

Exaggerated respiratory chemosensitivity and association with Sa_O₂ level at 3568 m in obesity

Ri-Li Ge^b, J.A. Stone^a, B.D. Levine^a, T.G. Babb^{a,*}

^a Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, and the University of Texas Southwestern Medical Center at Dallas, 7232 Greenville Ave, Dallas, TX 75231, USA

^b Research Center for High Altitude Medicine, Qinghai Medical College, 16 Kuntun Road, Xining, Qinghai 180001, PR China

Received 11 March 2004; received in revised form 19 October 2004; accepted 15 November 2004

Abstract

To investigate whether obesity is associated with alterations in respiratory chemosensitivity, we compared the ventilatory response to hypoxia (HVR) and hypercapnia (HCVR) in 9 obese men (BMI: $37.0 \pm 4.3 \text{ kg m}^{-2}$) and 10 lean men (BMI: $25.8 \pm 4.8 \text{ kg m}^{-2}$). HVR ($\Delta \dot{V}_E$, L min⁻¹ per $\Delta \text{Sa}_{\text{O}_2}$, %) was measured by a progressive isocapnic hypoxia technique, and HCVR ($\Delta \dot{V}_E / \Delta P_{\text{ETCO}_2}$, L min⁻¹ Torr⁻¹) was measured by a progressive hypercapnic method. HCVR, was greater ($p < 0.001$) in the obese men (2.68 ± 0.78) than in the lean men (1.4 ± 0.45) as was HVR ($p < 0.05$) (1.26 ± 0.65 versus 0.71 ± 0.43 , respectively). The difference ($\Delta \text{Sa}_{\text{O}_2}$, %, 4.30 ± 3.69 and 10.54 ± 3.45 in the lean and obese men, respectively, $p < 0.01$) between daytime (86 ± 1 and 86 ± 1 %) and nighttime Sa_O₂ (81 ± 3 and 76 ± 4 %) at a simulated altitude of 3658 m was significantly ($p < 0.05$) correlated with both HVR ($r = 0.51$) and HCVR ($r = 0.48$). These results suggest that chemosensitivity in mildly obese men is increased, not blunted. Furthermore, otherwise healthy, obese individuals have the potential for significant desaturation during sleep at high altitude possibly due to exaggerated sleep-disordered breathing.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Ventilatory response; Obesity; Chemoreflex; Nocturnal hypoxia

1. Introduction

Obesity is an epidemic problem in the United States and is among the most important health challenges

of the 21st Century (Surgeon General's Call to Action, USPHS 2001). More than 50% of Americans are classified as overweight and more than 22% are frankly obese (BMI ≥ 30). Although diabetes, heart disease, hypertension, and some forms of cancer are strongly associated with obesity, the associations between obesity and breathing limitations are less well understood.

* Corresponding author. Tel.: +1 214 3454622; fax: +1 214 3454618.

E-mail address: tonybabb@texashealth.org (T.G. Babb).

Obesity is characterized by an abnormally large adipose tissue mass. An excess weight on the thorax appears to lead to the development of various respiratory pathophysiological disorders. Specifically, additional weight on the thorax can lead to decreased chest wall compliance, increased respiratory resistance, increased elastic load of breathing, reduced lung volumes, sleep-disordered breathing, alveolar hypoventilation, and nocturnal hypoxemia (Luce, 1980). Obesity also influences resting metabolic rate, ventilatory demand, and ventilatory efficiency (Whipp and Davis, 1984), although this has not been studied in otherwise healthy mild-to-moderately obese men. Furthermore, the ventilatory response to hypoxia and hypercapnia have been reported to be reduced in morbid obesity compared with non-obesity (Burwell et al., 1956; Bray, 1985; Kunitomo et al., 1988; Gabutti et al., 2001). However, a number of conflicting results have also been reported, showing that the ventilatory response to hypoxia and/or hypercapnia in eucapnic obese subjects are increased (Kunitomo et al., 1988; Narkiewicz et al., 1999; Jokic et al., 2000) normal (Kronenberg et al., 1975; Nishibayashi et al., 1987) or decreased (Zwillich et al., 1975). These conflicting results could be related to the degree of obesity in the patients studied and/or the presence of co-morbidities in the obese individuals studied. The primary purpose of this study was to investigate the hypoxic and hypercapnic ventilatory response in otherwise healthy, mild-to-moderately obese adults. Moreover, since the ventilatory response to hypoxia is a critical factor for acclimatization to high altitude, we speculated that if chemosensitivity were blunted, then obese individuals could have a lower arterial oxygen saturation ($\text{SaO}_2\%$) after acute ascent to high altitude, particularly at night. Thus, altered chemosensitivity could be associated with decreased nighttime $\text{SaO}_2\%$ levels at high altitude, especially if the obese men had obesity-related gas exchange inefficiency as well (Jenkins and Moxham, 1991). Our previous data indicated that obese individuals with acute mountain sickness have significant desaturation during sleep at high altitude (Ge et al., 2003); we hypothesized that the hypoxic and hypercapnic ventilatory response would be correspondingly blunted in such patients. Therefore, our secondary purpose was to examine the relationship between ventilatory responses and $\text{SaO}_2\%$ levels at high altitude in mild-to-moderate obesity.

