Sleep and Breathing

HEART RATE VARIABILITY DURING SLEEP AT HIGH-ALTITUDE: EFFECT OF PERIODIC BREATHING

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Abstract:	Background: Heart rate variability (HRV) during sleep in normal subjects at high altitude shows a decrease in parasympathetic tone associated with an increase in the sympathetic one, which tends to be reversed with acclimatization. However, periodic breathing (PB) during sleep may influence this effect detected by HRV spectral analysis. Purpose: The aim of our study was to investigate HRV during sleep periodic breathing (PB) at high altitude in normal subjects at two different times of acclimatization i.e. two different levels of hypoxemia. Methods: Recordings of six healthy climbers (aged between 33 and 40 years), at sea level (SL) and at Everest North Base Camp (5180 m), during the 1st (BC1) and the 10th (BC2) overnight unattended polygraphy, were analyzed. PB was commonplace in all subjects at high altitude to a variable extent. At SL and at BC1 and BC2, HRV was evaluated overnight and separately during clear regular breathing (RB) and PB. Results: A mean overnight RR reduction at acute environmental hypoxic exposure that resumed to SL values after 10-day sojourn was observed. This reduction was mostly due by RR during RB, while during PB, RR values were not different from SL. Higher peaks of tidal volume were associated with higher HRV. Conclusions: The present study shows that in healthy subjects, PB with central apneas increases the amplitude of RR oscillations, and these oscillations are tightly related to respiratory amplitude. Oxygenation does not influence this phenomenon. Therefore, oscillations in ventilation itself should be taken into account when investigating HRV.

HEART RATE VARIABILITY DURING SLEEP AT HIGH-ALTITUDE: EFFECT OF PERIODIC BREATHING

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Abstract

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Results: A mean overnight RR reduction at acute environmental hypoxic exposure that resumed to SL values after 10-day sojourn was observed. This reduction was mostly due by RR during RB, while during PB, RR values were not different from SL. Higher peaks of tidal volume were associated with higher HRV.

Conclusions: The present study shows that in healthy subjects, PB with central apneas increases the amplitude of RR oscillations, and these oscillations are tightly related to respiratory amplitude. Oxygenation does not influence this phenomenon. Therefore, oscillations in ventilation itself should be taken into account when investigating HRV.

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Introduction

High-altitude environments are characterized by a low barometric pressure and consequent low PIO_2. Soon after ascent, physiological changes resulting from the decreased oxygen availability, limit the decrease in arterial oxygen content. These changes include increased ventilation and ventilatory responsiveness to chemical stimuli [1-2]. As a result, arterial hypoxemia is attenuated, but hypocapnia typically appears. In this condition, owing to the highly hypoxic environment, arterial oxygen saturation (SaO_2) is low and decreases further during sleep [3-4]. Periodic breathing (PB) respiration has been described in normal subjects at high altitude during sleep at arrival and up until a one-month stay [2,5]. Hypocapnic hypoxia seems to be the main determinant of PB during sleep in the subjects acutely exposed to high altitude [6,7].

Acute exposure to hypoxia causes an increase in resting HR, which contributes to offset the reduced arterial oxygen content and to maintain oxygen transport to tissues [8]. This rise is largely the result of increased sympathetic activity triggered by stimulation of peripheral chemoreceptors contained within the carotid bodies [9]. During sleep, heart rate (HR) was found to decrease during the respiratory pause of periodic breathing cycles with SaO_2 fall [10-12]. These studies showed HR fluctuations during the periodic breathing cycles with the lowest values reached during apnea and the highest during hyperpnea. The variation of HR in the frequency range of respiration, known as respiratory sinus arrhythmia, was already described by Ludwig in 1847 [13].

Power spectral analysis of HR variability (HRV) represents a tool to assess the sympatho-vagal balance [14]. At high altitude, spectral indexes have been mainly employed to evaluate the effects of hypobaric hypoxia on HRV at daytime [15-16]. Altitude-induced increase in HR has been attributed by HRV analysis, to an increased and dominant sympathetic tone [15,17] associated with a reduced vagal activity [15-16,18-19]. However, peripheral resistances decrease due to local vasodilatation induced by hypoxemia [20] and resting HR tends toward normoxic values due to acclimatization [10,21-22]. During chronic hypoxic exposure, sympathetic and parasympathetic activities have been shown to remain constant [15,19] or to progressively tend toward normoxic values [16,18]. HRV studies attempted to record autonomic activity during acclimatization to hypoxia [15-16,18-19], but only few studies are available on HRV during sleep in normal subjects at high altitude [23-24]. These studies report a decrease in parasympathetic tone associated with an increase in the sympathetic one, which tends to be reversed by acclimatization. However, PB during sleep

may influence this effect detected by HRV spectral analysis. Indeed, breathing pattern strongly influences power spectrum [25-26]. The respiratory component is mostly identified by the high frequency spectral band (HF), which reflects respiratory sinus arrhythmia and is said to reflect parasympathetic activity and includes the RR interval fluctuations in the range of normal respiratory rate [14]. Low frequency spectral band (LF) considered as a marker of both sympathetic and parasympathetic activity, reflects predominantly sympathetic activity. Reduction in respiratory frequency increases LF. Lipsitz et al [17] showed that low frequency heart rate oscillations were associated with alternating periods of apnea and hyperpnea. During sleep at high altitude, a variable amount of periodic breathing associated with a variable duty ratio (defined as the duration of the respiratory period divided by periodic breathing cycle duration) can be detected. Cornolo et al [24] showed LF/HF sleep increase during acute exposure to hypoxia probably because of an increase in the sympathetic tone associated with a fall in the parasympathetic control that tends to be reversed during acclimatization.

