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Editorial

Hypoxic Ventilatory Response in Highlander and Lowlander Chinese Patients with Sleep Apnea

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ABSTRACT: Purpose: The aim of the study was to compare Hypoxic Ventilatory Response (HVR) of sleep apnea in Uygur patients stemming from higher altitude and Chinese Han patients from sea level. Patients and Methods: 276 subjects with or without snoring from the Karamay community were recruited. 226 subjects (n = 71 Han OSA patients, n = 75 Uygur OSA patients, n = 52 for Uygur control subjects without OSA, n = 28 Han control subjects without OSA) were matched for age and gender. All patients were assessed via polysomnography (PSG). Lung function was assessed. Apnea-hypopnea index (AHI), mean SaO_2 ($MSaO_2$%), lowest SaO_2 ($LSaO_2$%), the number of desaturations ≥4% per hour (ODI4), FEV1/FVC ratio, HVR, $\triangle VE/\triangle SaO_2$ and the pulse responses to hypoxia changes ($\Delta Pulse/\Delta SaO_2$) were calculated. A multiple logistic regression using a binary outcome for HVR was applied. Results: (1) In control subjects without OSA, those living at high altitude (Uygur) had a lower HVR than control subjects living at sea level (Han) [$-0.35 L \cdot min^{-1}$ per $\%SpO_2$(-0.49 to -0.20 $L \cdot min^{-1}$ per $\%SpO_2$) vs.-0.44 $L \cdot min^{-1}$ per $\%SpO_2$(-0.55 to -0.21 $L \cdot min^{-1}$ per $\%SpO_2$)]. (2) Compared to patients with OSA living at sea level (Han), those OSA patients living at high altitude (Uygur) had a higher neck circumference [43 cm (range 39–45 cm) vs. 42 cm (41–46) cm], higher abdominal circumference [110 cm (102–120 cm) vs. 101 cm (98–111 cm], higher $LSaO_2$ [81% (72–85%) vs. 76% (68–81%)], lower AHI [26 events/h (16–43 events/h) vs. 36 events/h (24–62 events/h)] and lower ODI4 [15/h (7–29/h) vs. 37/h (20–54/h)]. (3) Considering patients with mild OSA, those who lived at high altitude (Uygur) had a weaker HVR compared to Han patients [-0.31 $L \cdot min^{-1}$ per $\%SpO_2$(-0.42 to -0.20 $L \cdot min^{-1}$ per $\%SpO_2$) vs.-0.47 $L \cdot min^{-1}$ per $\%SpO_2$(-0.59 to -0.21 $L \cdot min^{-1}$ per $\%SpO_2$)]. However, in moderate and severe OSA the difference in HVR between people living at high and low altitudes was not significant. Conclusion: In people living at high altitude (Uygur) compared to sea level (Han), HVR is weaker both in control subjects and those with mild OSA, but this difference between populations living at different altitudes in those with moderate and severe OSA is not obvious.

Keywords: Hypoxic ventilatory response (HVR); Obstructive sleep apnea (OSA); Polysomnography (PSG); Apnea-hypopnea index (AHI); Hypoxic pulse response (HPR)

1. Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by upper airway obstruction during sleep. Repeated nocturnal apnea and hypopnea at night leading to intermittent hypoxia and hypercapnia affect ventilatory control in patients with OSA [1–3]. In the time course of an apnea event, due to a stimulation of the respiratory centers by hypoxia and hypercapnia, the person briefly awakens and hyperventilates, such that the hypoxia and hypercapnia are corrected. In addition to upper airway obstruction, instability of ventilatory control, such as an altered HVR, hypercapnia, or metabolic acidosis, has been suggested to be involved in the pathogenesis of sleep disordered breathing (SDB) [4,5].

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Some studies report in OSA that with the progression and increase in the degree of hypoxia and hypercapnia, severe cases can develop respiratory failure [6,7]. The HVR is a classic reflex response to sensory input from peripheral arterial chemoreceptors. The carotid bodies are the most important arterial chemoreceptor for acute HVR in humans and most animals, and their adequate and physiological stimulus is PaO2 [8,9].

The HVR can be assessed by quantifying the sudden increase in minute ventilation during a short exposure to mild hypoxia, such as a 5-min exposure. Exposure to several short episodes of hypoxia can augment the HVR [10–14]. The amplified response to intermittent hypoxia is sustained for a long time even after the removal of the particular exposure [15]. Moreover, studies have found that the HVR is significantly greater in the morning compared to the evening [16]. Evening-to-morning variations in HVR might be important due to a possible relationship between these phenomena and modifying breathing stability in OSA. These phenomena have been observed in a wide variety of species, including healthy humans and those suffering from sleep apnea [17].