2. Methods

2.1. Subjects

We studied nine obese (age 35 ± 8 years, mean \pm S.D.) and 10 nonobese men (34 ± 8 years). Obesity was defined as a body mass index (BMI) $\geq 30 \text{ kg m}^{-2}$ and percent body fat (%BF) ≥ 30 . All subjects were recruited through local advertisements. None of the subjects had a history of cardiovascular or respiratory abnormalities; all were non-smokers. None of the subjects reported any sleep-related disorders or difficulties. All subjects received both written and verbal explanations of the experiment before giving written consent. The Institutional Review Board of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas approved this study.

2.2. Pulmonary function tests

All subjects underwent standard spirometry including maximal flow-volume loop, maximal voluntary ventilation, lung volume, and diffusing capacity (DL_{CO}) measurements in a whole body plethysmograph (6200 Autobox D_L , SensorMedics, Yorba Linda, CA). Pulmonary function testing was performed according to the guidelines of the American Thoracic Society (American Thoracic Society, 1995). Resting arterial blood gases were drawn and analyzed at sea level and at simulated altitude.

2.3. Resting measurements

Minute ventilation (\dot{V}_E) was measured using a dual pneumotachograph system, which is standard in our laboratory (Babb et al., 2003), attached to a two-way non-breathing valve (Babb, 1997). End-tidal CO_2 (P_{ETCO_2} , Torr) was measured with an end-tidal CO_2 monitor with display (model 602/11, Criticare Systems, Waukesha, WI) and O_2 and CO_2 gas fractions were measured throughout each measurement with mass spectrometry. $\text{SaO}_2\%$ was measured by pulse-oximetry using a finger probe (model 3700, Ohmeda, Louisville, CO).

2.4. Hypoxic ventilatory response (HVR)

HVR was measured using a modification of Weil's technique (Weil et al., 1971; West et al., 1986). The

subjects were asked to breathe quietly through the mouthpiece for 4 min and then switched into a reservoir bag at the end of normal expiration. Progressive isocapnic hypoxia was induced by a gradual addition of nitrogen to the reservoir bag that initially contained 17% O₂ and balance N₂. The test was continued for 10 min or until the SaO₂ dropped from 98 to 70%. SaO₂% was measured by pulse-oximetry using a finger probe (model 3700, Ohmeda, Louisville, CO). P_{ETCO₂} (end-tidal CO₂ monitor with display, model 602/11, Criticare Systems, Waukesha, WI) was maintained constant by the continuous addition of 100% CO₂ to the inspired gas. HVR was estimated as the slope of the line calculated by the linear regression relating \dot{V}_E to SaO₂ ($\Delta \dot{V}_E$ L min⁻¹ per Δ SaO₂%).

2.5. Hypercapnic ventilatory response (HCVR)

The progressive HCVR was performed according to the method by Weil et al. (1971) and West et al. (1986), and began with the subject quietly breathing room air through the breathing assembly while comfortably seated in a chair. The participant was on the mouthpiece for 6 min. Then \dot{V}_E , P_{ETCO₂}, pulse-oximetry, and heart rate data were collected for an additional 4 min. Immediately after the room air measurement, the subjects breathed from a reservoir bag, which initially contained 2% CO₂, 21% O₂ and balance N₂, attached to the inspiratory side of the breathing assembly while CO₂ concentration was progressively increased in the bag until the P_{ETCO₂} was ≥ 55 mmHg. The slope of HCVR was assessed by the linear regression relating \dot{V}_E to P_{ETCO₂} ($\Delta \dot{V}_E / \Delta P_{ETCO_2}$, L min⁻¹ Torr⁻¹).

