventilation and changes in peripheral chemoreflex function that occur in lowlanders acclimatising to high altitude.

### Effects of nPB on SNA and ventilation at high altitude

Acute hypoxia increases SNA (Guyenet, 2000) and ventilation (Dempsey et al., 2014) and both of these responses become more pronounced as the exposure extends (Fisher et al., 2018; Hansen & Sander, 2003; Lundby et al., 2018). In the present study, the 3-day sojourns in HH corresponding to 4000 m altitude increased MSNA burst frequency by ∼100%. That this increase was smaller than the 300% increase observed in men exposed for 10 days to a similar altitude (Lundby et al., 2018) presumably reflects that hypoxia-induced sympathoexcitation is a slow process that requires >3 days to fully develop (Hansen & Sander, 2003). The slow nature of hypoxia-induced sympathoexcitation is also illustrated in the current study by the increase in noradrenaline over

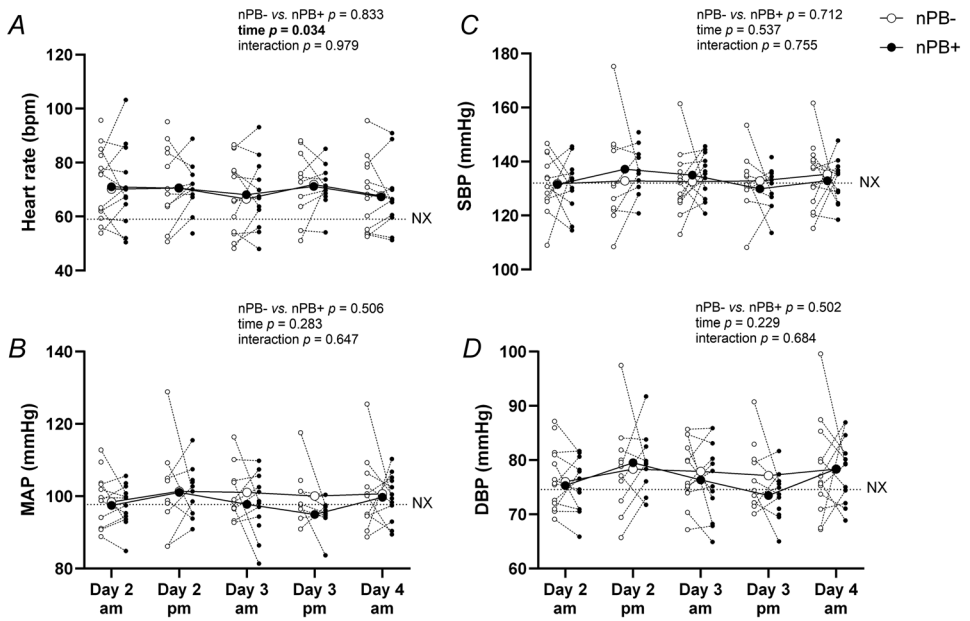


**Figure 3. Cardiovascular variables throughout the sojourns**
*A*, heart rate; *B*, MAP; *C*, SBP; *D*, DBP. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Large circles represent means and small circles individual values. As values measured in normoxia (NX) were collected 4 and 8 weeks prior to the sojourns, they were not included in the statistical analysis and are provided as average values (dotted lines) for visual reference only. $n$ = 13; 3 values (2 for nPB−, 1 for nPB+) are missing on Day 2 pm and Day 3 pm. Mixed models for repeated measurements were used for statistical analysis.

