

## Short Communication

## Sympathetic transduction to blood pressure following three days in hypobaric hypoxia: Influence of nocturnal periodic breathing

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## A B S T R A C T

We investigated whether three days of hypoxic exposure in a hypobaric chamber, and the associated nocturnal periodic breathing (nPB), reduce sympathetic nerve activity (MSNA) transduction to blood pressure (BP). While hypoxia did not affect MSNA transduction to BP, larger drops in BP occurred following cardiac cycles without sympathetic bursts, suggesting increased reliance on sympathetic vasoconstrictor support for beat-to-beat BP. Prevention of nPB by inspiratory carbon dioxide administration did not affect MSNA transduction to BP in hypoxia.

The acute regulation of local blood flow and blood pressure (BP) by the sympathetic nervous system is critical for the appropriate provision of oxygen to tissues. Short-term exposure to hypoxia (e.g., ~5–20 min) causes concomitant increases in sympathetic nerve activity which promotes global vasoconstriction, and peripheral vasodilatation through local mechanisms (Simpson et al., 2021). Notably, while  $\alpha$ -adrenergic mediated vasoconstriction is preserved in acute hypoxia (Dinenno et al., 2003), whether the transduction of muscle sympathetic nerve activity (MSNA) to BP alters is equivocal, as recently reviewed (Shafer et al., 2024). Longer-term exposure to hypoxia (e.g., >1 week) induces further increases in MSNA (Simpson et al., 2021) and attenuates the BP response to MSNA bursts. However, it is unclear whether this reduction in sympathetic transduction is already present after three days in hypoxia, which would be a typical time for recreational mountaineers to be exposed to the hypoxia of high altitude. Accordingly, the first aim of this study was to determine whether three days of hypoxic exposure in a hypobaric chamber reduce MSNA transduction to BP.

Nocturnal periodic breathing (nPB) often occurs during sleep in hypoxia (Weil, 2004) and could contribute to a reduction in MSNA transduction to BP since, at least at sea level, sleep-disordered breathing is associated with blunted sympathetic transduction (Steele et al., 2021).

Therefore, the second aim of this study was to explore the contribution of nPB to potential reductions in sympathetic transduction to BP during the three-day sojourn in hypoxia.

A local ethics committee (Bolzano Hospital, Italy, #76–2021) approved the study, which was conducted in accordance with the Declaration of Helsinki, except for registration in a database. The study protocol has previously been described in publications testing distinct hypotheses (Ibrahim et al., 2024; Roche et al., 2025). In brief, eleven male lowlanders (age  $28 \pm 4$  years, height  $1.79 \pm 0.07$  m, weight  $72 \pm 6$  kg, body mass index  $22 \pm 2$  kg/m<sup>2</sup>, systolic BP  $128 \pm 9$  mmHg, diastolic BP  $74 \pm 6$  mmHg), who were previously confirmed to be susceptible to hypoxia-induced nPB (i.e., exhibited an apnea-hypopnea index of  $\geq 30$  events/h during a screening night in hypobaric hypoxia equivalent to 4000 m altitude) were included. An additional 17 individuals, including 9 women, were screened but excluded because they did not surpass the apnea-hypopnea index threshold for inclusion. Participants were healthy, non-smokers, did not take any medication, had no history of severe high-altitude illness, and were not exposed to altitudes >2000 m within the 4 weeks preceding and during the study. Measurements were performed first in normoxia and then at the end of two 3-day sojourns in hypobaric hypoxia (equivalent to 4000 m