2.6. Measurements of SaO₂% at altitude

SaO₂ (model 3700, Ohmeda, Louisville, CO) was measured at 3685 m (12,000 ft) during the daytime and during sleep as described previously (Ge et al., 2003).

2.7. Statistical analysis

Data are expressed as mean \pm S.D. The differences between the groups (obesity versus nonobese) were analyzed using the Student's *t*-test. Linear regression analysis and correlation coefficients were used to assess the relationships between variables. Comparison and correlation were considered significant when $p < 0.05$.

3. Results

3.1. Subjects

The general characteristics of the participants are shown in Table 1. Data on these subjects have been previously reported (Ge et al., 2003).

3.2. Pulmonary function

Spirometry, lung volumes, and diffusing capacity are presented in Table 2. There were small but significant differences in pulmonary function and functional residual capacity (FRC) between the obese and nonobese participants. Of the resting sea level arterial blood gas measurements, only PaO₂ was significantly different ($p < 0.01$) between the lean (96 ± 7 Torr) and obese men (84 ± 9 Torr). Resting arterial blood gas measurements made after approximately 24 of simulated altitude were not different between the lean and obese men (51 ± 6 and 48 ± 6 Torr, PaO₂ respectively, for the nonobese and obese men).

3.3. HVR and HCVR

Fig. 1 shows the data points and regression line for HVR for one typical nonobese and one typical obese individual. Fig. 2 shows the average regression lines for HVR for the obese and nonobese individuals. HVR slope ($\Delta \dot{V}_E / \Delta SaO_2$) in the obese group was significantly ($p < 0.05$) higher than that of the nonobese group (Table 2). The distribution of the individual HVR slopes for the two groups is shown in Fig. 3A. Baseline \dot{V}_E and P_{ETCO₂} were 10.52 ± 4.21 L min⁻¹ and

Table 1
General Characteristics

Characteristics	Obese ($n = 9$)	Lean ($n = 10$)
Age (year)	35 \pm 7	35 \pm 8
Height (cm)	179.8 \pm 3.2	181.2 \pm 3.7
Weight (kg)	120.6 \pm 15.0**	82.4 \pm 13.6
BF (%)	37.5 \pm 5.0**	15.9 \pm 5.4
BMI (kg m ⁻²)	37.0 \pm 5.0**	25.0 \pm 4.0
Hb (g/dl)	15.4 \pm 1.1	15.2 \pm 1.6
Hct (%)	46.6 \pm 4.5	46.3 \pm 3.9

Values are mean \pm S.D. *n*: number of subjects; BF: percent body fat; BMI: body mass index; Hb: hemoglobin; Hct: Hematocrit.

** $p < 0.01$ compared with lean group.

Table 2
Pulmonary Functions and ventilatory response

	Obese (n=9)	Lean (n=10)
FVC	5.51 ± 0.6	6.07 ± 0.84
FEV1	4.19 ± 0.49*	4.68 ± 0.44
PEF	9.60 ± 1.32*	10.91 ± 0.93
TLC	7.03 ± 1.01	7.77 ± 1.27
FRC	2.70 ± 0.38**	3.95 ± 1.02
DL _{CO}	31.63 ± 1.9	34.37 ± 3.9
HVR ($\Delta \dot{V}_E$, L min ⁻¹ per ΔSa_{O_2} , %)	1.26 ± 0.65*	0.71 ± 0.43
HCVR ($\Delta \dot{V}_E / \Delta P_{ETCO_2}$, L min ⁻¹ Torr ⁻¹)	2.68 ± 0.76**	1.41 ± 0.45

Values are mean ± S.D. n: number of subjects; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; PEF: peak expiratory flow; TLC: total lung capacity, FRC: functional residual capacity; DL_{CO}: diffusion capacity of the lung; HVR: hypoxic ventilatory response; HCVR: hypercapnic ventilatory response.

* $p < 0.05$ compared with lean group.