**Table 2. Muscle sympathetic nerve activity, heart rate and respiratory responses to peripheral chemoreflex inhibition by transient hyperoxia**

| | | | | nPB− *vs.* nPB+ | |
|---|---|---|---|---|---|
| | Normoxia | nPB− sojourn | nPB+ sojourn | *P* value | Cohen's *d* |
| MSNA, bursts min$^{-1}$ | | | | | |
| Pre-hyperoxia | 20.1 ± 10.3 | 31.1 ± 11.5 | 31.6 ± 11.8 | 0.844 | 0.043 |
| Hyperoxia nadir | 14.7 ± 9.5 | 23.7 ± 10.9 | 27.2 ± 12.6 | 0.219 | 0.297 |
| Δ | −5.4 ± 3.0 | −7.3 ± 2.7 | −4.4 ± 5.1 | 0.037 | 0.711 |
| MSNA, bursts (100 HB)$^{-1}$ | | | | | |
| Pre-hyperoxia | 28.2 ± 15.0 | 33.3 ± 11.3 | 34.8 ± 9.9 | 0.611 | 0.141 |
| Hyperoxia nadir | 25.4 ± 16.1 | 32.4 ± 12.9 | 37.1 ± 13.7 | 0.225 | 0.353 |
| Δ | −2.8 ± 4.8 | −0.9 ± 5.7 | 2.4 ± 7.3 | 0.046 | 0.504 |
| Heart rate, beats min$^{-1}$ | | | | | |
| Pre-hyperoxia | 58.7 ± 9.0 | 78.6 ± 12.0 | 78.2 ± 10.6 | 0.840 | 0.035 |
| Hyperoxia nadir | 55.2 ± 8.0 | 70.1 ± 12.9 | 69.7 ± 11.8 | 0.846 | 0.032 |
| Δ | −3.4 ± 1.7 | −8.5 ± 3.4 | −8.5 ± 3.9 | 0.950 | 0.000 |
| Tidal volume, l | | | | | |
| Pre-hyperoxia | 0.77 ± 0.27 | 0.69 ± 0.13 | 0.70 ± 0.22 | 0.783 | 0.055 |
| Hyperoxia nadir | 0.68 ± 0.27 | 0.53 ± 0.14 | 0.54 ± 0.23 | 0.790 | 0.053 |
| Δ | −0.09 ± 0.06 | −0.16 ± 0.10 | −0.15 ± 0.11 | 0.948 | 0.095 |
| Breathing frequency, breaths min$^{-1}$ | | | | | |
| Pre-hyperoxia | 14.0 ± 4.6 | 18.3 ± 4.1 | 18.9 ± 4.7 | 0.549 | 0.136 |
| Hyperoxia nadir | 10.9 ± 4.1 | 11.7 ± 2.8 | 12.7 ± 3.6 | 0.151 | 0.310 |
| Δ | −3.0 ± 1.8 | −6.6 ± 3.3 | −6.2 ± 1.5 | 0.723 | 0.156 |
| Minute ventilation, l min$^{-1}$ | | | | | |
| Pre-hyperoxia | 10.0 ± 3.2 | 12.0 ± 1.9 | 12.2 ± 1.8 | 0.790 | 0.108 |
| Hyperoxia nadir | 7.7 ± 2.7 | 6.6 ± 1.0 | 7.0 ± 1.7 | 0.233 | 0.287 |
| Δ | −2.2 ± 1.1 | −5.4 ± 1.9 | −5.2 ± 1.6 | 0.695 | 0.114 |

Values are means ± standard deviation. MSNA, muscle sympathetic nerve activity; Pre-hyperoxia, average of the last 30 s preceding each hyperoxic bout, averaged over the 5 bouts; Nadir for $V_T$, $f_B$ and $V'_E$, individual single-breath nadirs identified over the last 45 s of each hyperoxic bout; Nadir for MSNA and HR, individual lowest 15 s average from the 15–30, 30–45 and 45-60 s intervals of each hyperoxic bout. Nadirs are averaged over the 5 bouts; Δ, change from pre-hyperoxia to nadir; $n$ = 12; Mixed models for comparison between the nPB− and nPB+ sojourn, accounting for values from initial normoxia measurements as co-factors. Effect sizes were computed using Cohen's *d*.

the course of the sojourns. That no significant increase in ventilation was found is probably attributable to the fact that measurements at sea level were not included in the analysis and that none were performed during the first 24 h of exposure, where the largest portion of ventilatory acclimatisation occurs (Forster et al., 1975). However, the gradual decrease in $P_{ETCO_2}$ throughout the sojourns indicates ongoing ventilatory acclimatisation.