Previous studies have compared the HVR between Tibetan and Andean highland residents. Tibetans have likely lived the longest at high altitudes, followed by Andeans, Europeans, and finally Han (ethnic Chinese) who mostly live at sea level. Male lifelong Tibetan residents of 3658 m had higher minute ventilation and similar SaO_2, $PETCO_2$, and $PaCO_2$ when compared with acclimatized Han individuals. Female Tibetans also ventilate as much as acclimatized Han newcomers at 3658 m [18]. Curran et al. [19] found that the Tibetan-Han individuals were similar to Tibetans in terms of their ventilation but resembled Han individuals with respect to HVR, suggesting that different genetic factors influence ventilation and HVR in these highland residents. Human and experimental animal studies demonstrate that inter-individual and genetic factors affect acute HVR and likely modify acclimatization and the hyperventilatory response to high altitude. Studies in Tibetan high-altitude residents have shown that lifelong high-altitude residents ventilate less than acclimatized newcomers due to acquired “blunting” of hypoxic ventilatory responsiveness18. However, the mechanisms responsible for ventilatory roll-off, hyperoxic hyperventilation, and acquired blunting of the HVR are poorly understood, especially as they pertain to high-altitude residents. Short-term (acclimatization, developmental) and long-term (genetic) responses to high altitude affect the HVR.

Many people are living in the Northwest Plateau of China, such as Tibetans living in the Qinghai-Tibet Plateau (average altitude 3500 m). Most of the Uygur population used to live in Kashgar and Hetian in the south of China, close to the Pamir Plateau, where the altitude ranges from 1400 m to 3000 m (average altitude 2500 m). Han people historically lived in the low-altitude and coastal regions (at sea level) of China. More recently, many Han and Uygur people have resided in Karamay (altitude 500 m) for more than 20 years. However, no comparison of HVR between Uygur and Han people has been performed until now.

We hypothesized that there are differences in HVR between Han and Uygur people with or without OSA, which are likely related to the severity of OSA, altitudes, and hypoxia genes.

2. Patients and Methods

2.1. Participants

This is a cross-sectional study based on the Karamay community. All participants are immigrants of Karamay for at least 10 years. We recruited 276 subjects with or without snoring from the Karamay community. The criteria for OSA were an apnea-hypopnea index (AHI) $\geq$ 5/h; 146 subjects had confirmed OSA by polysomnography (PSG). Furthermore, 80 subjects had no OSA. Patients with neurological, cardiac, chronic respiratory diseases, heart failure, stroke, and non-obstructive sleep apnea were excluded. Thirteen subjects with chronic obstructive pulmonary disease (COPD) were also excluded, and 39 subjects who did not complete the HVR test were also excluded. Finally, 226 subjects (71 Han OSA patients, 75 Uygur OSA patients, 52 normal Uygur subjects, 28 normal Han subjects) were included. A flow chart of study participants is depicted in Figure 1.