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altitude), where nPB was either allowed to occur (nPB+,  $\geq 3\%$  oxygen desaturation index (ODI)  $63 \pm 38$  events/h; 3 night average) or inhibited by increasing inspiratory CO<sub>2</sub> during the nights (nPB-, ODI  $15 \pm 7$  events/h; 3 night average). Hypoxic exposures occurred in a hypobaric chamber (terraXcube, Eurac Research, Italy; internal dimensions  $12 \times 6 \times 5$  m), at a barometric pressure of 462.3 mmHg, daytime temperature of 22 °C, nighttime temperature of 18–20 °C, and relative humidity of 30%. Four weeks of washout were provided between the two sojourns. Nocturnal measurements and interventions (i.e. respiratory monitoring and nPB prevention) took place between 2300 and 0700. Respiratory monitoring was performed by polysomnography (Morpheus recorder light, Micromed, Italy) during the first and third night, and by polygraphy (Alice PDx, Philips Respirionics, Amsterdam, The Netherlands) during the second night of the sojourns. Detailed information regarding scoring of nPB is available elsewhere (Ibrahim et al., 2024). During the nights of the nPB-, the fraction of inspired CO<sub>2</sub> (F<sub>i</sub>CO<sub>2</sub>), which was manually titrated to the lowest level that prevented nPB in a given individual, was 1.76% [1.07–2.44] (median [25–75% IQR]), with individual values ranging from 0.17% to 3.1%, whereas during the nPB+ sojourn it was  $\leq 0.2\%$ .

MSNA measurements were always performed at the same time of the day (1100) and preceded by at least 3 h of fasting, whilst no caffeine was consumed on that day. Moreover, there was no alcohol intake or exercise in the preceding 24 h. MSNA was identified using intraneural stimulation (Stimulus Isolator, ADInstruments, Sydney, Australia) and sampled using the NeuroAMP Ex device (ADInstruments), while beat-to-beat BP was acquired using finger photoplethysmography (Nova, Finapres Medical System, Enschede, The Netherlands). Sympathetic transduction

to BP was quantified using burst-triggered signal-averaging. Specifically, mean arterial pressure (MAP) responses to an MSNA burst were tracked over the following 15 cardiac cycles and the peak response identified. MAP responses to cardiac cycles not containing an MSNA burst were also tracked, and both the nadir response and average response over 15 cardiac cycles were identified. Data distributions were assessed using Q-Q plots and Shapiro Wilks tests. Normally distributed data were analyzed using repeated measures one-way analysis of variance (ANOVA), and Tukey's multiple comparisons post hoc tests were used when ANOVA identified a significant main effect. Non-normally distributed data were analyzed using Friedman tests with significant main effects explored using Durbin-Conover post hoc tests (Jamovi, v2.16.13).

Compared to normoxia ( $96 \pm 7$  mmHg), MAP was elevated for nPB+ ( $104 \pm 9$  mmHg,  $p = 0.007$ ) and a similar numerical increase occurred for nPB-, but this did not reach significance ( $103 \pm 8$  mmHg,  $p = 0.135$ ), with no difference between sojourns ( $p = 0.987$ ). MSNA burst frequency was increased from normoxia ( $18 \pm 10$  bursts.min<sup>-1</sup>) for both nPB+ ( $32 \pm 10$  bursts.min<sup>-1</sup>,  $p = 0.003$ ) and nPB- ( $32 \pm 15$  bursts.min<sup>-1</sup>,  $p = 0.017$ ), with no difference between sojourns ( $p = 0.996$ ). As illustrated in Fig. 1, the peak increase in MAP following a MSNA burst was not different ( $p = 0.695$ ) between normoxia ( $+2.8 \pm 2.2$  mmHg), nPB+ ( $+2.8 \pm 2.0$  mmHg) and nPB- ( $+3.3 \pm 2.3$  mmHg). However, compared to normoxia (nadir  $-1.3 \pm 0.6$  mmHg), the nadir MAP following cardiac cycles without a MSNA burst tended ( $p = 0.078$ ) to be greater for nPB+ ( $-2.0 \pm 0.9$ ) and nPB- ( $-2.3 \pm 1.6$  mmHg). Moreover, when expressed as an average response over 15 cardiac cycles, the reduction in MAP following cardiac cycles without an MSNA burst was augmented