The aim of our study was to investigate the effect of PB during sleep on HRV at high altitude in normal subjects. Our experimental design of paired studies at two different times of acclimatization allows comparisons between different levels of hypoxemia.

Methods

Nine males élite climbers, have been studied with overnight unattended polygraphy at sea level and at Everest North Base Camp (5180 m), during the 1st (BC1) and the 10th (BC2) night. Between the two times, all subjects climbed up to 7000m and spent ≥2 nights at 6100m with no use of oxygen and no symptoms of Acute Mountain Sickness. Lake Louise AMS Questionnaire score was not higher than three in any subject. Sea level (SL) evaluation was performed in Ferrara (9 m) within 4 weeks before departure. The altitude of 5180m was reached by jeep after a 4-day journey from Lhasa (3600 m) which had been reached by plane. No subject was allowed to consume medication known to modify the control of breathing, such as acetazolamide, theophylline, or benzodiazepines.

Recordings of six of these climbers (aged between 33 and 40 years, body mass index 22–25 kg/m^2), with normal respiratory function test and with good ECG quality at each of the three overnight cardio-respiratory

monitorings, were included in the study. The protocol was reviewed by the institutional review committee and informed consent was obtained.

Nocturnal monitoring was performed by the LifeShirt system (LifeShirt; VivoMetrics, Ventura, CA), an ambulatory multi-sensor, continuous monitoring system that we used to collect physiologic data throughout the night study via various sensors, including respiratory inductive plethysmography bands, body position, 1-lead electrocardiogram, SaO_2, and sound.

Signals were continuously sampled at 250 Hz and recorded on a compact flash memory card. Data were downloaded into a computer at the end of the recording period. Respiratory signals were subsequently analyzed to identify regular and periodic breathing cycles using software developed in our laboratory written in MATLAB R2008B (The MathWorks; Natick, MA). Breathing pattern, SaO_2 and HRV were analyzed. PB was defined as a cyclic increase in the amplitude of thoraco-abdominal movements, followed by respiratory pauses lasting at least 4 s. In each PB cycle, we measured respiratory time, pause duration (Fig. 1), duty ratio (respiratory time divided by total PB cycle duration), peak tidal volume during PB (measured as percentage of the closest stable regular breathing preceding PB), mean higher and mean lower SaO_2.

The beat-by-beat series intervals (RR) were extracted from ECG signal. Interpolation was applied for converting the non-equidistantly sampled RR interval time series to equidistantly sampled. A first order detrending procedure was then applied. For each RR series of 5 minutes, power spectral analysis using an autoregressive method was performed to assess HRV. Very low frequency (VLF 0-0.04 Hz), LF (0.04-0.15 Hz) and HF (0.15-0.40 Hz) spectral powers along with the LF-to-HF ratio (LF/HF) were estimated [19]. LF is considered as a marker of both sympathetic and parasympathetic activity mainly interpreted as an indicator of sympathetic influence. HF is a result of respiratory sinus arrhythmia mediated by the vagus reflecting momentary respiratory influences on the HR. The LF/HF ratio is an index of the sympatho-vagal balance.

Two time domain measurements of HRV, mean RR intervals and RR intervals standard deviation (SDNN), were also measured. HRV was assessed during overnight cardio-respiratory monitorings and separately during clear regualar breathing (RB) and PB [14].

Statistical analysis

Differences among SL, BC1 and BC2 and PB and RB were evaluated by the nonparametric Wilcoxon's test. Data are reported as mean ± SD. A $p<0.05$ was considered significant. Statistical analysis was performed by commercial software (JMP 8.0 SAS Institute Inc.).

Results

In all sleep studies performed at high-altitude, both RB and PB were observed to a variable extent among subjects. At sea level, no respiratory disturbances were observed. PB was commonplace in all subjects at Everest North BC. PB cycle duration, respiratory time and pause duration significantly increased from BC1 to BC2, while no difference in duty cycle was detected (Table 1). At sea level, mean and lower SaO_2 during sleep were 96.8±0.8% and 93.7±0.7% respectively. From BC1 to BC2 mean SaO_2 during wakefulness, the mean higher, and the mean lower SaO_2 significantly increased (Table 1).

RR fluctuated with ventilation, with an increase whenever ventilation was resumed or increased after a respiratory pause or hypoventilation (Fig. 2). The mean RR and SDNN of all subjects were calculated for all overnight cardio-respiratory recordings at SL, BC1 and BC2, and separately during RB and PB cycles at BC1 and BC2. Data showed a mean RR reduction at acute environmental hypoxic exposure that resumed to SL values after 10-day sojourn. This reduction was mostly due by RR during RB while during PB; RR values were not different from SL (Fig. 3). Data showed also an increase of SDNN at high altitude with lower values during RB and significantly higher values during PB (Fig. 4). Figure 5 shows how SDNN was linearly correlated with peak tidal volume during PB (i.e. higher the peak tidal volume, higher the RR variability).