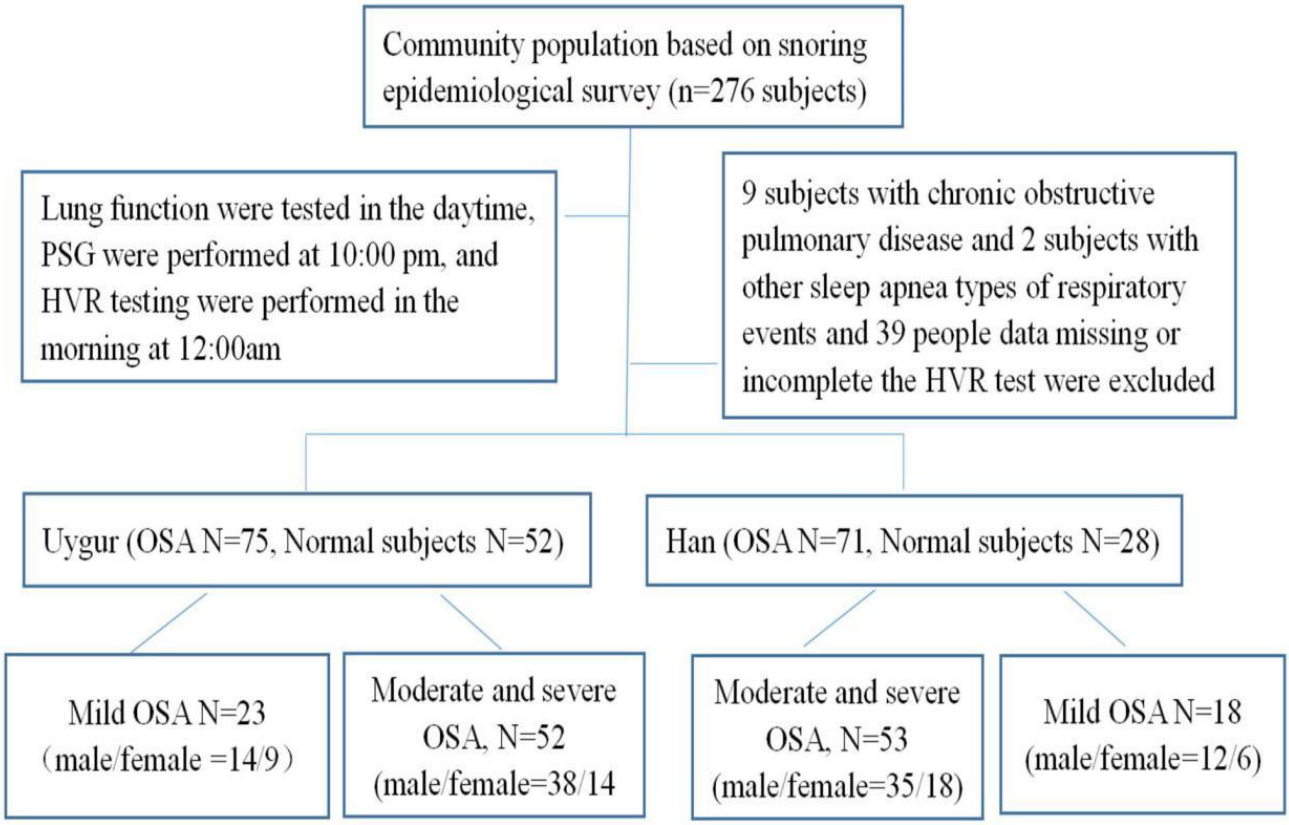


Figure 1. The flow chart of the study protocol.

2.2. Polysomnography

Uygur and Han patients aged > 18 years at Karamay Central Hospital (Xinjiang, China; altitude: 500 m) with clinically confirmed OSA were requested to participate in this study from January 2015 to December 2015. The study was approved by the hospital ethics committee (2013.LL−1). Written informed consent was obtained from all subjects enrolled in this study. Diagnosis of sleep apnea was confirmed according to the International Classification of Sleep Disorders (ICSD) II criteria [20] based on clinical assessment and PSG recordings. Cardiorespiratory PSG was performed according to international standards with a multi-channel physiological recorder (Embla Systems Inc. PSG N7000, San Carlos, CA, USA). Scoring rules were in accordance with the 2007 American Academy of Sleep Medicine Manual [21], defining apneas as a reduction of ≥90% of the baseline nasal airflow with a duration of at least 10 s. Hypopneas were defined as a nasal flow reduction of 30–90% of the baseline, lasting at least 10 s accompanied by an oxygen desaturation of ≥4%. Obstructive sleep apnea was classified per the apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour of monitoring: No OSA (AHI: <5); mild OSA (AHI: 5–14.9); moderate OSA (AHI: 15–29.9); and severe OSA (AHI: ≥30).

2.3. Assessment of Hypoxic Ventilatory Response and Hypoxic Pulse Response

Ventilatory response assessment was performed between 10:00 am and 12:00 pm. Responses to progressive hypoxia were assessed using the rebreathing technique according to Rebuck and Campbell [22]. End-tidal CO_2 ($ETCO_2$), SaO_2, and tidal volume were recorded using a blood gas analyzer (Model 5200 oximeter, Ohmeda, USA). Data were recorded at 10-second intervals. The breathing system used in this study consisted of a closed loop of pipes attached to a face mask, which allowed for control of inspired gases and measurement of $EtCO_2$, respiratory rate, tidal volume, and SpO_2. For the assessment of response to hypoxia, a poikilocapnic study was conducted. Participants rebreathed exhaled air that was filtered through a CO_2 absorbent (soda lime) to prevent CO_2 accumulation. The tests were stopped when the SpO_2 reached 75%. During the hypoxic rebreathing tests, $ETCO_2$ dropped on average from 5.6 ± 0.7% at 95% saturation to 4.8 ± 0.6% at 75% saturation ($p < 0.01$), indicating that the hypoxic testing was poikilocapnic and CO_2 accumulation was prevented. VE (minute ventilation) and pulse were plotted against the decline

in SaO_2 starting from 90% (during hypoxic testing). A linear slope was assumed, and the responsiveness to hypoxia was noted as the slope of the linear regression lines: VE/SaO_2 and $pulse/SaO_2$.

2.4. Statistical Analysis

Continuous variables were described as mean ± standard deviation (SD) or median with interquartile range (IQR). Normality was tested using the Kolmogorov-Smirnov test. Skewed variables were expressed as medians (interquartile range). For normally distributed and skewed variables, the *t*-test or non-parametric Wilcoxon test was used for the comparison of continuous parameters, respectively. Statistical comparisons were performed using the chi-square test or non-parametric test. Additionally, one-way ANOVA or K-independent samples testing for repeated measures was used to compare differences among groups. Hypoxic ventilator responses and AHI values were log-transformed to achieve normal distribution prior to statistical analysis. *p*-values were calculated for the transformed comparisons, and differences were considered significant at a level of $p < 0.05$. Multivariate logistic regression analysis was conducted to identify factors associated with HVR using logistic regression. Odds ratios and their 95% confidence intervals were reported. *p*-values less than 0.05 were considered to indicate statistically significant differences. Data analysis was performed using Statistical Package for Social Sciences software (SPSS version 19.0, Chicago, IL, USA).

