


Both Hypoxia and Hypobaria Impair Baroreflex Sensitivity but through Different Mechanisms



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Key words

baroreflex sensitivity, blood pressure, heart rate, hypobaria, hypoxia, hypocapnia

accepted 04.09.2022

published online 01.12.2022

Bibliography

Int J Sports Med 2023; 44: 177–183

DOI 10.1055/a-1960-3407

ISSN 0172-4622

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ABSTRACT

Baroreflex sensitivity (BRS) is a measure of cardiovagal baroreflex and is lower in normobaric and hypobaric hypoxia compared to normobaric normoxia. The aim of this study was to assess the effects of hypobaria on BRS in normoxia and hypoxia. Continuous blood pressure and ventilation were recorded in eighteen seated participants in normobaric normoxia (NNx), hypobaric normoxia (HNx), normobaric hypoxia (NHx) and hypobaric hypoxia (HHx). Barometric pressure was matched between NNx vs. NHx (723 ± 4 mmHg) and HNx vs. HHx (406 ± 4 vs. 403 ± 5 mmHg). Inspired oxygen pressure (PiO₂) was matched between NNx vs. HNx (141.2 ± 0.8 vs. 141.5 ± 1.5 mmHg) and NHx vs. HHx (75.7 ± 0.4 vs. 74.3 ± 1.0 mmHg). BRS was assessed using the sequence method. BRS significantly decreased in HNx, NHx and HHx compared to NNx. Heart rate, mean systolic and diastolic blood pressures did not differ between conditions. There was the specific effect of hypobaria on BRS in normoxia (BRS was lower in HNx than in NNx). The hypoxic and hypobaric effects do not add to each other resulting in comparable BRS decreases in HNx, NHx and HHx. BRS decrease under low barometric pressure requires future studies independently controlling O₂ and CO₂ to identify central and peripheral chemoreceptors' roles.

Introduction

The physiological effects of altitude in humans are often studied in normobaric hypoxia (NHx) according to the air equivalent model. This model posits that the inspired oxygen pressure (PiO₂) matters without any influence of the barometric pressure *per se* [1]. However, in recent years, differences between NHx and “real altitude”

(hypobaric hypoxia, HHx) have been reported [2]. In HHx compared to NHx arterial oxygen saturation was lower [3, 4], sleep more disturbed [5], and oxidative stress more pronounced [6], whilst acute mountain sickness symptoms were more severe [7]. Subtle effects on heart rate variability were also reported [8]. Although still subject of debate [9, 10], at equivalent PiO₂ HHx appears as a stronger

stimulus than NHx, which suggests an influence of the decreased barometric pressure *per se*, at least in hypoxia.

But an additional hypobaric normoxic condition (HNx) is needed to isolate the effect of hypobaria. By comparing NNx vs. HNx in normoxia and NHx vs. HHx hypoxia, it becomes possible to further disentangle the specific effects of environmental hypoxia and hypobaria. The HNx condition requires lowering barometric pressure combined with increasing inspired oxygen so that PiO_2 remains similar to NNx values. Similar situations may occur in aviation when breathing 100% oxygen in a depressurized cabin.

The cardiovagal baroreflex aims at regulating blood pressure. A decrease in arterial blood pressure (BP) reduces baroreceptor afferent discharge leading to a decrease in parasympathetic tone and an increase sympathetic tone, triggering an increase in HR, cardiac contractility, and vascular resistance therefore countering the decrease in BP. A rise in pressure does the contrary. The cardiovagal baroreflex is challenged in numerous conditions such as during altitude exposure [11, 12].

Baroreflex sensitivity (BRS) is a measure of cardiovagal baroreflex function [13]. In hypoxic conditions, there is a resetting of the cardiovagal baroreflex operating point to higher pressures [14–16], associated to a parasympathetic withdrawal [17–19] which results in decreased BRS [20] in acute and chronic hypoxia [21]. This decrease in BRS is clear above 4,500 m [22]. Previous studies reported lower BRS values in NHx and HHx than in NNx but without differences between the two hypoxic conditions at 2,250 and 3,450 m [11].

In order to better assess the respective influence of environmental hypoxia and hypobaria on BRS, the aim of the present study was to investigate the potential effects of decreased barometric pressure *per se* on the cardiovagal baroreflex sensitivity at rest in normoxia (NNx vs HNx) and severe hypoxia corresponding to an altitude of 5,000 m (NHx vs HHx).

