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Hypocapnia is Associated with Increased Upper Airway Expiratory Resistance during Sleep

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Abstract

We hypothesized that hypocapnia is responsible for increased expiratory resistance during NREM sleep. Hypocapnia was induced by hypoxic hyperventilation in 21 subjects (aged 29.4 ±7.8 yrs, 10 women, BMI 24.4±4.3 kg/m^2). Isocapnic hypoxia was induced in 12 subjects of whom, 6 underwent hypocapnic hypoxia in the same night. Upper airway resistance (R_{UA}) was measured at the linear pressure-flow relationship during inspiration and expiration. Inspiratory flow limitation (IFL) was defined as the dissociation in pressure-flow relationship. (1) Expiratory R_{UA} increased during hypocapnic but not isocapnic hypoxia relative to control (11.0±5.6 vs. 8.2±3.6 cmH_2O/L/s; $p<0.05$, and 11.4±5.0 vs. 10.9±4.4 cmH_2O/L/s; p=NS, respectively). (2) No gender difference was found in R_{UA} (p=NS). (3) Increased expiratory R_{UA} correlated with the IFL change during hypocapnic but not isocapnic hypoxia. (4) No changes were noted in inspiratory R_{UA} or IFL. Expiratory R_{UA} increased during hypocapnia and was associated with IFL, indicating upper airway narrowing. Gender does not influence the upper airway response to hypocapnic hypoxia.

Keywords

hypocapnia; hypoxia; expiratory; upper airway resistance

1. INTRODUCTION

The pathogenesis of obstructive sleep apnea involves an interaction between unstable ventilatory control and unfavorable pharyngeal anatomy (Badr et al., 1995; Badr, 1996; Isono et al., 1997; Rowely et al., 2002; Schwab et al., 1995). Ventilatory motor output is an important determinant of upper airway patency during sleep (Hudgel et al., 1998 and Warner et al., 1987). In fact, complete upper airway obstruction occurs at the nadir of ventilatory motor output during periodic breathing in individuals with a collapsible upper airway (Warner et al., 1987). Likewise, pharyngeal narrowing or occlusion occurs during hypocapnic central apnea and induced hypocapnic hypopnea (Badr et al., 1994 and Sankri-Tarbichi et al., 2009). Interestingly, compromised pharyngeal patency during induced

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hypocapnic hypopnea occurred during expiration only, and manifested by increased resistance and expiratory pharyngeal narrowing, with no changes occurring during inspiration (Sankri-Tarbichi et al., 2009).

Expiratory pharyngeal narrowing during hypopnea could be explained by reduced ventilatory motor output or by hypocapnia per se. Decreased lung volume and diminished intra-luminal pressure during hypopnea suggest that reduced ventilatory drive is responsible for expiratory pharyngeal narrowing.,(Series et al., 1990 and Van de Graaff, 1988). Conversely, hypocapnia, per se, independent of ventilatory drive could lead to pharyngeal narrowing. Evidence implicating hypocapnia per se includes activation of the pharyngeal constrictors and laryngeal expiratory muscles by hypocapnia (Feroah et al., 2000; Kuna et al.,1993; Kuna and Vanoye, 1997; Praud et al., 1990; Sears et al., 1990) and the reduced tonic muscle activity under hypocapnic conditions in a feline preparation (Frankshtein and Sergeeva., 1983). Therefore, we hypothesized that hypocapnia per se would lead to expiratory pharyngeal narrowing during sleep independent of ventilatory motor output. To this end, we used hypoxic hyperventilation to induce hypocapnia without decreased ventilatory motor output, during sleep in healthy individuals.

2. METHODS

2.1 Subjects

The Human Investigation Committee of the Wayne State University School of Medicine and the Dingell Veterans Affairs Medical Center approved the experimental protocol. Informed written consent was obtained. Female subjects were not pregnant nor on birth control pills. Subjects were asked to restrict their sleep the night before the study to total sleep of 4–6 hours, and study was done under spontaneous natural sleep.