What underlies the progressive increases in SNA and ventilation at high altitude is incompletely understood, but a role of nPB has repeatedly been proposed (Dempsey et al., 2014; Simpson et al., 2024). nPB can occur at altitudes as low as 1500–2000 m (Bloch et al., 2015; Latshang, Lo Cascio, et al., 2013) and, at least in men, is almost universal above 4000 m (Ainslie et al., 2013; Bloch et al., 2010). At sea level, sleep-disordered breathing leading to IH and experimental IH both elicit persistent sympathoexcitation (Maier et al., 2022; Tamisier et al., 2011) and an increased hypoxic ventilatory response (Narkiewicz et al., 1999; Pialoux et al., 2009; Tamisier et al., 2009). Since nPB leads to oscillations in $S_{aO_2}$ resembling those associated with IH, it appeared intuitive that nPB would also have similar stimulatory effects on SNA and ventilation. In contrast to our hypotheses, however, the markedly higher nPB during the nPB+ sojourn did not lead to a more pronounced increase in either SNA or ventilation. It could be speculated that 3 nights of nPB were not sufficient to elicit detectable effects on SNA and ventilation. Nevertheless, at sea level, persistent increases in SNA and ventilation already occur after IH lasting ≤1 h (Keough et al., 2021; Limberg et al., 2022). Even if only short-lived, such effects would have been detected in our study since we measured catecholamines and ventilation every morning just 30 min after waking up. It is also

**Table 3. Muscle sympathetic nerve activity and cardiorespiratory variables after recompression to normoxia**

| | | | | Post nPB− *vs.* Post nPB+ | |
|---|---|---|---|---|---|
| | Normoxia | Post nPB−sojourn | Post nPB+ sojourn | *P* value | Cohen's *d* |
| MSNA, bursts $min^{-1}$ | 18.6 ± 9.8 | 28.5 ± 13.4 | 32.7 ± 13.5 | 0.085 | 0.312 |
| MSNA, bursts $(100\ HB)^{-1}$ | 31.6 ± 15.8 | 38.9 ± 13.2 | 44.0 ± 13.8 | 0.098 | 0.378 |
| Heart rate, bpm | 59.0 ± 9.2 | 73.2 ± 13.9 | 73.1 ± 12.3 | 0.934 | 0.008 |
| Mean arterial pressure, mmHg | 97.7 ± 7.5 | 100.3 ± 5.3 | 105.3 ± 6.6 | 0.083 | 0.835 |
| Minute ventilation, l $min^{-1}$ | 8.6 ± 3.1 | 9.5 ± 2.5 | 9.2 ± 2.2 | 0.441 | 0.127 |
| Tidal volume, l | 0.73 ± 0.22 | 0.64 ± 0.14 | 0.61 ± 0.20 | 0.352 | 0.174 |
| Breathing frequency, breaths $min^{-1}$ | 12.4 ± 4.5 | 15.4 ± 4.7 | 16.0 ± 4.5 | 0.330 | 0.130 |
| Peripheral $O_2$ saturation, % | 96.7 ± 1.2 | 96.5 ± 0.9 | 96.4 ± 0.9 | 0.764 | 0.111 |
| End tidal $CO_2$, mmHg | 34.7 ± 4.0 | 27.7 ± 3.0 | 27.2 ± 2.6 | 0.531 | 0.178 |

Values are means ± standard deviation. MSNA, muscle sympathetic nerve activity. Normoxia values are given for reference without statistical comparison; $n$ = 12; Mixed models for comparison between the post nPB− and post nPB+ sojourns were used for statistical analysis. Effect sizes were computed using Cohen's *d*.

unlikely that nPB during the nPB+ sojourn was too mild to increase SNA and ventilation since IH at sea level provokes such effects with fewer $O_2$ desaturations per hour than those elicited by nPB during the nPB+ sojourn (Foster et al., 2009; Pialoux et al., 2009; Tamisier et al., 2009, 2011). A likely explanation seems that the powerful sympathoexcitatory and hyperventilatory responses to the continuous HH of the sojourns overruled any additional effects of nPB. As discussed in the next paragraph, the continuous hypoxia could have even prevented nPB from increasing SNA and ventilation by counteracting the effects of $S_{aO_2}$ oscillation on the peripheral chemoreflex.