Materials and Methods

Ethics

This study was performed according to the Declaration of Helsinki and was approved by Swiss Research Ethics Committee of Zürich (Swissethics, BASEC ID: 2018–00006). The trial was registered on ClinicalTrials.gov (ID: NCT03439202). The participants were informed about all procedures of this study and gave their written informed consent before participation.

Participant recruitment and screening

Eighteen healthy pilot trainees (14 men and 4 women, age 26 ± 3 years; height 177 ± 9 cm; weight 70 ± 11 kg) participated voluntarily in this study. None of the participants were exposed to hypoxia before enrolment in the present study and/or no relevant altitude exposure was reported in the preceding four weeks preceding the trials. A physician screened the participants during a familiarization visit to ensure they were healthy and did not report any medical or altitude-related issues. None of the participants were on medication during this study.

Study design

This study was conducted at the Aeromedical Center (AeMC) of the Swiss Air Force, in Dübendorf, Switzerland. During a single visit the participants were exposed to four conditions: normobaric normoxia (NNx, Dübendorf, 440 m, barometric pressures in ► **Table 1**), hypobaric normoxia (HNx), normobaric hypoxia (NHx) and hypobaric hypoxia (HHx), in a randomized order and single-blind. Each condition lasted 30 min and was carried out at local barometric pressure or at a simulated altitude of 5,000 m in the Swiss army hypobaric chamber hypobaric chamber. Each condition was preceded by 30 min of rest in NNx. Decompression to 5,000 m took about 2 min in the two hypobaric conditions (HNx and HHx).

During the twenty-four hours before the visit, the participants were asked to avoid physical exercise or heavy meals, and to refrain from alcohol and caffeine consumption. Each condition started with a 5-min adaptation period followed by a concentration test (KLT-R test [23] including arithmetic and working memory tasks) and 6 min seated at rest.

Conditions

Barometric pressure was matched between the two normobaric (NNx vs. NHx) and between the two hypobaric (HNx vs. HHx) conditions, whilst the inspired oxygen pressure (PiO_2) was matched between the normoxic (NNx and HNx) and between the hypoxic (NHx and HHx) conditions (cf. ► **Table 1**). Matching was achieved by adjusting the barometric pressure in the hypobaric chamber or the inspired oxygen fraction (FiO_2) using tanks of gas mixtures of known concentrations [24]. Participants breathed 11.2% or 39.4% O_2 (0.03% CO_2 , balance N_2) during NHx and HNx, respectively, whilst the barometric pressure was decreased comparably in HNx and HHx (cf. ► **Table 1**). For blinding, the altimeter in the hypobaric chamber was hidden and changes in pressure and gas concentrations administered through the mask were not communicated to the participants.

Blood pressure recording

Blood pressure was recorded at a sampling frequency of 1,000 Hz using a photoplethysmography device combined to a double cuff (NIBP100D, Biopac Systems, Inc. Goleta, CA, USA). Blood pressure was recorded continuously from the double cuff installed on the index and the middle fingers. The device was connected to a computer for data storage using dedicated software (Acqknowledge, Biopac Systems, Inc. CA, USA). Signal processing was performed offline using custom Matlab routines (MATLAB, R2019b, MathWorks, Natick, MA, USA).

Ventilatory data

The gas analyzer (K5, Cosmed, Rome, Italy) was calibrated outside of the hypobaric chamber before each session. This procedure was recommended by the manufacturer and gives reliable results for ventilation (E), tidal volume (VT), and respiratory frequency (Rf). Flow was calibrated with a 3 L syringe. Zero CO_2 calibration was performed using a scrubber. A second point calibration was performed using a certified gas mixture (16% O_2 and 5% CO_2). Ventilatory data were recorded breath-by-breath and exported with proprietary software for later analysis (OMNIA, Cosmed, Roma, Italy) as instructed by the manufacturer [25, 26]. The PiO_2 measured with the

► **Table 1** Barometric pressure, inspired pressure in oxygen (PiO₂) and pulse saturation (SpO₂) at rest.