2.2. Equipment and measurements

The subjects were connected to the circuit with a silicone rubber mask connected to a heated pneumotachometer, used to measure ventilation and timing. Four cylinders containing the following gases: 100% nitrogen (N_2), 8% oxygen (balanced with N_2), 100% O_2 and 7% CO_2 were connected to the inspiratory line. Supraglottic pressure (P_{sg}) was measured using a pressure transducer tipped catheter (Model TC-500XG, Millar Instruments, Houston, TX). All signals were recorded using Powerlab data acquisition software (National AD-Instruments, Austin, TX) for further analysis.

2.3. Protocol 1: Hypocapnic Hypoxia

The study was conducted in the supine position during stable NREM sleep. Twenty one healthy subjects (11 men and 10 women) participated in this protocol. Following a period of stable N2 or N3 sleep on room air for at least 5 minutes, the subjects had short episodes (3 min) of hypocapnic hypoxic exposure to maintain pulse oximetry (SpO_2) between 80–88%. Hypoxia was abruptly terminated with 1–2 breath of 100% O_2. Successful hypocapnic trials were those in which $P_{ET}CO_2$ dropped during the hypoxic exposures by at least 1 mmHg from baseline.

2.4. Protocol 2: Isocapnic Hypoxia

To ascertain the potential independent effect of hypocapnia, isocapnic hypoxia was induced in 12 subjects, six of whom underwent both hypocapnic and isocapnic hypoxia protocols on the same night. Isocapnia was maintained by adding 7% CO_2 gas into the breathing circuit to maintain $P_{ET}CO_2$ at control levels.

2.5. Data Analysis

Three control and hypoxia breaths were analyzed for ventilatory parameters, flow, inspiratory flow limitation (IFL), and P_{sg} measured at the nadir SpO_2. For each hypoxia trial inspiratory and expiratory R_{UA} was measured from three control and hypoxia breaths. R_{UA} was measured on the linear portion of the pressure-flow loop during inspiration and expiration. IFL was determined quantitatively using previously validated mathematical method (Mansour et al., 2002), to detect the dissociation in pressure-flow linear relationship during inspiration.

2.6. Statistical Analysis

A commercially available computer statistical package was used to analyze the data (Sigma Stat 3.5, SPSS). Paired two tailed t-tests were used to compare the mean values of each ventilatory parameter, supraglottic pressure and inspiratory and expiratory R_{UA} between control and hypoxia breaths. Friedman Repeated Measures Analysis of Variance on Ranks was used in six subjects who had both protocols to compare expiratory R_{UA} to compare the three types of breaths: control vs. hypocapnic hypoxia vs. isocapnic hypoxia. A Pearson Product Moment Correlation was used to ascertain the potential determinants of increased IFL. IFL was measured quantitatively for each subject and the change in IFL was defined as the percentage of change in the number of breaths with IFL between control and hypoxia. The correlation between the change in IFL and the following putative variables were assessed: age, gender, neck circumference, BMI and the change in expiratory resistance between control and hypoxia periods (hypocapnic then isocapnic hypoxia, respectively)

To assess the effect of gender on expiratory R_{UA} two-way repeated-measures analysis of variance was used to compare 10 men and 10 women matched for body mass index (BMI ± 4 units). The two factors were male vs. female and eupnea vs. hypocapnic hypoxia. The overall significance level was considered at 0.05.

3. RESULTS

3.1. Protocol 1: Effect of hypocapnic hypoxia on ventilation and upper airway mechanics

Hypocapnic hypoxia was associated with increased expiratory R_{UA} relative to the control period (11.0±5.6 vs. 8.2±3.6 $cmH_2O/L/s$; $p<0.05$) and no change in inspiratory R_{UA} in comparison to control (8.5±3.9 vs. 8.4±4.9 $cmH_2O/L/s$, respectively, p=NS), as illustrated in figure 3. Table 1 includes a summary of the demographics, SpO_2 and $P_{ET}CO_2$ levels. Figure 2 depicts the pressure-flow relationship for individual control, and hypoxia breaths from a representative normal subject. Hypocapnic hypoxia was associated with increased inspiratory flow limitation compared to control. Furthermore, hysteresis of the pressure-flow loop was more pronounced in comparison to control or isocapnic hypoxia.