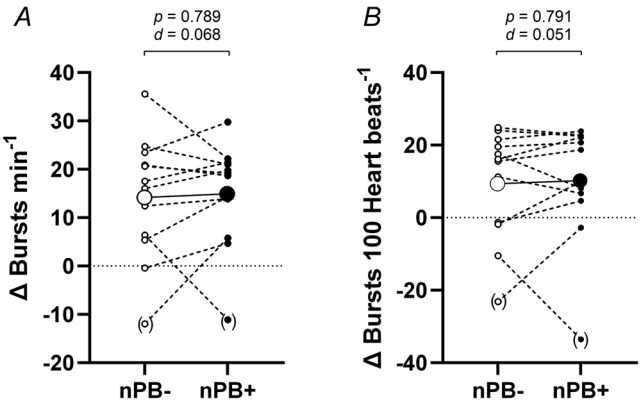


**Figure 4. Changes in muscle sympathetic nerve activity from normoxia to the last day of the sojourns**
Changes (Δ) in burst frequency (*A*) and burst incidence (*B*) from normoxia to the last day of the nPB− and nPB+ sojourns. Large circles represent means and small circles individual values. Circles in bracket represent values that are likely underestimated; $n$ = 12; Mixed models for comparison between the nPB− and nPB+ sojourn were used for statistical analysis, and effect sizes were computed using Cohen's *d*.

## Effects of nPB on the peripheral chemoreflex at high altitude

As at sea level IH induces sensitisation and sensory long-term facilitation of the peripheral chemoreflex (Narkiewicz et al., 1999; Tamisier et al., 2011), we expected nPB to increase tonic chemoreflex activity during wakefulness in HH. Nevertheless, peripheral chemoreflex inhibition resulted in a slightly larger MSNA reduction after the nPB− than after the nPB+ sojourn, and the ventilatory response was similar between the sojourns, arguing against a stimulatory effect of nPB on chemoreflex activity. That peripheral chemoreflex inhibition did not fully return MSNA to NX values is in line with earlier studies using hyperoxia (Hansen & Sander, 2003) or dopamine infusion (Fisher et al., 2018) to inhibit the peripheral chemoreflex at high altitude. Persistent sympathoexcitation during peripheral chemoreflex inhibition presumably reflects that other mechanisms such as increased pulmonary artery pressure (Moore et al., 2022; Simpson et al., 2020) and hypovolaemia increase SNA during extended high altitude exposure (Hansen & Sander, 2003; Simpson et al., 2024).

At sea level, the effects of IH on peripheral chemoreflex function have been attributed to an increase in reactive oxygen species (ROS) in carotid bodies secondary to upregulation of the prooxidant hypoxia-inducible factor 1$\alpha$ (HIF-1$\alpha$) and concomitant suppression of the anti-

oxidant HIF-2$\alpha$ (Prabhakar et al., 2012). In contrast, continuous hypoxia seems to promote accumulation of both HIF-1$\alpha$ and HIF-2$\alpha$ in carotid bodies (Jaśkiewicz et al., 2022) and the antioxidant effect of the increased HIF-2$\alpha$ may have prevented carotid body ROS production in response to nPB. Moreover, ROS production in the carotid bodies primarily occurs in the response to the rapid reoxygenation phase of IH (Lavie, 2015). During nPB in hypoxia, full reoxygenation does not occur, which could further attenuate ROS production in the carotid bodies.