	NNx	HNx	NHx	HHx
Barometric pressure (mmHg)	723 ± 4	406 ± 4 a	723 ± 4	403 ± 5 a
PiO ₂ (mmHg)	141.2 ± 0.8	141.5 ± 1.5	75.7 ± 0.4 ab	74.3 ± 1.0 ab
SpO ₂	99.4 ± .5	98.3 ± 2.1	83.5 ± 6.0 ab	74.7 ± 5.1 abc
Normobaric normoxia (NNx); hypobaric normoxia (HNx); normobaric hypoxia (NHx); hypobaric hypoxia (HHx); a: p < 0.05 for difference with NNx; b p < 0.05 for different with HNx; c p < 0.05 different from NHx.				

gas analyzer were as expected given the known concentrations of the gas tanks which increases confidence in the measures realized in the challenging HNx condition.

Blood pressure and baroreflex analyses

Systolic blood pressure (SBP) peaks, and heart beat-to-beat time intervals, defined as the time intervals between successive systolic peaks (inter-beat intervals, IBI), were extracted directly from the BP recordings. The sequence method was used to compute BRS. It is based on the identification of at least three consecutive beats in which an increase (or decrease) in SBP is followed by an increase (or decrease) in IBI. Three conditions were necessary for a SBP-IBI sequence to be qualified for BRS computations: 1) a minimum change of 1 mmHg between two consecutive SBP values and a minimum change of 5 ms for IBI [27]; 2) the minimum correlation coefficient between changes in SBP and changes in IBI was 0.85 and 3) at least five sequences were necessary to validate a BRS estimate. The slope of the regression line between changes in SBP and IBI was used as BRS estimates and all the computed slopes were averaged to obtain the BRS.

This method allows a direct interpretation of the causal link between blood pressure and heart rate changes [28]. It is one of the most used. The computations are automatic and standardized, which virtually eliminates intra- and inter-participant measurement variability [29]. The baroreflex nature of these spontaneous beat-to-beat interval systolic pressure sequences was demonstrated by showing in cats that the number of sequences markedly dropped (– 89%) after the surgical opening of the baroreflex loop by sinoaortic denervation [30]. Consistency of the various methods for BRS computation in hypoxia has been shown recently [31].

Beat-to-beat heart rate (HR) was directly computed from the IBI intervals. Mean, systolic, and diastolic blood pressure were extracted from the continuous blood pressure recordings.

Heart rate variability analysis

RR intervals were recorded in parallel with the continuous blood pressure trace using a chest strap (watch RS800CX + sensor H7 + chest belt, Polar, Kempele, Finland). The RR intervals from the resting period were first inspected to remove ectopic beats from the recordings. Ectopic beats were then compensated by means of interpolation to calculate normal-to-normal intervals. From the normal-to-normal intervals, the following heart rate variability (HRV) parameters were extracted: the root mean square of the successive differences (RMSSD); the spectral power in the low-frequency (pLF, 0.04–0.15 Hz) and high-frequency bands (pHF, 0.15–0.40 Hz) in ms²; and the values (expressed in normalized units) for

LF and HF, respectively. However, since these two indexes are perfectly correlated, only normalized HF (nHF) are presented and discussed. The spectral power was estimated using a fast Fourier transform on the resampled normal-to-normal intervals (4 Hz) using a window length of 250 data points and an overlap of 50%. All computations were performed using custom MATLAB routines.

Statistical analysis

Data are presented as mean ± SD. Normality of data was tested using the Shapiro-Wilk test before performing a two-way repeated measures [hypoxia vs. normoxia x hypobaria vs. normobaria] ANOVA. The p level for significance was set at 0.05. Values for p are presented < 0.05, or < 0.01 or < 0.001. The Tukey-Kramer *post hoc* test was performed when appropriate. All analyses were completed using custom MATLAB routines.

Results

Barometric pressure was matched between the two pairs of conditions, NNx vs. NHx and HNx vs. HHx. Also, PiO₂ was matched between NNx vs. HNx and NHx vs. HHx (► **Table 1**).

BRS decreased comparably in HNx, NHx and HHx compared to NNx (p < 0.01, p < 0.05 and p < 0.001, respectively, ► **Fig. 1**) whilst there were no differences in heart rate (HR, ► **Fig. 1**), mean, systolic and diastolic blood pressures between the four conditions.