The RR spectral power of HF band expressed as percentage of the total spectral power, and LF/HF ratio are shown in Figure 6. HF power was significantly lower at HA compared to SL mostly due to lower values during PB at both BC1 and BC2. The LF/HF ratio showed higher values during PB. No difference was observed among RB at SL, BC1 and BC2, and between PB at BC1 and BC2. Figure 7 shows the significant relationship between LF/HF and duty ratio.

Discussion

We conducted experiments to study cardiorespiratory interactions during sleep in conditions of environmental hypobaric hypoxia in a group of normal subjects during the 1st and the 10th night at 5,180 m. The 10-day period of acclimatization was associated with an improvement in hypoxemia.

Our results show that at HA, mean overnight RR decreases initially and increases with acclimatization. RR variability (SDNN) did not increase consistently at HA, a decrease in HF (mainly linked to parasympathetic activity) and an increase of LF/HF ratio (mainly linked to sympathetic activity predominance) compared to SL during overnight were observed. These findings as regard spectral behavior are in accordance with previous reports [23-24]. Cornolo et al [24], at 4,350 m above SL reported an increase in LF/HF at day 1-2, which evidences a dominant adrenergic control, mainly due to the greater decrease in HF than LF [18]. Di Rienzo et al. [23] observed that the traditional spectral indexes of HRV significantly changed at 3500 m with respect to SL. These changes are compatible with the aforementioned autonomic response to high-altitude hypoxia. They also observed concomitant decreases in the mean RR value, and a decrease in the HF power (suggestive of a reduction in the parasympathetic drive to the heart) and an increase in the LF/HF ratio, all additional markers of the sympathetic activity predominance.

However, at HA the overnight recording includes both regular and PB that determines a lack of stationarity of RR signal that is required for spectral analysis. Stationarity means that there is no shifting in the base level of the signal; longer is recording, less is stationarity. Hence, the best approach is to divide the recording into short segments and perform analysis on them. At high altitude, spectral indexes have been mainly employed to evaluate the effects of hypobaric hypoxia on HRV at daytime [15-16]. To our knowledge, no previous study has evaluated the effects of PB and RB separately on HRV during sleep in normal subjects with HA induced PB.

Early environmental hypoxic exposure induced a mean RR reduction that resumed after 10-day sojourn. This reduction was mostly due by RR during RB while during PB, RR values were higher. SDNN was similar during RB at HA and during sleep at SL, while it was higher during PB at HA with a significant influence of respiratory amplitude.

HF decreases with HA induced hypoxia as can be observed during overnight analysis. However, if we look at RB and PB separately, this decrease is due to PB and is similar at BC1 and BC2, two different hypoxemic

conditions, while HF during RB at HA is not different from SL. LF/HF had an interesting behavior since it appears that the predominance in sympathetic tone and fall in parasympathetic control induced by hypoxia has not a major result, since the mechanical effect of PB showed a marked effect. Linear correlation between LF/HF and duty ratio confirmed PB influence, i.e. increase of respiratory duration of PB cycle is associated with parasympathetic predominance.

Heart failure patients have a different behavior of HRV during Cheyne-Stokes respiration compared to RB [27-28]. Szollosi et al. [27] found time domain measures of RR variance (SDNN), significantly influenced by breathing condition, showing a marked increase during Cheyne-Stokes respiration compared to stable breathing. Similarly, to our results, they found an increased LF/HF ratio during breathing fluctuations, underlining the effect of breathing condition. Our results confirm this effect by the relationship between LF/HF and duty ratio of PB, i.e. longer the respiratory pause, lower the effect of respiration as highlighted by the lower HF. Leung et al found Cheyne-Stokes respiration accompanied by HR fluctuations with peaks during hyperpnea and reductions during apnea. Inhalation of CO_2 completely abolished apneas and hypopneas, restored RB and eliminated HR fluctuations. Supplemental O_2 at doses sufficient to eliminate O_2 desaturation with persistence of PB resulted in HR oscillation persistence [28]. Similarly Lorenzi-Filho et al. [29] showed that in healthy subjects during voluntary RB and PB, the amplitude of oscillations in HR during periodic breathing increases, and entrains these oscillations at the frequency of the periodic breathing. Hypoxia and CO_2 retention were not involved in this process. Furthermore, the magnitude of the oscillations was proportional to oscillations in ventilation. Similarly, we found in healthy subjects at HA that SDNN was similar to SL during RB and that PB was associated with a significant increase. Our results showed similar behaviour since improvement of SaO_2 from BC1 to BC2 did not determine a significant change in SDNN during sleep RB and PB.

Several factors could influence cardio-circulatory behaviour during the respiratory phase of periodic breathing. Studies in healthy subjects showed HR fluctuations similar to respiratory fluctuations during voluntary normoxic periodic breathing [29]. Hypoxia could also be involved in the increasing HR trend during the respiratory period because it causes HR to accelerate through stretch receptor stimulation while ventilation is maintained (pulmonary inflation reflex) [30]. Similarly, to the respiratory phase, factors like hypoxemia and baroreceptor activity could influence cardio-circulatory behaviour during the respiratory

pause. A possible hypothesis is that hypoxia played a role in the HR decrease, since hypoxia induces bradycardia in the absence of ventilation (diving reflex) [30].