To ascertain the potential determinants of increased inspiratory flow limitation, the following putative variables were assessed: age, gender, neck circumference, BMI and the change in expiratory resistance between control and hypoxia periods (hypocapanic then isocapnic hypoxia, respectively). The change of expiratory resistance was the only variable that correlated with the presence of IFL during hypocapnic but not isocapnic hypoxia ($r=0.51$, $p<0.05$ and $r=-0.16$, p=NS; respectively).

3.2. Protocol 2: Effect of isocapnic hypoxia on ventilation and upper airway mechanics

Isocapnic hypoxia was induced in 12 subjects (six of whom had also undergone hypocapnic hypoxia experiments on the same night). The ventilatory effects of isocapnic hypoxia were similar to hypocapnic hypoxia (Table 2). Similar to hypocapnic hypoxia, there was significant change in minute ventilation between isocapnic hypoxia and control, mainly due

to increased tidal volume. There was no significant change in R_{UA} between isocapnic hypoxia and control (8.2±4.3 to 8.1±6.0 cm H_2O/L/s and 12.3±5.2 to 11.1±5.0 cm H_2O/L/s cmH_2O/L/s, during inspiration and expiration, respectively, p=NS) as illustrated in figure 4.

3.3. The differential effect of hypocapnic versus isocapnic hypoxia on upper airway mechanics

Figure 5 illustrates the inspiratory and expiratory resistance in 6 subjects, who underwent both, isocapnic and hypocapnic hypoxia trials, in a random order. The comparison of the changes in R_{UA} during inspiration and expiration under control, hypocapnic and isocapnic conditions revealed that under hypocapnic hypoxia there was a trend to increased expiratory R_{UA} in comparison to each of control and isocapnic hypoxia (p=0.06); no change in inspiratory R_{UA} was noted.

3.4. The effect of gender on upper airway mechanics during hypocapnic hypoxia

The induction of hypocapnic hypoxia in 10 men and 10 women (matched for age and BMI) resulted similar drop in $P_{ET}CO_2$ (44.4±3.3 to 41.1±3.3 mmHg and 38.9±4 to 36.6±3.0 mmHg, in men and women respectively) and hypoxia levels (nadir SaO_2 were 85.4±1.4% and 85.3±1.4% for men and women, respectively). Hypocapnic hypoxia was associated with an increased expiratory R_{UA} in both men and women compared to control breaths (from 8.9±4.4 to 11.4±6.0 cm H_2O/L/s and 7.7±2.7 to 11.5±5.2 cmH_2O/L/s, for men and women, respectively). There was no gender difference in inspiratory or expiratory R_{UA} (p=NS) (figure 6).

4. DISCUSSION

Our study demonstrated the following novel findings: (1) hypocapnic but not isocapnic hypoxia was associated with increased expiratory upper airway resistance; (2) the increased expiratory resistance associated with increased inspiratory flow limitation under hypocpnic condition; (3) gender does not influence the upper airway resistance under hypocapnic hypoxia.

4.1. Methodological Considerations

Our laboratory has utilized pressure-flow relationship during inspiration and expiration (Badr et al., 1991; Badr et al., 1994; Tarbichi et al., 2003; Sankri-Tarbichi et al., 2009) to assess dynamic changes in upper airway during spontaneous sleep. Nevertheless, several considerations may influence the interpretation of the findings, including the inability to directly measure upper airway caliber and obtain multiple levels within the upper airway. We accepted in our hypocapnic hypoxia protocol at least *1 mmHg drop in* $P_{ET}CO_2$ for successful hypocapnia. Although this drop in $P_{ET}CO_2$ seems relatively small, several studies in humans revealed that this level of hypocapnia is sufficient to induce central hypopnea and/ or apnea especially when associated hypoxia that causes narrowing in the CO_2 reserve (Badr et al., 1995; Xie et al., 2001). Although this study aimed to assess the relative effect of hypocapnia on upper airway patency independent of ventilatory motor output, we did not measure the later or isolate its effect on upper airway such as inhibiting the vagal tone activity on the airway. It has been previously shown however, in dog model (Abbrecht et al, 1989) that atropine administration immediately reversed the constriction of smooth muscle at different levels of the respiratory tract. It is not feasible to administer atropine to our healthy human subjects at least in our current protocol. Finally our experimental interventions paradigm, were performed in normal subjects, therefore inferences to patients with sleep apnea who develop hypocapnic hypoxia after airway occlusion should be made with caution.