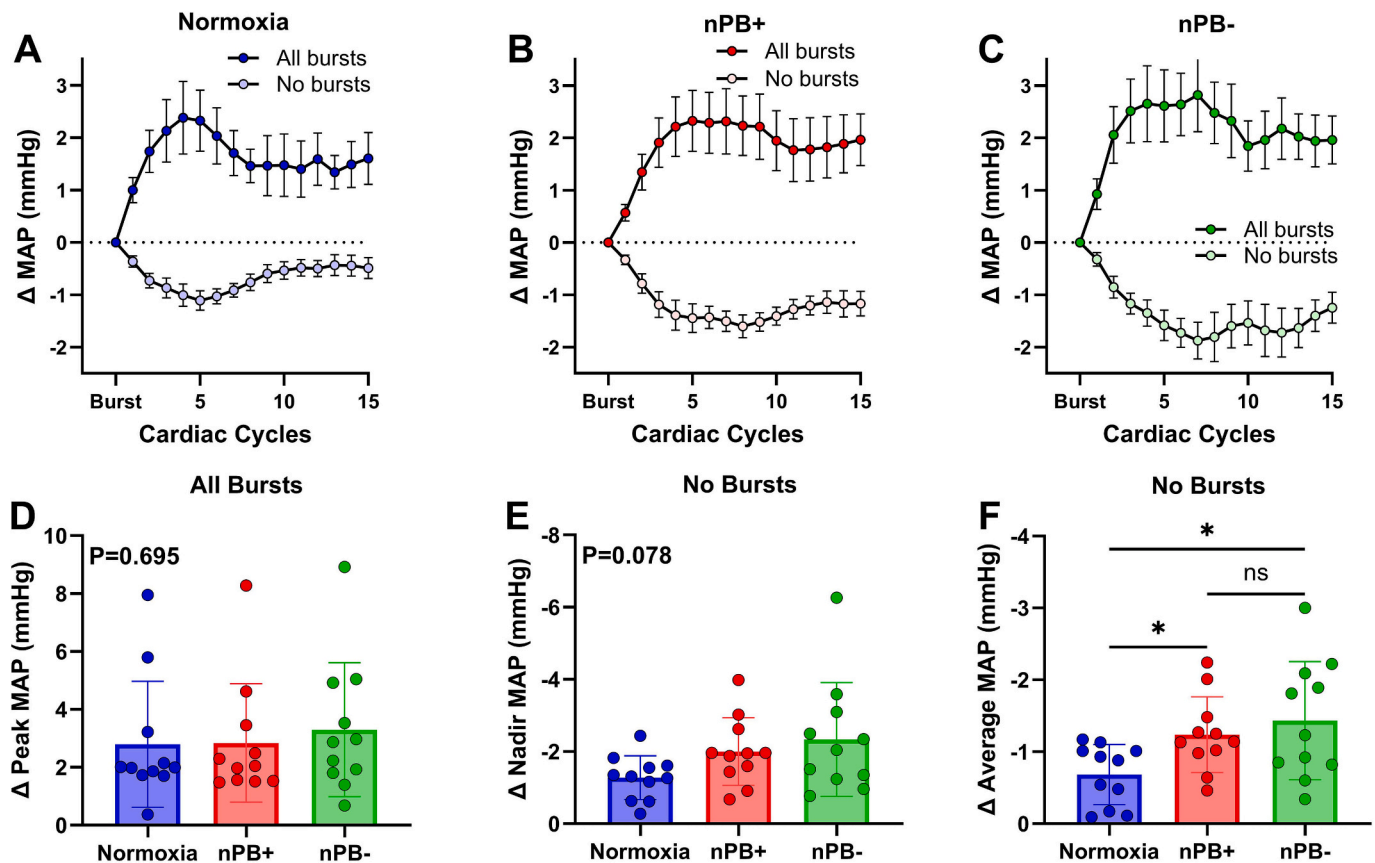


Fig. 1. Mean arterial pressure (MAP) time course following muscle sympathetic nerve activity (MSNA) bursts and non-burst cardiac cycles at sea level (A), and during 3-day sojourns in hypobaric hypoxia where nocturnal periodic breathing was either allowed to occur (nPB+) or inhibited nPB- (C). Peak  $\Delta$ MAP to MSNA bursts (D), nadir  $\Delta$ MAP to non-burst cardiac cycles (E), and average  $\Delta$ MAP to non-burst cardiac cycles (F).