Altogether, the available evidence does not support a major role of hypoxemia in modulating cardiovascular variability. The hypothesis of a tonic as opposed to a phasic effect of hypoxia in cardiovascular modulation during sleep at high altitude can be inferred by the mean RR behaviour.

Conclusion

The present work shows that in healthy subjects, periodic breathing with central apneas increases the amplitude of RR oscillations, and these oscillations are tightly related to respiratory amplitude. Oxygenation does not influence this phenomenon. Therefore, oscillations in ventilation itself should be taken into account when investigating the pathophysiology of HRV. Further investigations are needed to clarify the influence, if any, of sleep stages.

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LEGENDS

Figure 1: Periodic breathing (PB) at Everest North Base Camp (5180m) during sleep from one subject. Arrows indicates respiratory phase (V) and respiratory pause (P) and PB cycle duration (V+P).

Figure 2: RR-interval during regular and periodic breathing at Everest North Base Camp (5180m).

Figure 3: Mean RR interval in the group of 6 subjects during sleep at sea level (SL), Everest North Base Camp (5180m) during the 1st night (BC1), and during the 10th night (BC2); and mean RR interval during sleep regular breathing (RB) and sleep periodic breathing (PB) at BC1 and BC2.

Figure 4: Mean SDNN in the group of 6 subjects during sleep at sea level (SL), Everest North Base Camp (5180m) during the 1st night (BC1), and during the 10th night (BC2); and mean RR interval during sleep regular breathing (RB) and sleep periodic breathing (PB) at BC1 and BC2.

Figure 5: Scattergram of individual data points at Everest North Base Camp (5180m) during the 1st night (BC1) and during the 10th night (BC2) for SDNN during regular breathing (RB) and periodic breathing (PB). The regression line shows a linear correlation between SDNN and peak tidal volume during PB (Vt) measured as % of the closest stable regular breathing preceding PB.

Figure 6: Spectral analysis of heart rate variability at sea level (SL), Everest North Base Camp (5180m) during the 1st night (BC1), and during the 10th night (BC2). High frequency power (HF); Low frequency-to-high frequency ratio (LF/HF). Bars and lines show means ± SD in the group of 6 subjects.

Figure 7: Scattergram of individual data points at Everest North Base Camp (5180m) during the 1st night (BC1) and during the 10th night (BC2) for low frequency-to-high frequency ratio (LF/HF) during periodic breathing (PB). The regression line shows a linear correlation between LF/HF and duty ratio.