** $p < 0.01$ compared with lean group.

39.60 ± 5.55 Torr, respectively, for the lean men, and 13.03 ± 3.55 and 38.03 ± 3.89, respectively, for the obese men for the HVR test. These baseline P_{ETCO_2} values for each group were not significantly different from resting Pa_{CO_2} values, which were drawn at rest earlier, of 42 ± 3 Torr in the lean men and 40 ± 2 in obese men.

During hypercapnia, the increase in \dot{V}_E was dramatically greater in the obese subjects than in the lean subjects. Fig. 4 shows the data points and regression line for HCVR for one typical nonobese and one typical obese individual. The average HCVR in the obese subjects was significantly ($p < 0.01$) greater than in lean subjects (Table 2). Fig. 5 shows the average regression lines for HCVR for the nonobese and obese men. The distribution of the individual HCVR slopes for the two groups is shown in Fig. 3B. Baseline \dot{V}_E and P_{ETCO_2} were 9.76 ± 2.52 L min⁻¹ and 41.00 ± 4.66 Torr, respectively, for the lean men, and 11.24 ± 2.71 and 39.38 ± 3.63, respectively, for the obese men. These

baseline P_{ETCO_2} values for each group were not significantly different from resting Pa_{CO_2} values, which were drawn at rest earlier, of 42 ± 3 in the lean men and 40 ± 2 Torr in obese men.

The HVR and HCVR slopes were significantly correlated ($p < 0.01$) for the two groups (Fig. 6). Thus, a higher HVR slope usually resulted in a higher HCVR slope.

3.4. Sa_{O_2} % at altitude

The difference (4.30 ± 3.69 and 10.54 ± 3.45% for the lean and obese men, respectively) between daytime (86 ± 1% for both the lean and obese men) and nighttime Sa_{O_2} (81 ± 3 and 76 ± 4% for the lean and obese men, respectively, $p < 0.01$) at simulated altitude of 3658 m (ΔSa_{O_2}) was highly correlated to both HVR and HCVR (Fig. 7). That is, the greater HVR and HCVR, the greater the decrease in Sa_{O_2} % at night.

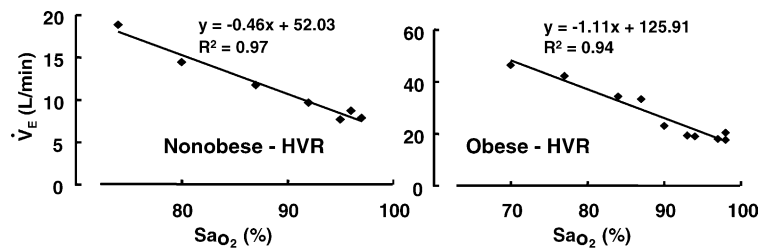


Fig. 1. Slope of the hypoxic ventilatory response (HVR) in one typical nonobese man (left panel) and one typical mild-to-moderately obese man (right panel).

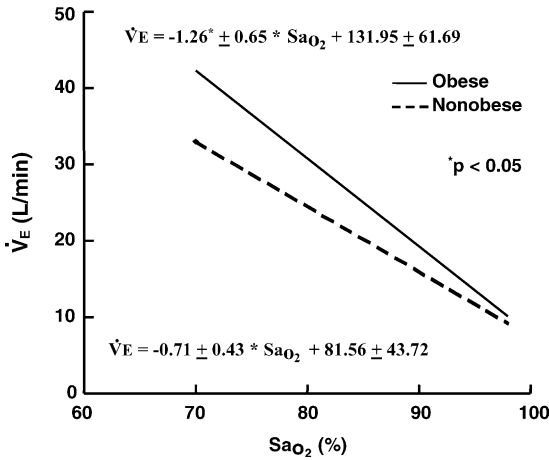


Fig. 2. Slope of the hypoxic ventilatory response (HVR) in mild-to-moderately obese and nonobese men. * $p < 0.05$, significant difference between mean slopes. For the HVR test, baseline \dot{V}_E and P_{ETCO_2} were 10.52 ± 4.21 and 39.60 ± 5.55 , respectively, for the lean men, and 13.03 ± 3.55 and 38.03 ± 3.89 for the obese men, respectively. On average, the HVR slope was determined individually using 9 ± 1 data points with an $R^2 = 0.91 \pm 0.08$ for the lean men and 10 ± 2 data points with an $R^2 = 0.94 \pm 0.06$ for the obese men.