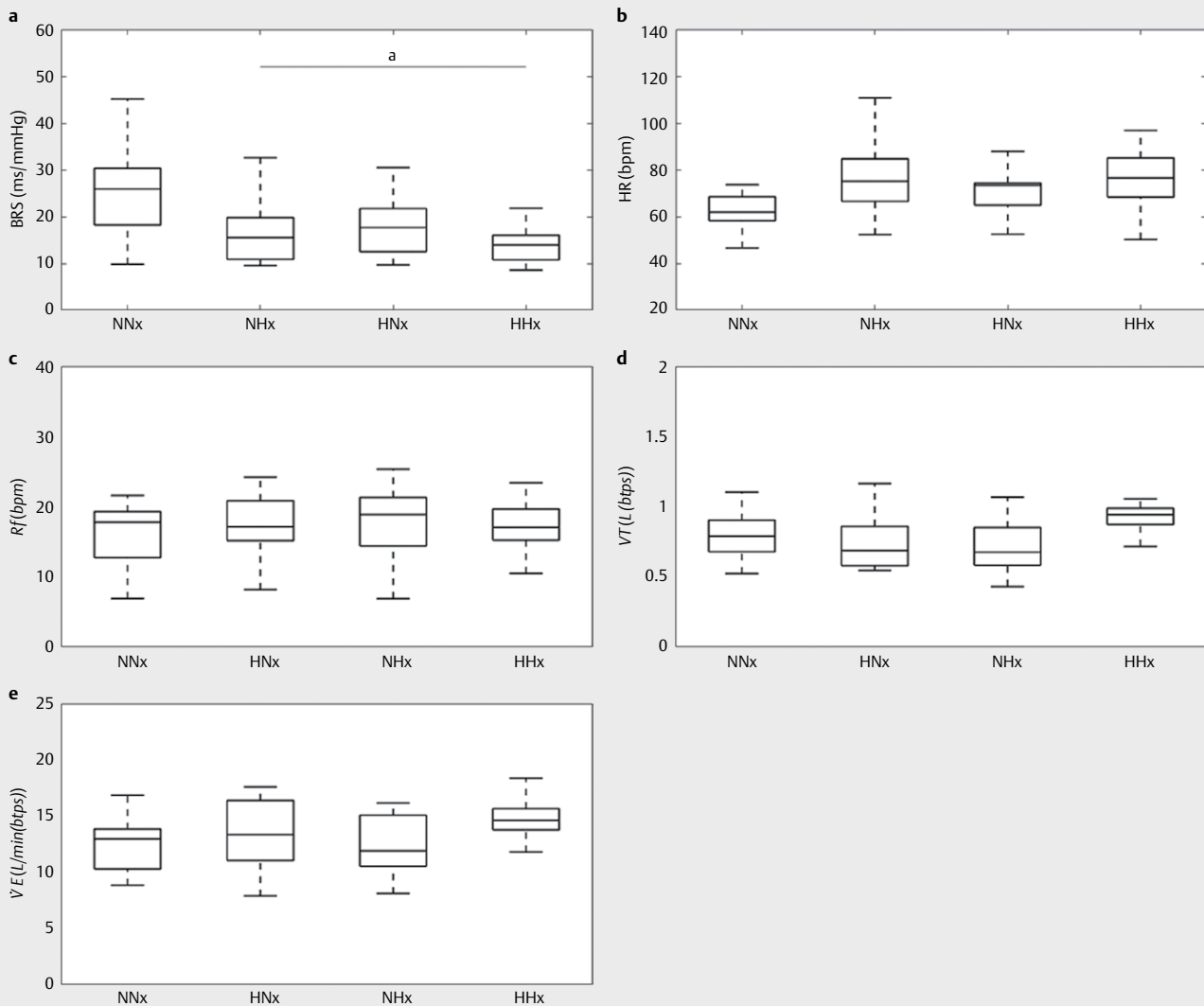
Results for E, VT, and Rf, are shown in ► **Fig. 1**. All values were comparable between conditions.

Blood pressure parameters are detailed in ► **Table 2**. Mean, systolic and diastolic blood pressures were comparable between conditions.

► **Table 3** summarizes the HRV results. RMSSD significantly decreased in HHx compared to NNx and HNx (p < 0.01 for both) and there was a tendency for a decrease in NHx compared to NNx (p < 0.10). There was a tendency for decreases in HF and nHF in HHx compared to NNx (p < 0.10 for all).