Figure
Click here to download Figure: Figure HRV HRV at HA.pptx

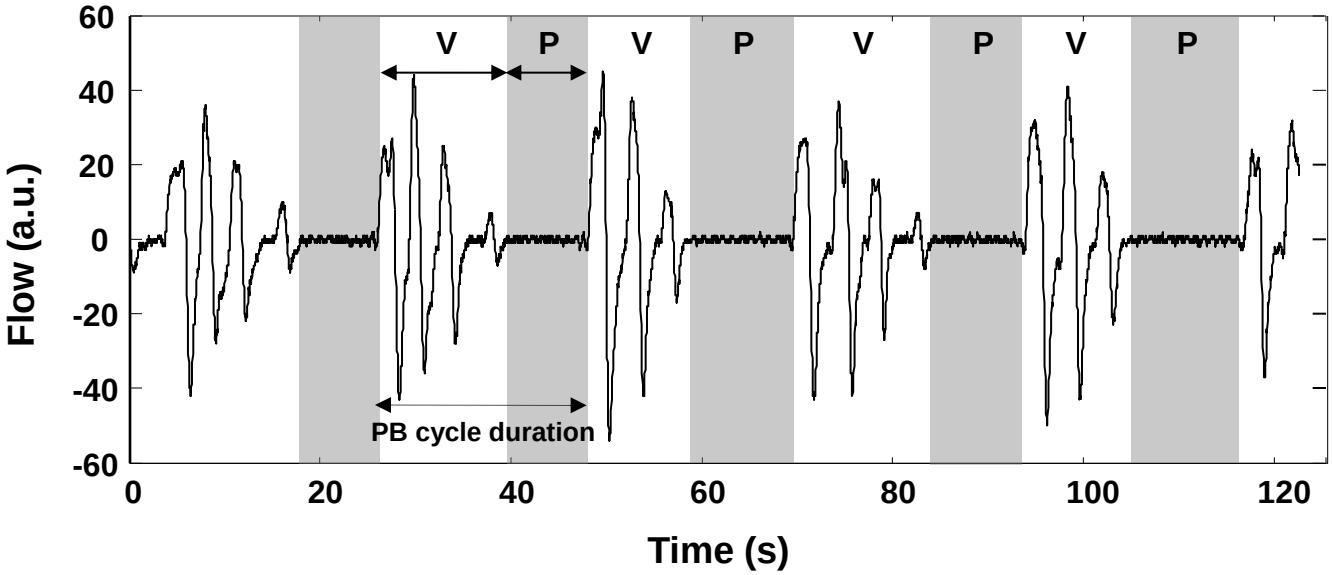
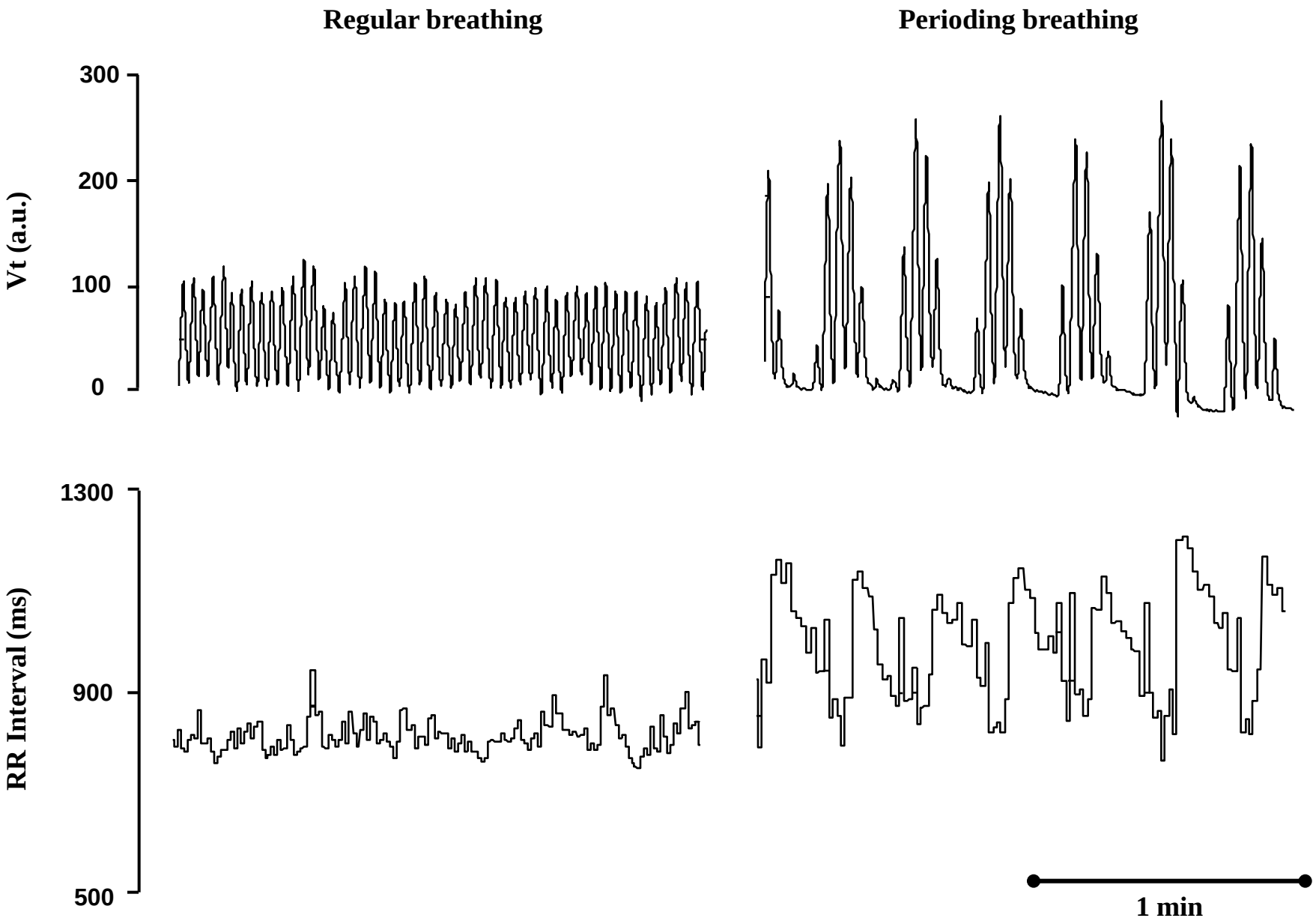


Fig. 1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Perioding breathing
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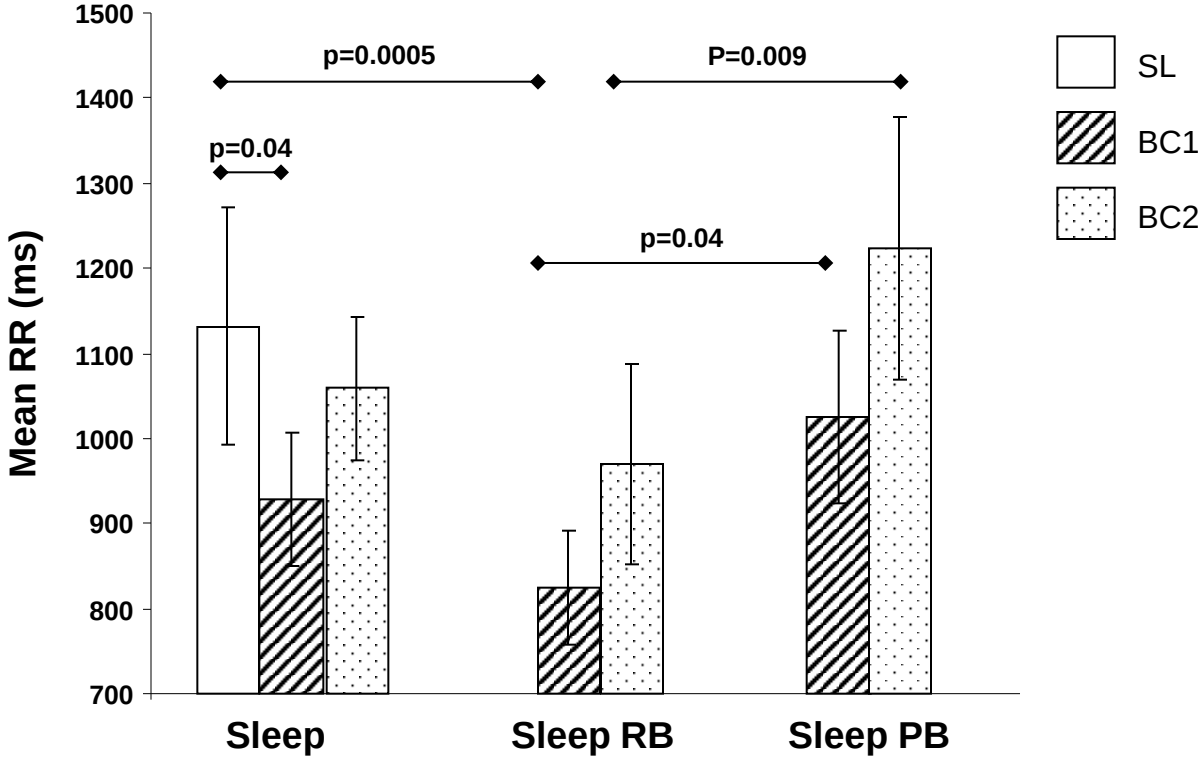
100
0
RR Interval (ms)
1300
900
500
1 min