4. Discussion

The main finding of the present study was that the ventilatory response to hypoxia and hypercapnia in mild-to-moderately obese adults were exaggerated, not attenuated as suggested by traditional thinking. Paradoxically, obese individuals with an increased ventilatory response to hypoxia and/or hypercapnia had the potential for significant desaturation during sleep at high altitude. This finding could have potentially important clinical relevance for obese individuals traveling to higher elevations where they could be more likely to develop acute mountain sickness (Ge et al., 2003).

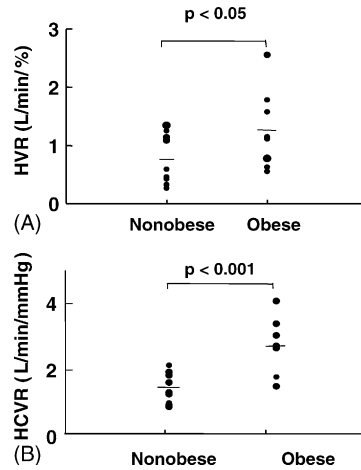


Fig. 3. Individual values for hypoxic ventilatory response (panel A; HVR) and progressive hypercapnic ventilatory response (panel B; HCVR) for obese and nonobese men.

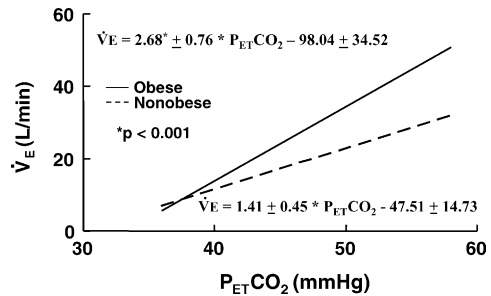


Fig. 5. Slope of the hypercapnic ventilatory response (HCVR) in mild-to-moderately obese and nonobese men. ** $p < 0.01$ significant difference between mean slopes. For the HCVR test, baseline \dot{V}_E and P_{ETCO_2} were 9.76 ± 2.52 and 41.00 ± 4.66 , respectively, for the lean men, and 11.24 ± 2.71 and 39.38 ± 3.63 , respectively, for the obese men. On average, the HCVR slope was determined individually using 7 ± 1 data points with an $R^2 = 0.95 \pm 0.06$ for the lean men and 8 ± 3 data points with an $R^2 = 0.87 \pm 0.10$ for the obese men.

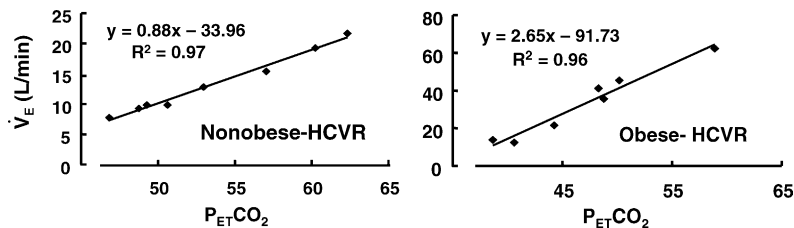


Fig. 4. Slope of the hypercapnic ventilatory response (HCVR) in one typical nonobese man (left panel) and one typical mild-to-moderately obese man (right panel).

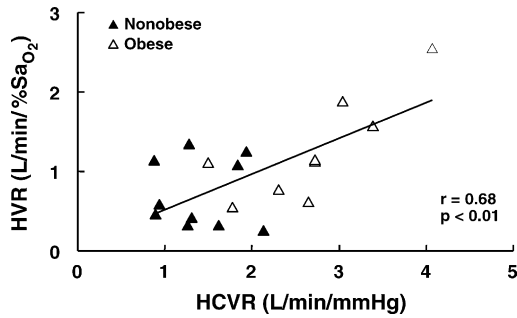


Fig. 6. Relationship between hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) for mild-to-moderately obese and nonobese men.