4.2. Effect of Hypocapnia on Upper Airway Mechanics

We have shown increased expiratory resistance and the development of elastic hysteresis in the pressure-flow loops during hypocapnic, but not isocapnic hypoxia. Increased expiratory resistance during hypocapnic hypoxia was not due to changes in ventilatory motor output or changes in lung volume as previously shown (Bonora and M. Vizek, 1999). Although this study did not determine precisely the central ventilatory motor output, since we are measuring ventilation rather than a neural output, we can state that ventilatory motor output during hypocapnic hypoxia was elevated relative to control (room air) conditions. Evidence includes increased ventilation (30% increase in VE), without decreased airflow resistance (table 2). Therefore, we believe that increased expiratory resistance during hypocapnic hypoxia was due to hypocapnia and was independent of lung volume changes or changes in ventilatory motor output

The presence of elastic hysteresis in the pressure-flow loops during hypocapnic hypoxia is consistent with increased pharyngeal wall compliance. Hysteresis manifests by wider and curvilinear changes between inspiration and expiration as the elastic properties of the passive upper airway determine its behavior (Schneider,et al., 2002)[Error! Reference source not found.]. Thus, tissue friction retards the dilatation of the upper airway during inflation, whereas deflation occurs immediately upon release of the inflating pressure. Thus, the upper airway becomes more susceptible to deformation during expiration.

4.3. Susceptibility to pharyngeal narrowing, is expiration a vulnerable phase?

Decreased upper airway muscle activity increases pharyngeal wall compliance and the susceptibility to deformation and collapse. However, the mechanical consequences may vary depending on the respiratory phase. During inspiration, there is a progressive increase in lung volume and a concomitant increase in the magnitude of caudal traction; two factors that may mitigate pharyngeal narrowing and preserve upper airway patency. In addition, inspiratory sub-atmospheric thoracic pressure may be transmitted through the cervical anatomic spaces, promoting upper airway patency by decreasing transmural pressure. Conversely, reduced lung volume during expiration and the transmission of expiratory surrounding pressure may promote pharyngeal narrowing and increased expiratory resistance. Supporting evidence includes the presence of hysteresis in upper airway in sleep apnea patients, manifesting by higher critical opening pressure during expiration relative to inspiratory critical collapsing pressure under relative hypotonia (Schneider,et al., 2002).

Our finding that hypocapnia was associated with increased expiratory resistance and hysteresis corroborates previous studies implicating hypocapnia as a mechanism of decreased pharyngeal stiffness. In an isolated canine upper airway preparation Fouke et al (1986) demonstrated increased pharyngeal compliance (the pressure-volume relationship) under hypocapnic conditions. Likewise, upper airway collapsibility (Pcrit) is higher (airway more collapsible) in feline preparations under hypocapnia (Rowley et al., 1997). This may be explained by reduced tonic muscle activity under hypocapnic conditions (Frankshtein and Sergeeva., 1983).

4.4. Implications to the pathogenesis of obstructive sleep disordered breathing

Our findings have significant implications regarding the pathogenesis of obstructive sleep apnea. The occurrence of pharyngeal narrowing during hypocapnic hypoxia suggests that hypocapnia promotes pharyngeal collapse, beginning during the expiratory phase of the respiratory cycle. In fact, we noted that increased expiratory resistance was associated with the inspiratory flow limitation (IFL). Similar observations were found in several human (Badr et al., 1994) and animal studies (Fouke et al., 1986; Rowley et al., 1997). During sleep

apnea the cessation of ventilation for several seconds leads to hypoxia and/or arousal which will stimulate the ventilation and produce hypocapnia as a ventilatory overshoot phenomenon (i.e., hyperventilation). This in turn perpetuates breathing instability and can result in repetitive upper airway narrowing/occlusion during sleep. A less recognized phenomenon is that hypocapnic central apnea may also influence the development of obstructive sleep apnea. There is evidence that patients with sleep apnea and snorers with evidence of inspiratory flow limitation are dependent on ventilatory motor output to preserve upper airway patency. In these individuals, pharyngeal obstruction occurs when ventilatory drive reaches a nadir during induced periodic breathing (Onal et al., 1986; Hudgel et al., 1998). The occurrence of complete pharyngeal collapse during central apnea, combined with mucosal and gravitational factors may impede pharyngeal opening and necessitate a substantial increase in drive that eventually leads to the sequence of events that are responsible for perpetuating breathing instability (Onal et al., 1986; Warner et al., 1987). Therefore, hypocapnia may represent a critical link between a narrow upper airway and the occurrence of complete upper airway obstruction, confirming the role of CO_2 in maintaining pharyngeal patency during sleep.