Fig. 2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1400
1300
1200
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700
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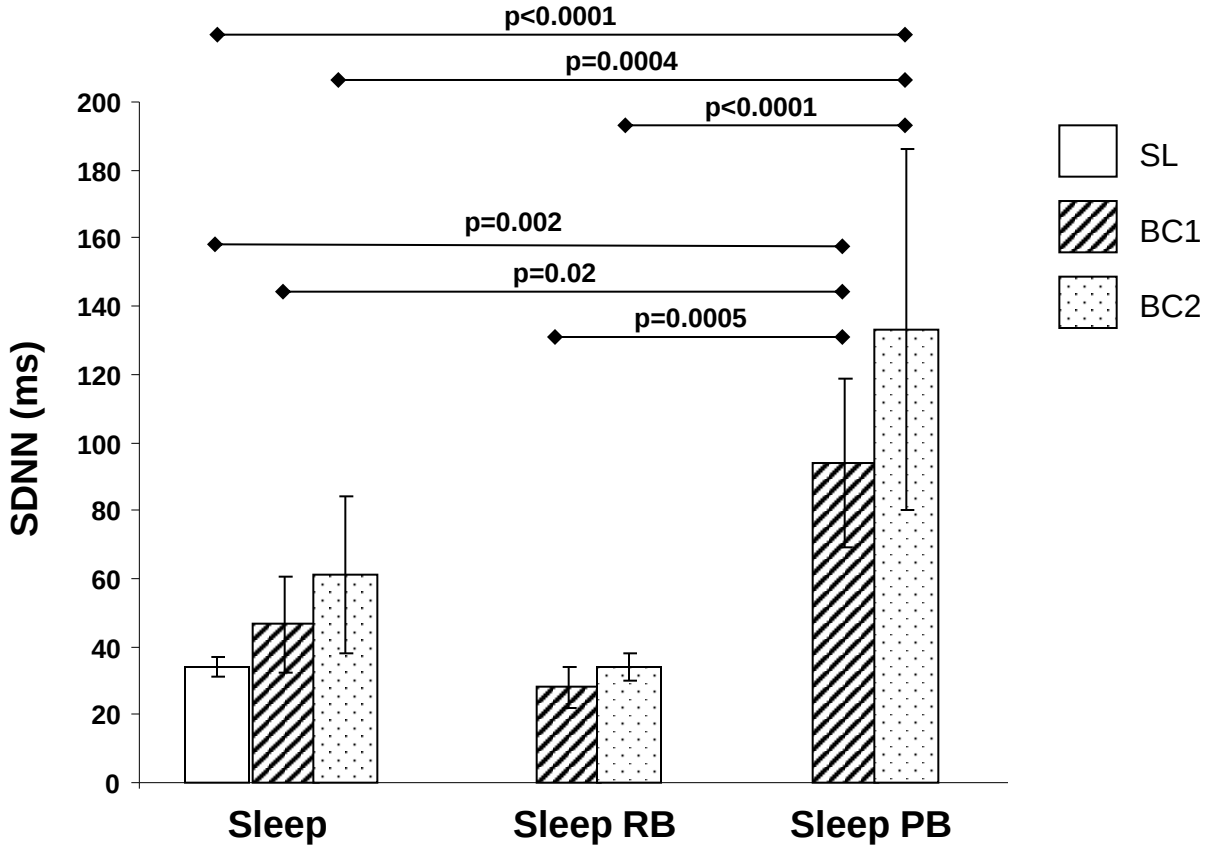
p=0.04
SL
BC1
BC2
Sleep
Sleep RB
Sleep PB