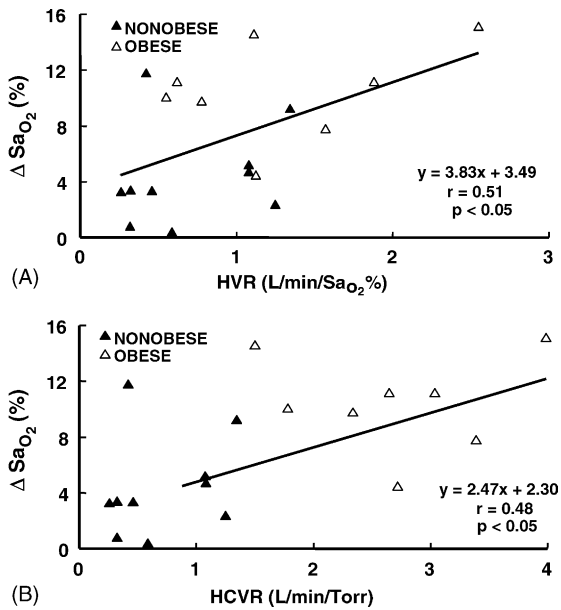


Fig. 7. Relationship between the change in SaO_2 % (4.30 ± 3.69 and 10.54 ± 3.45 for the lean and obese men, respectively) from daytime to nighttime at a simulated altitude of 3568 m (ΔSaO_2 %) and hypoxic ventilatory response (HVR, panel A) and hypercapnic ventilatory response (HCVR, panel B) for mild-to-moderately obese and nonobese men.

Previous studies have revealed conflicting results regarding chemo-sensitivity in obesity, with some studies reporting increased (Narkiewicz et al., 1999; Jokic et al., 2000), normal (Kronenberg et al., 1975; Nishibayashi et al., 1987; Chapman et al., 1990), or decreased (Zwillich et al., 1975; Kunitomo et al., 1988) ventilatory response to hypercapnia and hypoxia. However, it has generally been agreed that the

morbidity obese are often characterized by hypoventilation, which is termed obesity-hypoventilation syndrome (OHS). The exact factors responsible for the development of OHS are unclear, but abnormal ventilatory regulation, such as blunted peripheral and/or central chemoreceptors, in these OHS patients may be involved (Zwillich et al., 1975). Obese patients with sleep-disordered breathing have also shown an attenuated (Zwillich et al., 1975) and augmented HVR and HCVR (Buyse et al., 2003). Conventional reasoning suggests that blunted HVR and/or HCVR could be responsible for nighttime desaturation in obese individuals at altitude.

Contrary to conventional thinking, the results of this study provide no support for the concept of impairment in ventilatory chemoresponsiveness in mild-to-moderate obese individuals who are otherwise healthy. In the present study, the respiratory chemosensitivity, particularly the hypercapnic chemoreflex, in the mild-to-moderately obese individuals was significantly greater than that of the nonobese individuals. These results are consistent with a previous study by Narkiewicz et al. (1999). They reported that the resting HCVR was significantly higher in eucapnic obese subjects when compared with normal-weight subjects, suggesting that the resting HCVR in mild-to-moderate obesity is not blunted, just as we found. The origin for the conflicting results regarding chemosensitivity could be related to the type of obese individual studied. It appears that those who are morbidly obese or have developed symptoms or co-morbidities may have substantially different responses in comparison to volunteers who have mild-to-moderate obesity and are otherwise healthy.

The mechanism underlying the higher chemosensitivity in obese volunteers is unclear since this was not the original intent of this investigation. However, we can address some of the relevant issues. The lower resting PaO_2 in the obese men could have influenced both HCVR and HVR. That is, since PaO_2 was lower in the obese group, there could have been a greater degree of potentiation between CO_2 and hypoxia at the carotid bodies during the HCVR test. Because we did not use a hyperoxic background gas mixture during the HCVR test, we cannot resolve this issue. Also, because the lower PaO_2 in the obese men could have been due to subtle changes in the relationship between lung ventilation-perfusion in the obese men, it is possible