Note: y-axes in E and F are reversed. Mean  $\pm$  SD.  $N = 11$ .  $P$  values in panels D and E represent results of Friedman tests. Statistical notation in panel F represent results of Tukey's test.

compared to normoxia ( $-0.7 \pm 0.4$  mmHg) after nPB+ ( $-1.2 \pm 0.5$  mmHg;  $p = 0.016$ ) and nPB- ( $-1.4 \pm 0.8$  mmHg;  $p = 0.018$ ), with no difference between nPB+ and nPB- ( $p = 0.719$ ).

Our results indicate that three days of hypobaric hypoxia exposure (equivalent to 4000 m altitude) are insufficient to blunt MSNA transduction to BP. Nevertheless, more pronounced drops in MAP following cardiac cycles without sympathetic bursts were observed following the hypoxic exposure, indicative of an increased importance of sympathetic vasoconstrictor support to beat-to-beat BP. Hypoxia not only triggers sympathoexcitation, but also peripheral vasodilation via local mechanisms (Blitzer et al., 1996). During cardiac cycles without sympathetic bursts, the latter effect presumably leads to a more pronounced BP drop than in normoxia and explains an increased reliance on sympathetic support of BP. Alternatively, the larger decrease in BP following non-bursts might be a compensatory response that attenuates the hypertensive effects of sustained increases in MSNA in hypoxia. Finally, our results are not consistent with the concept that 3 nights of hypoxia-induced nPB affect MSNA transduction to BP.

It should be considered whether the use of CO<sub>2</sub> to prevent nocturnal periodic breathing could have had a confounding effect on the main outcomes of the current study. However, this seems unlikely for several reasons, as discussed in our previous work relating to this project (Roche et al., 2025). In brief, the increase in the partial pressure of end-tidal CO<sub>2</sub> during nPB- compared to nPB+ was small ( $\sim 1.5$  mmHg on average) and restricted to the night, with more than four hours of washout before measurements were made. It should also be noted that the effects of acutely increasing arterial CO<sub>2</sub> on MSNA resolve rapidly after restoration of normocapnia, unlike those of hypoxia which persist after termination of the stimulus (Xie et al., 2001). We acknowledge the limited sample size ( $n = 11$ ) that is not uncommon in such technically demanding human studies and recognize the potential for type II errors. Finally, Nardone et al. (2021) have demonstrated in a cross-sectional study that a higher MSNA is associated with a lower MSNA transduction to BP. Whether this represents a methodological or physiological issue remains contentious. Nevertheless, it somewhat complicates the interpretation of differences in sympathetic transduction to BP between normoxia and hypoxia in the current study, since MSNA burst frequency was increased in hypoxia. Nevertheless, since this increase in MSNA would have, if anything, been expected to reduce MSNA transduction to BP, it cannot have masked the hypothesized negative effect of hypoxia on MSNA transduction to BP. Furthermore, the absence of a difference in MSNA transduction to BP between nPB+ and nPB- cannot be explained by different increases in MSNA as this was identical for the two sojourns.

Our results have implications for the understanding of the regulation of MSNA in hypoxia. Hypoxia triggers sympathoexcitation that persists or increases further as the hypoxic exposure extends, even as acclimatization processes progressively normalize arterial oxygenation (Hansen and Sander, 2003). The mechanisms governing this persistent sympathoexcitation during extended hypoxia remain incompletely understood. The present findings provide experimental support for the notion that, at least during the first 3 days of hypoxic exposure, an increased MSNA is required for stabilization of BP in the face of hypoxia-induced local vasodilation.

#### CRedit authorship contribution statement

**James P. Fisher:** Writing – review & editing, Writing – original

draft, Visualization, Formal analysis, Conceptualization. **Johanna Roche:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Amanda G. Duffy:** Writing – review & editing, Software, Formal analysis. **Abubaker Ibrahim:** Writing – review & editing, Investigation. **Rachel Turner:** Writing – review & editing, Investigation. **Giovanni Vinetti:** Writing – review & editing, Investigation. **Matteo Cesari:** Writing – review & editing, Methodology, Formal analysis. **Michael Furian:** Writing – review & editing, Investigation. **Amra Stefani:** Writing – review & editing, Resources, Funding acquisition. **Hannes Gatterer:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Birgit Högl:** Writing – review & editing, Resources, Methodology, Funding acquisition, Conceptualization. **Christoph Siebenmann:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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