3. Results

3.1. Description of Normal Subjects and Patients with OSA

Among the 146 patients with OSA, there were 71 Han patients and 75 Uygur patients. Additionally, there were 80 normal Han control subjects and 80 normal Uygur control subjects who were matched for age and BMI. The basic demographic characteristics, AHI, parameters of nocturnal hypoxia, HVR, and HPR are presented in Table 1. Among the control subjects, Uygur people had a weaker hypoxic responsiveness than Han people ($p < 0.05$).

Table 1. Characteristics of Included HVR in Uygur and Han with OSA and normal subjects.

	Han Normal Subjects (*n* = 28)	**Han OSA (*n* = 71)**	**Uygur Normal Subjects (*n* = 52)**	**Uygur OSA (*n* = 75)**	***p*-Value**
Gender, male/female	19/9	47/24	28/24	52/23	0.156
age, years	48 ± 8	51 ± 9	50 ± 7	52 ± 8	0.074
BMI, kg/m^2	28 ± 4	29 ± 5	29 ± 4	32 ± 4 [abc]	0.000
NC, cm	40(38, 43)	42(41, 46) [a]	40(38, 43)	43(39, 45) [ac]	0.005
AC, cm	98(94, 110)	101(98, 111)	102(95, 111)	110(102, 120) [abc]	0.015
AHI, events/h	4(3, 6)	36(24, 62)	3(2, 6)	26(16, 43) [abc]	0.000
ODI_4, events/h	7(4, 13)	37(20, 54)	3(0, 5)	15(7, 29) [abc]	0.034
$MSaO_2$, %	94(92, 95)	92(91, 94)	94(93, 95)	93(92, 94) [ac]	0.043
$LSaO_2$, %	85(80, 86)	76(68, 81)	87(83, 89)	81(72, 85) [abc]	0.000
FEV_1/FVC, %	85(80, 86)	81(78, 85)	83(79, 85)	82(79, 85)	0.935
Sleep efficiency, %	83.4 ± 11.6	82.0 ± 10.7	77.0 ± 14.1	81.1 ± 8.5	0.152
Baseline $EtCO_2$ (%)	4.75 ± 0.63	5.02 ± 0.46	4.83 ± 0.76	5.28 ± 0.58	0.264
HVR, $\Delta V_E/\Delta SaO_2$, $L \cdot min^{-1}$ per $\%SpO_2$	−0.44(−0.55, −0.21)	−0.38(−0.52, −0.23)	−0.35(−0.49, −0.20) [ab]	−0.30(−0.40, −0.19) [abc]	0.022
HPR, $\Delta Pulse/\Delta SaO_2$, events$\cdot min^{-1}$ per % SpO_2	−0.98(−2.14– −0.24)	−0.79(−0.94, −0.51)	−0.99(−1.15, −0.69)	−0.86(−1.13, −0.57)	0.072

Notes: Data are means ± SE or median (25th,75th); Compared with the Basic Demographic Characteristics, AHI, noctnalhypoxia, HVR and HPR Included Participants among four groups(Han normal subjects, Uygur normal subjects, Han patients with OSA, and Uygur patients with OSA).significant differences with a Superscript of a, b and c. Abbreviations: BMI: body mass index; NC: Neck circumference; AC: Abdominal circumference; AHI: apnea hypopnea index; ODI_4:the number of desaturations ≥ 4% per hour; $MSaO_2$: mean SaO_2; $LSaO_2$: lowest SaO_2; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; FEV_1/FVC ratio; Δ: change in; VE: minute ventilation, SaO_2: oxygen saturation; HVR, $\Delta V_E/\Delta SaO_2$:change in minute ventilation/change in oxygen saturation, HPR, $\Delta Pulse/\Delta SaO_2$:change in minute pulse/change in oxygen saturation. [a] vs. Han normal subjects, $p < 0.05$; [b] vs. Han OSA, $p < 0.05$; [c] vs. Uygur normal subjects, $p < 0.05$.

3.2. HVR in Patients with Mild OSA

The general condition of mild OSA patients, including Han and Uygur individuals, was matched for age, sex, and BMI. The results comparing nocturnal hypoxia and HVR are presented in Table 2. Uygur patients with mild OSA had a weaker HVR than Han patients ($p < 0.05$).

Table 2. Comparison of HVR between Uygur and Han with mild OSA.