that the relationship between P_{aCO_2} and P_{ETCO_2} was also affected. However, there was no difference between resting P_{aCO_2} and baseline P_{ETCO_2} measured before the HCVR or HVR tests (i.e., see HVR and HCVR results). Therefore, we believe it is unlikely that the increase in HCVR in the obese subjects was due to some systematic change in the relationship between arterial and end-tidal CO_2 . During the HVR test, P_{aO_2} could have been lower in the obese men at any reading of $SA_{O_2}\%$ than in the nonobese men and thus contributed to the increased slope. This could have been true despite the fact that resting $SA_{O_2}\%$ was not different between the nonobese and obese men (98 ± 1 and $97 \pm 1\%$, respectively). Since, we did not have arterial lines in these subjects, nor could we have justified placing arterial lines in these patients, we cannot resolve this basic issue completely. Alternatively, evidence from animal models of obesity, have suggested that plasma leptin, a protein produced by adipose tissue that circulates to the brain and interacts with receptors in the hypothalamus to inhibit eating, could modulate the central chemoreflex (O'Donnell et al., 2000; Fitzpatrick, 2002).

We also found that the slope of HVR and HCVR was correlated to the magnitude of desaturation at night during simulated altitude exposure, which is in contrast to conventional reasoning and our original hypothesis. This finding suggests that an obese person who has a higher HVR and HCVR may show a greater hypoxemia at night when sleeping at altitude, but not during daytime exposure to altitude. This relationship may be associated with high altitude periodic breathing with apnea (West et al., 1986; Eichenberger et al., 1996). Lahiri et al. (1983) reported that persons with higher HVR have more periodic breathing, and therefore, severe nocturnal hypoxemia, whereas persons with blunted HVR, such as Sherpas, have more regular breathing. Masuyama et al. (1989) also found a significant, positive correlation between the degree of periodic breathing at 5360 m and the levels of HVR and HCVR. Our results are quite consistent with these previous data in that we found the level of HVR and HCVR to be highly correlated with the magnitude of nocturnal desaturation at simulated altitude. We speculate that the obese individuals who have a lower $SA_{O_2}\%$ during sleep might also have had severe sleep-disordered breathing, such as periodic breathing with apnea. The higher ventilatory chemosensitivity to hypoxia and hypercapnia may produce respiratory alkalosis that acts on the central

respiratory center, causing periodic breathing with apnea (Lahiri et al., 1983; West et al., 1986; Masuyama et al., 1989; Eichenberger et al., 1996). During apnea, $SA_{O_2}\%$ decreases and P_{aCO_2} increases, this stimulates both peripheral and central chemoreceptors, causing a recurrent hyperpnea and apnea cycle. The increased sensitivity, therefore, may make the control of breathing during sleep unstable at high altitude.

In summary, we found that respiratory chemosensitivity, in particular the central chemoreflex, in obese subjects to be significantly greater than that of nonobese subjects. This finding suggests that the resting ventilatory response to hypoxia and hypercapnia in mild-to-moderate obesity is exaggerated, not attenuated. Furthermore, in contrast to conventional thinking, otherwise healthy, mildly obese individuals with increased HVR and HCVR have the potential for significant desaturation during sleep at high altitude probably due to exaggerated sleep-disordered breathing.

Acknowledgements

The authors gratefully thank Paul Chase, Brenda Wyrick, Sarah Witkowski, Julie Zuckerman, Belinda Schwartz and all staffers of the hypobaric chamber for their contributions and support of this project. The US Wilderness Medicine Association, American Lung Association, and Natural Science Foundation of China (NSFC) supported this work.

References

- American Thoracic Society, 1995. Standardization of spirometry (1994 update). *Am. J. Respir. Crit. Care Med.* 152, 1107–1136.
- Babb, T.G., 1997. Ventilatory response to exercise in subjects breathing CO_2 or HeO_2 . *J. Appl. Physiol.* 82, 746–754.
- Babb, T.G., DeLorey, D.S., Wyrick, B.L., 2003. Ventilatory response to exercise in aged runners breathing $He-O_2$ or inspired CO_2 . *J. Appl. Physiol.* 94, 685–693.
- Bray, G.A., 1985. Complications of obesity. *Ann. Intern. Med.* 103, 1052–1062.
- Burwell, C.S., Robin, E.D., Whaley, R.D., Bickelmann, A.G., 1956. Extreme obesity associated with alveolar hypoventilation: a Pickwickian Syndrome. *Am. J. Med.* 21, 811–818.
- Buyse, B., Markous, N., Cauberghs, M., Van Klaveren, R., Muls, E., Demedts, M., 2003. Effect of obesity and/or sleep apnea on chemosensitivity: differences between men and women. *Respir. Physiol. Neurobiol.* 134, 13–22.