Discussion

This study investigated the effect of hypobaria on cardiovagal baroreflex sensitivity in both normoxic and hypoxic conditions. The main result is a large and specific effect of hypobaria *per se*, at rest in normoxia despite that no specific effects were found on HR or blood pressure. This influence of hypobaria on BRS was less evident in hypoxia.



► **Fig. 1** Baroreflex sensitivity (BRS, panel a), heart rate (HR, panel b), respiratory frequency (Rf, panel c), tidal volume (VT, panel d) and ventilation (E, panel e) in normobaric normoxia (NNx), hypobaric normoxia (HNx), normobaric hypoxia (NHx) and hypobaric hypoxia (HHx), during rest.; a: $p < 0.05$ for difference with NNx,.

► **Table 2** Blood pressure data.

Parameter	NNx	HNx	NHx	HHx
BPmean (mmHg)	93 ± 14	98 ± 14	91 ± 13	89 ± 11
BPsys (mmHg)	126 ± 23	130 ± 22	125 ± 18	125 ± 15
BPdia (mmHg)	77 ± 11	85 ± 14	79 ± 13	75 ± 12

Normobaric normoxia (NNx); hypobaric normoxia (HNx); normobaric hypoxia (NHx); hypobaric hypoxia (HHx).

Decreased BRS in hypoxia

The comparable decrease in BRS at rest in the two hypoxic conditions (NHx and HHx, when compared to NNx) confirms previous findings in the literature [20, 21]. The known hypoxic effect did not add to the hypobaric effect observed in HNx resulting in values similar between HHx, NHx and HNx.

The reduction in BRS in acute hypobaric hypoxia is probably mediated by the carotid body chemoreceptors [32]. Previous studies

suggested that acute hypobaric hypoxia initiates a persistent increase in chemo-afferent activity to the rostro-ventrolateral medulla via the nucleus tractus solitarius, which results in long-lasting sympathoexcitation, likely accompanied by a parasympathetic withdrawal [33, 34]. The decreased BRS in hypoxic conditions is associated to these modifications of the autonomic balance [15]. Accordingly, there was a decrease in RMSSD, a tendency for a decrease in HF (both markers of parasympathetic activity) and a tendency

► **Table 3** HRV data.

	NNx	HNx	NHx	HHx
RMSSD (ms)	49 ± 20	37 ± 17	30 ± 20 (a)	18 ± 15 ab
LF (ms ²)	1317 ± 732	1374 ± 1263	1184 ± 1665	559 ± 637
HF (ms ²)	1068 ± 771	911 ± 775	752 ± 979	329 ± 530 (a)
nHF (%)	42 ± 14	41 ± 11	38 ± 8	30 ± 13 (a)

Normobaric normoxia (NNx); hypobaric normoxia (HNx); normobaric hypoxia (NHx); hypobaric hypoxia (HHx).; p < 0.10; a: p < 0.05 for difference with NNx; b p < 0.05 for different with HNx.

for a shift in the autonomic balance toward sympathetic dominance (decreased nHF) in the HHx conditions (► **Table 3**). An important trigger may be the central chemoreceptors, which are known to be more responsive to CO₂ than the peripheral ones [35, 36] and therefore may play a pivotal role in BRS decrease in case there was a decrease in arterial CO₂, likely the case in hypoxic conditions [31], and hypothetical in hypobaric normoxic conditions.

Hypoxia has been reported to induce venodilation [37], which may impact cardiac preload and heart rate response. This additional mechanism may affect BRS in hypoxic conditions, but its role remains to be investigated in hypobaric conditions.

The classical explanations are directly linked to the changes in blood gases (and potentially in the cerebrospinal fluid), affecting the chemoreceptors. In humans, the baro- and chemo-reflex arcs coincide, so that sensory information regarding BP and arterial blood gas homeostasis converge in an integrative fashion [38]. There is a negative relationship between the baro- and chemo-reflexes; i. e., the cardiovagal baroreflex activation inhibits the chemoreflex and vice versa [39]. Therefore, in case of hypocapnia in hypoxic conditions, heightened activation of the chemoreceptors likely resulted in a resetting of the cardiovagal baroreflex operating point to higher pressures, which in turn resulted in the decreased BRS [21, 32].