	Han (*n* = 18)	**Uygur (*n* = 23)**	***p*-Value**
Gender, male/female	12/6	14/9	0.524
age, years	49 ± 8	50 ± 9	0.470
BMI, kg/m^2	28 ± 5	30 ± 4	0.066
NC, cm	41(38, 43)	40(38, 44)	0.356
AC, cm	99(91, 110)	102(96, 111)	0.075
AHI, events/h	8(6, 11)	6(3, 15)	0.910
ODI_4, events/h	9(6, 16)	5(2, 12)	0.525
$MSaO_2$, %	94(92, 95)	94(93, 95)	0.896
$LSaO_2$, %	85(79, 90)	83(79, 85)	0.847
FEV_1/FVC %	85(80, 86)	82(72, 90)	0.896
Sleep efficiency, %	82.7 ± 9.2	80.5 ± 10.6	0.432
Baseline $EtCO_2$ (%)	5.11 ± 0.38	5.32 ± 0.50	0.143
HVR, $\Delta V_E/\Delta SaO_2$, L·min^{-1} per %SpO_2	−0.47(−0.59, −0.21)	−0.31(−0.42, −0.20) [b]	0.023
HPR, ΔPulse/ΔSaO_2, events·min^{-1}·per %SpO_2	−0.96(−1.24, −0.69)	−0.98(−1.16, −0.64)	0.426

Notes: Data are means ±SE or median (25th, 75th) from Table 2, which shows a significant difference between Han and Uygur with mild OSA in HVR, [b] vs. Han (OSA) $p < 0.05$.

3.3. HVR in Patients with Moderate and Severe OSA

The general condition of moderate and severe OSA patients, including Han and Uygur individuals, was matched for age and sex. Nocturnal hypoxia and HVR were compared and presented in Table 3. It appears that the difference in HVR between Uygur and Han patients with moderate and severe OSA seemed to have disappeared.

Table 3. Comparison of HVR between Uygur and Han with moderate and severe OSA.

	Han (*n* = 53)	**Uygur (*n* = 52)**	***p*-Value**
Gender, male/female	35/18	38/14	0.450
age, years	49 ± 10	51 ± 7	0.058
BMI, kg/m^2	29 ± 5	32 ± 4b	0.010
NC, cm	43(41, 46)	43(40, 45)	0.540
AC, cm	101(98, 111)	110(102, 121) [b]	0.011
AHI, events/h	36(24, 62)	30(23, 50)	0.222
ODI4, events/h	37(20, 54)	20(6, 41) [b]	0.008
$MSaO_2$, %	92(91, 94)	93(92, 94)	0.207
$LSaO_2$, %	76(68, 81)	79(70, 85) [b]	0.045
FEV1/FVC %	81(78, 85)	82(79, 85)	0.542
Sleep efficiency, %	80.7 ± 10.7	80.4 ± 10.5	0.947
Baseline $EtCO_2$ (%)	5.36 ± 0.19	5.65 ± 0.35	0.275
HVR, $\Delta VE/\Delta SaO_2$, L·min^{-1} per % SpO_2	−0.38(−0.52, −0.24)	−0.35(−0.49, −0.16)	0.409
HPR, ΔPulse/ΔSaO_2, events·min^{-1}·per % SpO_2	−0.80(−0.94, −0.51)	−0.89(−1.11, −0.57)	0.176

Notes: Data are means ± SE or median (25th,75th) from Table 3, it is showed significant difference between Han and Uygur with moderate and severe OSA in BMI, AC, ODI4 and $LSaO_2$. [b] vs. Han(OSAHS) $p < 0.05$.

3.4. Regression: Related Factors with HVR

Table 4 presents the results of multiple logistic regression analyses performed on HVR as a binary outcome using normal and abnormal reference values. The cut-off points for abnormal outcomes were defined as values below <−0.56 and above >−0.14. The normal reference value was determined to be −0.35 ± 0.21. The 95% two-sided reference value range was calculated as x ± 1.96 SD. This analysis aimed to identify independent predictors, employing forward stepwise methods with Wald Chi-square statistical tests. Ten predictors were initially entered into the model using the

stepwise technique. Eventually, only AHI, sex, and NC remained in the final model, indicating that OSA severity, sex, and neck circumference were predictors of HVR.