- Chapman, K.R., Hiral, H.S., Rebeck, A.S., 1990. Ventilatory responses to hypercapnia and hypoxia in patients with eucapnic morbid obesity before and after weight loss. *Clin. Sci. (Lond)* 78, 541–545.
- Eichenberger, U., Weiss, E., Riemann, D., Oelz, O., Bartsch, P., 1996. Nocturnal periodic breathing and the development of acute high altitude illness. *Am. J. Respir. Crit. Care Med.* 154, 1748–1754.
- Fitzpatrick, M., 2002. Leptin and the obesity hypoventilation syndrome: a leap of faith? *Thorax* 57, 1–2.
- Gabutti, A., Spicuzza, L., Porta, C., Bernardi, L., 2001. Functions and changes of chemoreflex in physiological and pathological conditions. *Recenti. Prog. Med.* 92, 433–445.
- Ge, R.L., Chase, P.J., Witkowski, S., Wyrick, B.L., Stone, J., Levine, B.D., Babb, T.G., 2003. Obesity: associations with acute mountain sickness. *Ann. Intern. Med.* 139, 258–266.
- Jenkins, S.C., Moxham, J., 1991. The effects of mild obesity on lung function. *Respir. Med.* 85, 309–311.
- Jokic, R., Zintel, T., Sridhar, G., Gallagher, C.G., Fitzpatrick, M.F., 2000. Ventilatory responses to hypercapnia and hypoxia in relatives of patients with the obesity hypoventilation syndrome. *Thorax* 55, 940–945.
- Kronenberg, R.S., Gabel, R.A., Severinghaus, J.W., 1975. Normal chemoreceptor function in obesity before and after ileal bypass surgery to force weight reduction. *Am. J. Med.* 59, 349–353.
- Kunitomo, F., Kimura, H., Tatsumi, K., Kuriyama, T., Watanabe, S., Honda, Y., 1988. Sex differences in awake ventilatory drive and abnormal breathing during sleep in eucapnic obesity. *Chest* 93, 968–976.
- Lahiri, S., Maret, K., Sherpa, M.G., 1983. Dependence of high altitude sleep apnea on ventilatory sensitivity to hypoxia. *Respir. Physiol.* 52, 281–301.
- Luce, J.M., 1980. Respiratory complications of obesity. *Chest* 78, 626–631.
- Masuyama, S., Kohchiyama, S., Shinozaki, T., Okita, S., Kunitomo, F., Tojima, H., Kimura, H., Kuriyama, T., Honda, Y., 1989. Periodic breathing at high altitude and ventilatory responses to O₂ and CO₂. *Jpn. J. Physiol.* 39, 523–535.
- Narkiewicz, K., Kato, M., Pesek, C.A., Somers, V.K., 1999. Human obesity is characterized by a selective potentiation of central chemoreflex sensitivity. *Hypertension* 33, 1153–1158.
- Nishibayashi, Y., Kimura, H., Maruyama, R., Ohyabu, Y., Masuyama, H., Honda, Y., 1987. Differences in ventilatory responses to hypoxia and hypercapnia between normal and judo athletes with moderate obesity. *Eur. J. Appl. Physiol.* 56, 144–150.
- O'Donnell, C.P., Tankersley, C.G., Polotsky, V.P., Schwartz, A.R., Smith, P.L., 2000. Leptin, obesity, and respiratory function. *Respir. Physiol.* 119, 163–170.
- Weil, J.V., Byrne-Quinn, E., Sodal, I.E., Filley, G.F., Grover, R.F., 1971. Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. *J. Clin. Invest.* 50, 186–195.
- West, J.B., Peters Jr., R.M., Aksnes, G., Maret, K.H., Milledge, J.S., Schoene, R.B., 1986. Nocturnal periodic breathing at altitudes of 6300 and 8050 m. *J. Appl. Physiol.* 61, 280–287.
- Whipp, B.J., Davis, J.A., 1984. The ventilatory stress of exercise in obesity. *Am. Rev. Respir. Dis.* 129, S90–S92.
- Zwilling, C.W., Sutton, F.D., Pierson, D.J., Greagh, E.M., Weil, J.V., 1975. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am. J. Med.* 59, 343–348.