Fig. 3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p<0.0001
p=0.002
p=0.02
p=0.0005
SDNN (ms)
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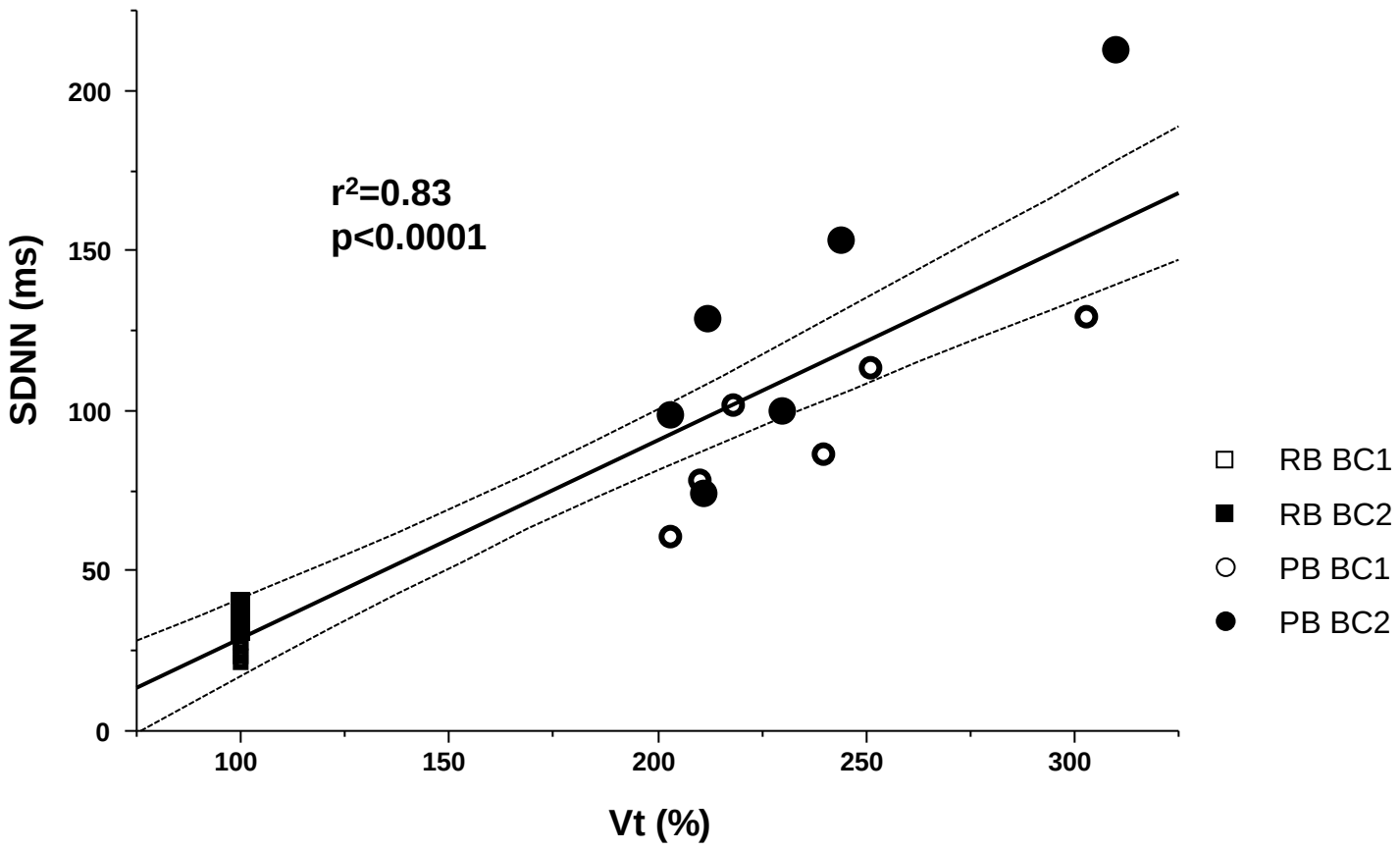
140
120
100
80
60
40
20
0
Sleep
Sleep RB
Sleep PB
SL
BC1
BC2

Fig. 4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Vt (%)
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p<0.0001
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100
150
200
100
150
200
250
300
RB BC1
RB BC2
PB BC1
PB BC2