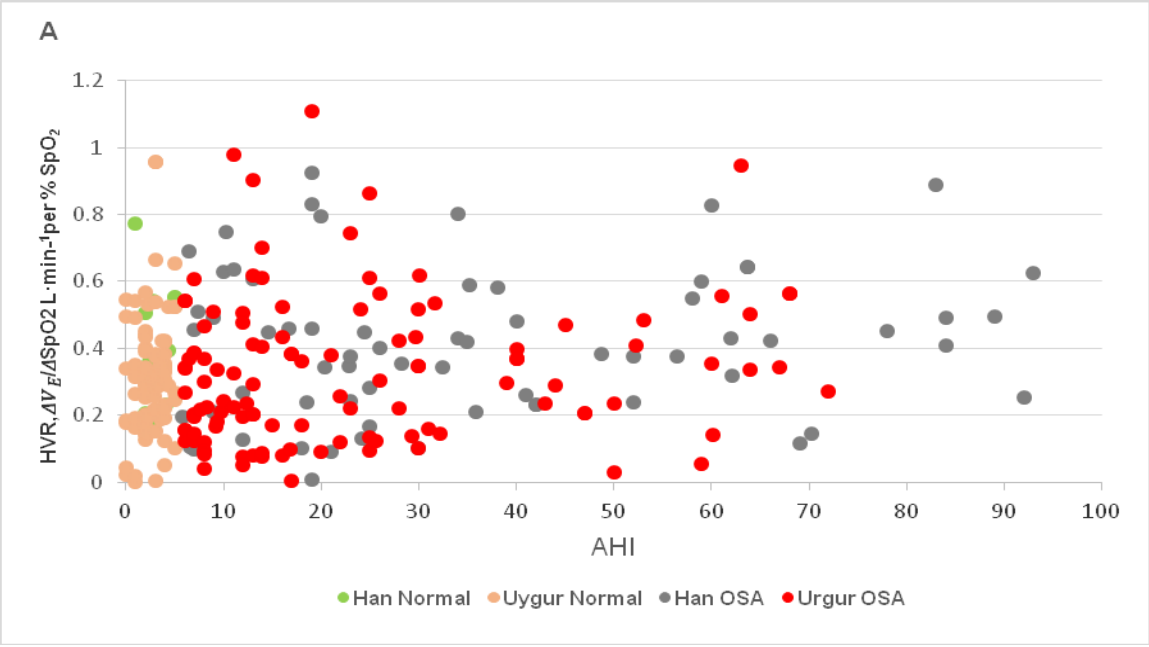
Table 4. Multivariate logistic regression of factors predictive of HVR.

	Regression Coefficient(B)	Wald	Model OR（95% Confidence Interval）	*p*-Value
AHI, evens/h				
<5	1.505	5.457	4.502(1.274–15.909) *	0.019
5–15	0.144	0.088	1.155(0.446–2.991)	0.767
16–29	−0.093	0.036	0.911(0.349–2.381)	0.849
≥30	1(reference)			
Gender				
Male/female	−1.201	4.544	0.301(0.100–0.908) *	0.033
neck- circumference	0.158	4.437	1.171(1.011–1.356) *	0.035

Notes: n = 226 adjusted for the confounding effects of baseline characteristics, including age, gender, ethnicity (Han and Uygur), body-mass index (normal, overweight, obese), neck-circumference, waist-circumference (Small, Medium, Large), OSA severity [mild OSA (AHI5–14.9); moderate OSA (AHI 15–29.9); severe OSA (AHI ≥ 30)]. Mean SaO_2 ($MSaO_2$) and Lowest SaO_2 ($LSaO_2$). * $p < 0.05$ showed that AHI, Gender and NC were predictive for HVR differences.

3.5. HVR and HPR among Normal Subjects and Patients with OSA

The HVR and HPR of patients with OSA and normal subjects were compared. It was found that there was a decrease in HVR in Uygur individuals with OSA and Uygur individuals without OSA compared to Han individuals with OSA and Han individuals without OSA, respectively ($p < 0.05$) (Figure 2A). Additionally, there was a decrease in HPR in both Han and Uygur individuals with OSA compared to Han and Uygur normal subjects, but the difference was not significant (Figure 2B).