### Effects of nPB on SNA and ventilation after return to sea level

After return from high altitude, SNA and ventilation transiently remain elevated (Dempsey et al., 1979; Hansen & Sander, 2003) and we speculated that nPB− induced sensory long-term facilitation of the peripheral chemoreflex contributes to these effects. This is, however, not supported by our results since also following recompression to NX, MSNA and ventilation were similar between sojourns. The absence of any differences between sojourns aligns with our other findings supporting the hypothesis that nPB does not contribute to the changes in chemoreflex function, SNA and ventilation that occur during early acclimatisation to high altitude.

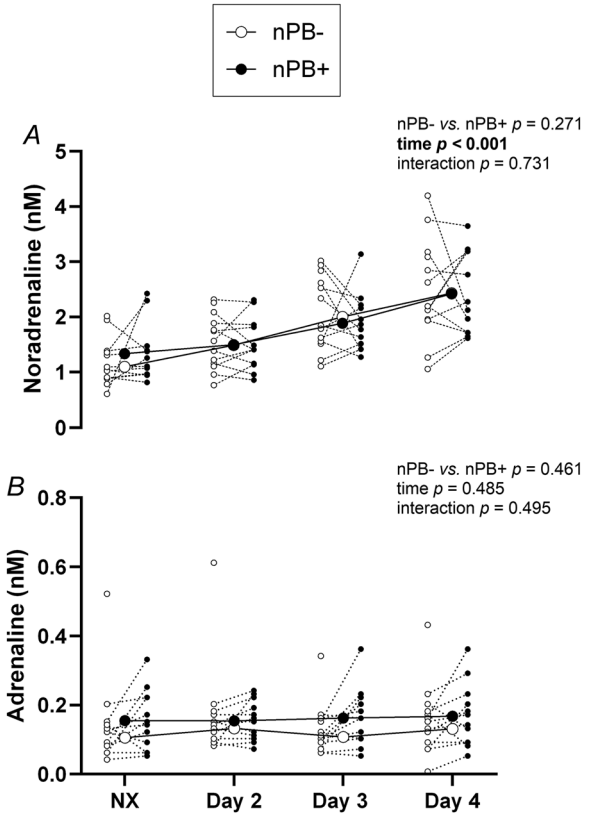


**Figure 5. Catecholamines throughout the sojourns**
*A*, noradrenaline; *B*, adrenaline. The first time point was measured in normoxia (NX) just before the onset of the sojourns. Large circles represent means and small circles individual values; $n$ = 13; Mixed models for repeated measurements were used for statistical analysis.

### Methodological considerations

We selected a 3-day study duration based on evidence that most of ventilatory acclimatisation (Dempsey et al., 1979) and sympathoexcitation (Mazzeo & Reeves, 2003) occur within this period, alongside a significant increase in arterial $O_2$ tension (Forster et al., 1975) and full recovery of arterial $O_2$ content (Schlittler et al., 2021), thus reducing the hypoxic stimulus and pointing towards an alternative mechanism increasing ventilation and SNA. We also expected the 4-week washout period between the two sojourns to be sufficient for complete deacclimatisation, as $P_{aCO_2}$ reductions associated with a 3–5 day sojourn at 4300 m resolve within 24 h after return to sea level (Dempsey et al., 1979). In addition, it appeared appropriate to measure and report baseline ventilation at the same time point as the peripheral chemoreflex inhibition measurements, which were conducted during the MSNA recordings. The complexity of the methodology also made a longer study duration unfeasible, and whether a longer high-altitude acclimatisation would have unmasked an effect of nPB on the assessed parameters warrants further investigation.