Our study also confirmed that gender did not influence the pharyngeal response to hypocapnia during sleep. This observation corroborates previous work demonstrating no gender difference in the mechanical response of the upper airway to hypocapnic hypoxia (Schneider et al., 2002). It has been shown previously that other determinants may explain the gender difference in the prevalence of sleep-disordered breathing including differences in the susceptibility to develop hypocapnic central apnea (Zhou et al., 2003), or upper airway compliance (before adjustment for neck circumference), as described by Rowley et al., 2002. On the other hand, inspiratory upper airway resistance and collapsibility were found similar between men and women (Tarbichi et al., 2003; Rowley et al., 2001). Thus, the increased prevalence of sleep-disordered breathing in men cannot be attributed to the gender influence on the response of the upper airway to hypocapnia.

In summary, we have shown the occurrence of increased expiratory resistance associated with inspiratory flow limitation during hypocapnic hypoxia, which indicates expiratory pharyngeal narrowing. Expiratory upper airway compromise during hypocapnic hypoxia may contribute to pharyngeal narrowing during sleep but does not account for the gender difference in the prevalence of sleep-disordered breathing.

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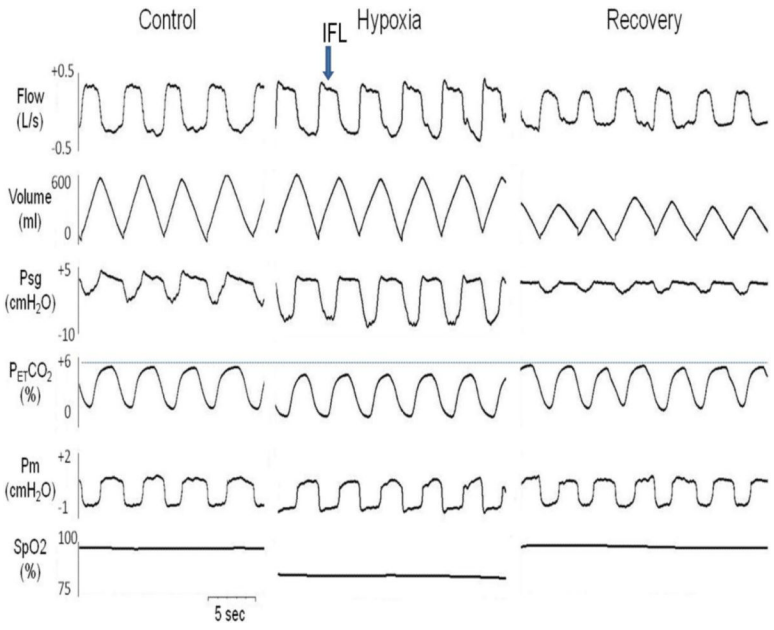

Figure 1.

Polygraph record of a hypoxia trial that illustrates breaths during control, brief hypocapnic hypoxia (1–3min) and recovery during NREM sleep. The dotted line represents the baseline $P_{ET}CO_2$. Note that hypocapnic hypoxia associated with the development of IFL (arrow). Abbreviations: Psg, supraglottic pressure; Pm, mask pressure; $P_{ET}CO_2$, end-tidal CO_2; SpO_2, pulse oximetry; IFL, inspiratory flow limitation.