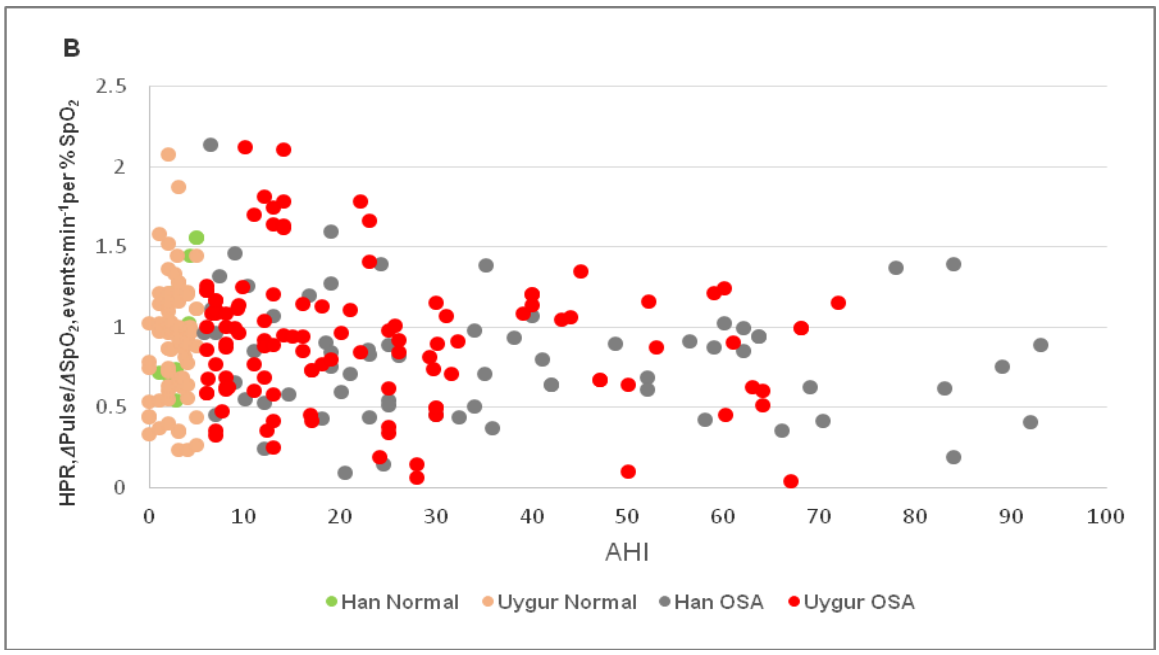


Figure 2. (**A**) Comparison of HVR among Han Normal, Uygur Normal, Uygur OSA, and Han OSA. Notes: The data show a decrease of HVR in Uygur OSA and Uygur Normal compared with Han OSA and Han normal subjects, respectively (red dots and yellow dots vs. gray dots and green dots. p = 0.022). (**B**) Comparison of HPR among Uygur Normal, Han Normal, Uygur OSA, and Han OSA. Notes: The data show a decrease of HPR in Uygur and Han OSA compare with Uygur and Han Normal subjects (red and gray color vs. yellow and green color). Abbreviations: HVR: Hypoxic ventilatory response; HPR: Hypoxic pulse response; OSA: Obstructive sleep apnea.

4. Discussion

The main findings from this study were as follows:

Compared to Han patients, Uygur patients with mild OSA had reduced HVR. Surprisingly, this difference was not observed in those with moderate and severe OSA in both Han and Uygur groups. We also found that the pulse responses to hypoxia were decreased in Han and Uygur patients with OSA. Regarding our hypothesis, we found that Uygur patients with OSA had higher BMI, neck circumference (NC), and abdominal circumference (AC) than Han patients with OSA. However, OSA in Han patients was more severe than in Uygur patients, and the severity of OSA could not be solely explained by BMI, NC, and AC. The difference in HVR between Han and Uygur patients may be attributed to OSA severity, living environment altitude, certain genes that affect maxillofacial structures (Han people tend to have a smaller jaw and mandibular retraction compared to Uygur people), and lifestyle factors (e.g., the staple food of Uygur people is beef, mutton, and some vegetables). Our study indicates that the degree of obesity is higher in Uygur people compared to Han people, and the AHI and nocturnal hypoxemia are more severe in Han patients with OSA compared to Uygur patients. These differences may be caused by promoting an unnecessarily high flow response in the upper airway opening, which may perpetuate cycling and exacerbate OSA [23]. However, further confirmation is needed. The habitation altitude of Uygur people differs from that of Han people, which may be related to the extent, duration, and exposure to hypoxia, as well as diseases associated with sustained and intermittent hypoxia (such as chronic obstructive pulmonary disease combined with OSA). Additionally, HVR may be limited to individuals who have not been previously exposed to intermittent hypoxia (healthy individuals) or individuals exposed to mild intermittent hypoxia (people with mild sleep apnea). In contrast, HVR and upper airway muscle activity can be induced in individuals exposed to severe forms of intermittent hypoxia for a long period of time (e.g., untreated older individuals with severe sleep apnea living at high altitudes). If carbon dioxide levels are not maintained, exposure to intermittent hypoxia can increase breathing instability, possibly due to enhanced chemoreflex sensitivity, as reported by Gold et al. [24]. However, there are genetic differences in HVR among individuals [25]. Our study has shown that HVR is weaker in Uygur patients compared to Chinese Han patients with sleep apnea. Previous studies, as mentioned by Lorna G. Moore et al.18, focused on lifelong high-altitude residents or immigrants from high-altitude areas. In this study, the living altitudes between Han and Uygur people varied from sea level to 2500 m. On the other hand, Karamay is a newly established city, and Uygur people migrated from high-altitude areas (average altitude: 2500 m) to Karamay (500 m) about 20–30 years ago. However, Han people are accustomed to living in low-altitude areas (sea level) and migrated to

Karamay over 30 years ago. HVR differences between groups are influenced by genetic factors, and varying degrees of admixture with lowland groups may be a source of variation in HVR. The contribution of environmental factors and interactive genes in response to high altitude (continuous hypoxia) and OSA severity (intermittent hypoxia) likely explain this phenomenon.