We inhibited nPB by increasing $F_{ICO_2}$ since this approach can be temporally restricted to the night and allows for participant blinding. We furthermore expected the method to not disturb sleep, which was confirmed by a high sleep efficiency during both sojourns (Ibrahim et al., 2024). The increased $F_{ICO_2}$ did also not decrease $S_{pO_2}$ during sleep (see Table 1), which is important since such an $S_{pO_2}$ reduction could have increased chemoreflex activation and thus masked an opposing effect of the nPB prevention. As expected, the increased $F_{ICO_2}$ enhanced $P_{ETCO_2}$ during the nights of the nPB− sojourn, which might have increased SNA and/or ventilation during wakefulness. Nevertheless, we consider this unlikely since the increase in $P_{ETCO_2}$ was small (∼1.5 mmHg, see Table 1) and restricted to nighttime. Moreover, while higher than during the nPB+ sojourn, nocturnal $P_{ETCO_2}$ during the nPB− sojourn was still well below normocapnic values and no correlation was found between $P_{ETCO_2}$ during the final night of the nPB− sojourn and the changes in MSNA burst frequency during the corresponding sojourn ($r = 0.41$, $P = 0.216$). A further consideration is whether periodic breathing occurred also during wakefulness, where it was not inhibited. Such 'awake periodic breathing' has previously been observed, albeit at considerably higher altitude (Latshang, Turk, et al., 2013). Since we did not assess the presence of awake periodic breathing, we

cannot exclude it as a potential confounding factor during the nPB− sojourn.

While sympathoexcitation and increases in ventilation can persist for days after return from high altitude (Dempsey et al., 1979, 2014; Hansen & Sander, 2003), we performed post-sojourn measurements only 10 min after recompression to sea level to limit the number of microneurographic procedures by taking advantage of the microelectrodes already in place from the post-sojourn measurement. The possibility that differences in post-recompression MSNA and ventilation between the nBP− and nBP+ sojourns would have been found at a later time point can thus not be excluded.

Although not statistically significant, small-to-moderate and large effect sizes of nPB on post-recompression MSNA and blood pressure, respectively, were observed. Further studies are warranted to clarify whether a significant impact of nPB on these variables was overlooked due to the limited sample size.

Our study included only male participants since none of the female volunteers surpassed the AHI threshold for study inclusion during the screening night. This is in line with previous studies reporting the susceptibility to high altitude-induced nPB to be much lower in women than in men (Bird et al., 2023; Caravita et al., 2015; Lombardi et al., 2013; Torlasco et al., 2020). The lower nPB susceptibility of women may be related to a reduced hypoxic ventilatory response to central and combined central and peripheral chemoreflex activation (Gentile et al., 2022; Sayegh et al., 2022). Whatever the explanation, given that our results do not support any consequences of nPB in men, it is most unlikely that the milder nPB experienced by women plays a role in their SNA and/or ventilatory responses to high altitude.

### Clinical implications

At sea level, repeated sleep apnoea and the resulting oscillations in $S_{aO_2}$ have detrimental consequences for cardiovascular health (Javaheri et al., 2017; Lévy et al., 2008) with chronic sympathoexcitation governed by the peripheral chemoreflex as cardinal mechanism (Narkiewicz et al., 1999; Tamisier et al., 2011). Given that worldwide more than 200 million people live at altitudes >2000 m (Tremblay & Ainslie, 2021), it is crucial to evaluate whether altitude-induced nPB sets in motion the same pathophysiological process. The absence of an effect of nPB on SNA and peripheral chemoreflex activity in the current study argues against this. However, our findings pertain to early acclimatisation and whether this remains true during longer high altitude acclimatisation or at different altitudes warrants further investigation.

In conclusion, nPB does not contribute to the increases in SNA and ventilation resulting from 3 days of acclimatisation to an altitude of 4000 m. Based on these findings, it seems unlikely that nPB at high altitude entails the detrimental effects on cardiovascular health that sleep apnoea has at sea level.

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## Additional information

### Data availability statement

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

### Competing interests

The authors have no conflict of interest to declare.

## Author contributions

C.S., B.H. and J.R. designed the protocol, C.S., J.R., B.H., and A.I. planned and conducted the research. All listed authors acquired, analysed, or interpreted the data. J.R. drafted the article and all authors critically revised and approved the final version of the manuscript. All listed authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; and all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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## Keywords

acclimatisation, altitude, central sleep apnoea, chemoreflex, $CO_2$, microneurography

## Supporting information

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