Effect of hypobaria on BRS: large in normoxia and minimal in hypoxia

Previous study suggested that pulmonary blood flow through intrapulmonary arteriovenous anastomoses, was decreased by hypobaria, independent of the hypoxia severity [40]. Previous work has shown that hypobaric decompression increased total lung capacity, functional residual capacity, closing capacity, and residual volume [41] which may be attributed to a greater volume of air trapped in the alveoli at lower atmospheric pressure. An increase in lung volume increases compression of alveolar capillaries [42, 43] and may contribute to modify arterial O₂ and/or CO₂ content in the HNx condition. However, the decrease in arterial CO₂ in the HNx condition is a subject of debate. At 5,260 m, no differences in P_aCO₂ were reported between rest and high intensity exercise (as shown by RER ~.99) despite induced hyperventilation [40]. However, a light decrease in arterial CO₂ in the HNx condition cannot be totally excluded and may have influence BRS.

Limitations

The present work used a spontaneous cardiovagal BRS, which only estimates sensitivity or gain around the operating point of the cardiovagal baroreflex stimulus-response curve. In HHx conditions, a

resetting of the cardiovagal baroreflex operating point to higher pressures, coupled with an upward resetting of sympathetic vascular baroreflex, without any alterations in BRS, was observed [44]. The main variable of interest of the present study was the cardiovagal baroreflex and there was no assessment of the sympathetic vascular baroreflex component.

Respiration is a confounding factor for the characterization of the cardiovagal baroreflex control from spontaneous fluctuations [45]. In the present study no change in ventilation or breathing pattern was observed, therefore limiting the effects of respiration as a confounding factor.

In this paper, BRS is reported according to the sequence method, which is the most commonly used and which allows a direct interpretation of the causal link between blood pressure and heart rate changes. However, Bernardi's ratio of the standard differences, the frequency and the transfer function methods were also used [31]. The conclusion of this work would not have been different with the other methods.

Eighteen participants may be seen as a rather small sample size in regards of the number of factors of the analysis (effect of hypoxia and hypobaria). However, each participant underwent all the conditions in a randomized order thereby minimizing the inter-individual variability. In addition, our group of participants was rather homogeneous (all military aircraft pilot trainees), therefore despite a small sample size the statistical results remain interesting and contains original data.

Perspectives

Overall, our results indicate that humans exposed to HNx conditions, such as military aircraft pilots, may experience decreased BRS that may impact their cerebral perfusion. Future studies need to determine the mechanisms and the adequate response to prevent decreased cerebral perfusion and impaired cognitive and motor performances. Small doses of inspired CO₂ may increase the cardiovagal baroreflex function and may prevent the performance impairment [46]. Future studies should focus on the relationship between pulmonary O₂ and CO₂ diffusion, blood content and cardiovagal baroreflex function in the four conditions, attempting to further disentangle the chemo- and baro-reflex arcs to better understand the mechanisms of blood pressure regulation in conditions of hypobaria and/or hypoxia.

Conclusion

This study was the first to demonstrate a specific effect of hypobaria *per se* on BRS. This finding is of interest in space physiology since

it has direct consequences for astronauts exposed to microgravity or aircraft pilots when depressurization occurs, with large clinically significant physiological alterations. The effects of hypocapnia and hypoxia did not add to each other so that the decrease in BRS was comparable between HNX, NHX and HHX conditions. The hypothesis that adequate additional inspired CO₂ in hypobaric-induced hypocapnic conditions would prevent impaired BRS requires further investigation. Particularly there is a need to clamp P_{ET}-CO₂ in various hypobaric vs normobaric and hypoxic vs normoxic conditions to control the effects of capnia independently of the other controlling variables.

Data availability

The data that support the findings of this study are openly available in Zenodo at <http://doi.org/10.5281/zenodo.4297460>, reference number <https://zenodo.org/record/4297460#.X8Tab7fjKUK>.

Author Contribution

GPM designed the study. MRA collected the data. NB and MRA analyzed the data. NB did the signal processing. NB wrote the article and prepared the figures. GPM and BK reviewed the article. All the authors approved the final version of the manuscript and declare no conflict of interest.

Conflict of Interest

The authors declare that they have no conflict of interest.

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