Weil et al. [25] conducted the first measurements of HVR in lifelong residents of Leadville, Colorado (3100 m) using a progressive, isocapnic test. When studied shortly after descending to 1600 m, lifelong male residents had lower HVR and lower hypercapnic ventilatory response (HCVR) compared to shorter-term residents at 3100 m or permanent residents at lower altitudes. In our study, we found that the level of end-tidal CO_2 ($EtCO_2$) at the end of the study was associated with the response to hypoxia. Both Han and Uygur OSA patients showed higher $EtCO_2$ levels than normal subjects, but there were no differences among the four groups. During the test, CO_2 accumulation was prevented. Lahiri et al. [26] found that hypercapnia 2 mmHg above the eucapnic $PETCO_2$ significantly decreased HVR in lifelong Andean high-altitude residents, while it increased HVR in acclimatized newcomers. This likely explains the lower HVR in Andeans compared to Tibetans. Beall et al. [27] discovered that the hypercapnia present in testing conditions may have depressed HVR to an extent that it was not possible to detect an age-related decline. This suggests that different individuals may differ in terms of the inhibitory effect of $PETCO_2$ on HVR. The duration of hypoxic testing may also be important. Sugimori et al. [28] found that test duration affects HVR differently in high responders compared to low responders, with a shorter (3–5 min) test underestimating HVR in high responders and overestimating it in low responders. Longer tests allow for more ventilatory measurements, standardize the magnitude of hypoxic stimulus among subjects, and better control for isocapnia. In our study, the HVR test lasted for approximately 3–6 min, and although CO_2 accumulation was prevented, the duration of the test and $PaCO_2$ (such as $ETCO_2$ or transcutaneous carbon dioxide) could affect HVR. At sea level, hypoxia is relatively rare for healthy individuals. However, it is often observed in various clinical conditions. Depression of HVR has been observed in individuals native to high altitudes. People living in or visiting high altitudes experience persistent hypoxia. On the other hand, those who have lived at very high altitudes for extended periods do not show increased hemoglobin concentration as a possible response to increased hypobaric hypoxia. This difference may indicate that adaptation through increased hemoglobin concentration to enhance the blood's oxygen-carrying capacity may not be an optimal solution for prolonged exposure to hypoxia. This is strongly associated with diseases such as acute mountain sickness (AMS) and/or chronic mountain sickness (CMS). The prevalence of CMS is significantly lower among Tibetans compared to Han people or Andeans at similar altitudes. This evidence suggests that Tibetans are better adapted than other populations [29]. CMS is associated with increased mortality and higher susceptibility to cardiac consequences and stroke in patients with moderate-to-severe pulmonary hypertension [30–32].

Based on the findings of this study, we hypothesize that HVR is influenced by the ethnic background and adaptation to different altitudes. We also propose that HVR may be associated with AHI values and sex, while remaining independent of age and BMI. One study discovered that individuals with positive human leukocyte antigen (HLA)-DQB1*0602 status had lower HVR, suggesting the involvement of genetic predisposition [33]. However, a recent study showed that an increase in HVR was only associated with sex and not with HLADQB1*0602. Specifically, HVR was found to be higher in men compared to women [34]. Additionally, we were surprised to find that there was no significant difference in pulse responses to hypoxia between Han and Uygur patients with OSA, although these responses were lower in OSA patients compared to normal subjects. Further research is necessary to validate this finding. Parts of the study had been presented at the annual workgroup meeting on sleep disordered breathing by the German Society for Pneumology. The abstract for the oral presentation had been published in the journal Pneumology [35].

5. Limitations

Several limitations need to be taken into account in this study. Firstly, we did not perform hypercapnic responsiveness (HCVR) measurements. Therefore, the difference in HCVR between Han and Uygur individuals with or without OSA remains unclear. Secondly, the HVR measured in this study relies on the CO_2 responsiveness of both central and peripheral chemoreceptors. The ventilatory response to hypoxia is influenced by $PaCO_2$ levels, leading to the typical isocapnic measurement of HVR, where CO_2 accumulation is prevented. Thirdly, the sample size in this study was relatively small.

6. Conclusions

The main finding of the study revealed that individuals with OSA living in high-altitude to low-altitude regions exhibit a diminished response to hypoxia compared to those with OSA residing at sea level. However, this difference was only observed in individuals with mild OSA. Interestingly, the severity of OSA is greater in Han people than in Uygur people, yet the HVR is weaker in Uygur individuals. This phenomenon can be attributed to differences in residing altitudes, duration of residency in low and high-altitude areas, and variations in maxillofacial structures between Uygur and Han populations. It is important to note that HVR is significantly influenced by environmental and genetic factors, as well as the severity of OSA.

Author Contributions

Z.-M.H., X.-L.J., F.H., T.P. conceived or designed the study. X.-S.D., Q.-L.Z., M.-R.H., P.D. acquired, analyzed, or interpreted data. Z.-M.H., X.-L.J. drafted the manuscript and revised it critically for important intellectual content. T.P. approved the final version for publication and agreed 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 were appropriately investigated and resolved.

Ethics Statement

All procedures carried out in studies involving human participants complied with the ethical standards of the institutional and national research committees, as well as with the 1964 Helsinki Declaration and its subsequent amendments or similar ethical standards. The study was submitted to the Ethics Committee of Karamay Central Hospital (Number 2013.LL-1) and was approved on 31 December 2013.

Informed Consent Statement

All patients signed the informed consent form.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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