Fig. 5

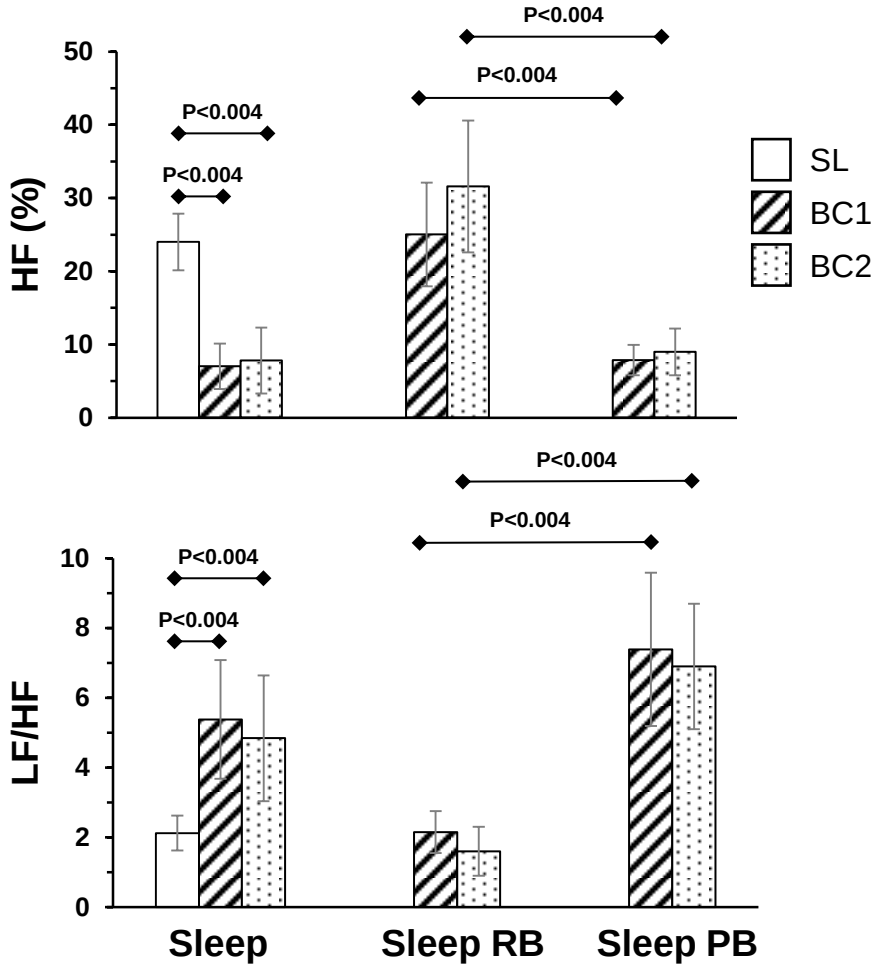
P<0.004
P<0.004
P<0.004
P<0.004
50
40
30
20
10
0
HF (%)
SL
BC1
BC2
P<0.004
P<0.004
P<0.004
P<0.004
10
8
6
4
2
0
LF/HF
Sleep
Sleep RB
Sleep PB

Fig. 6

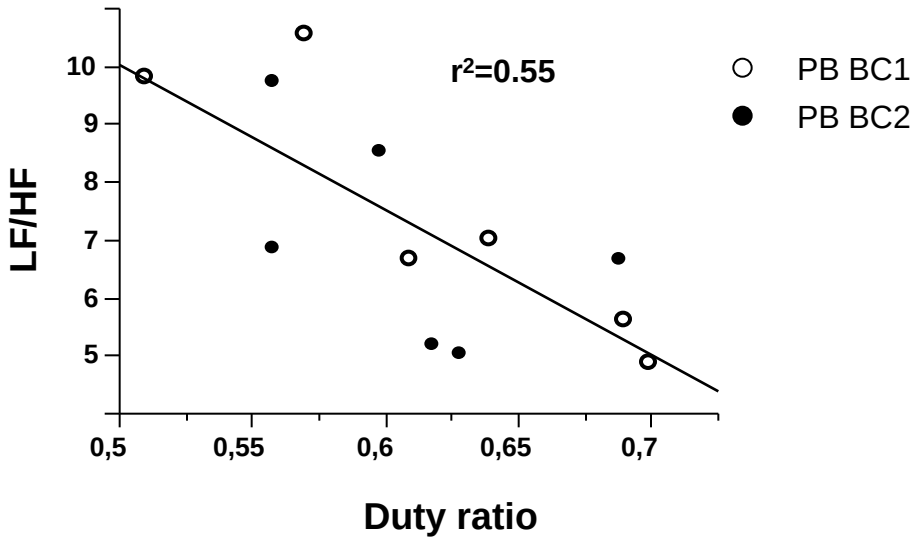

Fig. 7

Table
Click here to download Table: Table 1.doc

Table 1. *Arterial oxygen saturation (*SaO_2*) and periodic breathing (PB) characteristics at high altitude*

	BC1	**BC2**	**P**
Awake SaO_2	79.5 ± 2.4	83.4 ± 1.3	0.016
Mean lower SaO_2 during PB	69.1 ± 2.1	73.8 ± 3.2	0.02
Mean higher SaO_2 during PB	77.4 ± 3.9	82.7 ± 2.3	0.01
Ventilatory time (s)	13.68 ± 1.15	16.74 ± 0.91	<0.0001
Pause duration (s)	8.41 ± 2.22	10.76 ± 2.01	<0.0001
PB length (s)	22.09 ± 2.12	27.50 ± 2.35	<0.0001
Duty ratio	0.62 ± 0.07	0.61 ± 0.04	NS

Values are means ± SD; NS, not significant

Cover Letter

To: Dr. med. Nikolaus Netzer Editor-in-Chief
Sleep and Breathing

Manuscript: **HEART RATE VARIABILITY DURING SLEEP AT HIGH-ALTITUDE: EFFECT OF PERIODIC BREATHING**

Dear Editor-in-Chief,

On behalf of my co-authors, I am submitting you the enclosed original research entitled **"Heart rate variability during sleep at high-altitude: effect of periodic breathing"** for possible publication in **Sleep and Breathing**. We hope it may be of interest to the readers of the journal and suitable for publication.

All authors have read and approved the manuscript and agree with its submission to **Sleep and Breathing**. Our research was aimed to analyse HRV during sleep periodic and regular breathing at high altitude in healthy subjects at two different times of acclimatization.

The manuscript has not been published elsewhere and is not under consideration by other journals.

If accepted in **Sleep and Breathing**, will not be republished in any other journal in the same or similar form.

The authors have no financial or other relationships that might lead to a conflict of interest.

Waiting for your kind reply, we thank you for the consideration.

Sincerely,

Giuseppe Insalaco, MD