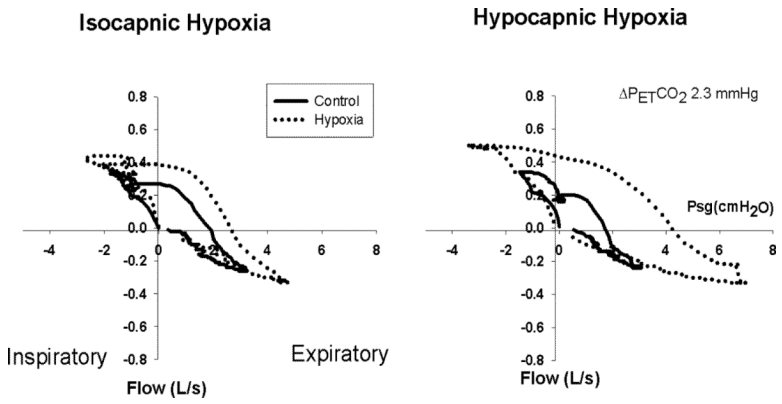

Figure 2.

Representative single breaths examples of pressure- flow relationships from one subject during control and hypoxia. Right panel (hypocapnic hypoxia) depicts the increased upper airway resistance (R_{UA}) during expiration and the development of flow limitation during inspiration. Note significant hysteresis in the pressure-flow loop of hypocapnic breath compared to control. Left panel (isocapnic hypoxia) depicts the lack any significant change in the IFL or R_{UA}.

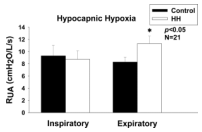

Figure 3.

Grouped data for upper airway resistance during control and hypocapnic hypoxia breaths during inspiration and expiration. Note the increased expiratory resistance during hypocapnic hypoxia. All presented data are mean ± SE.

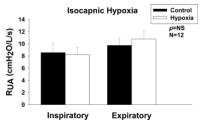

Figure 4.

Grouped data for upper airway resistance during control and isocapnic hypoxia breaths during inspiration and expiration in 12 subjects. All presented data are mean ± SE.

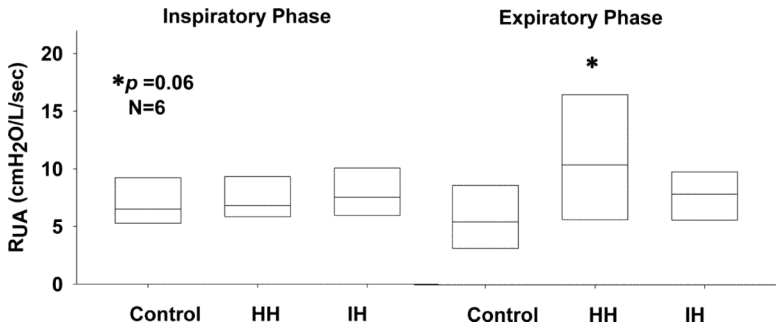

Figure 5.

Grouped data for inspiratory and expiratory upper airway resistance R_{UA} during control (C), hypocapnic hypoxia (HH), and isocapnic hypoxia breaths (IH). Note that expiratory, not inspiratory, R_{UA} for HH increased in comparison with control and isocapnic hypoxia breaths from the same 6 subjects (*p=0.06*). Each box plot is composed of three horizontal lines that display the 25^{th}, 50^{th} and 75^{th} percentiles of the variable.

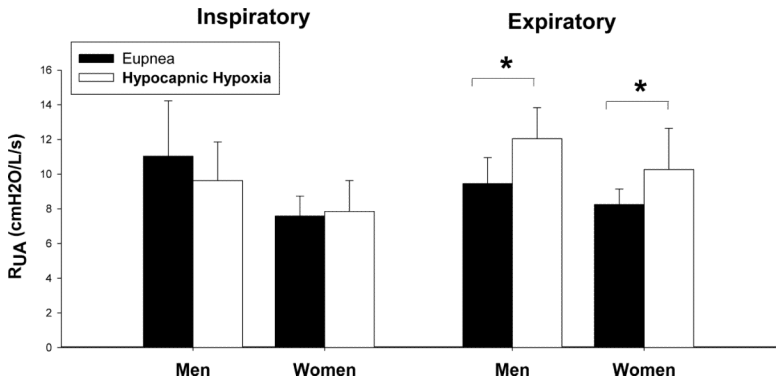

Figure 6.

Grouped data for inspiratory and expiratory upper airway resistance R_{UA} during control (C), hypocapnic hypoxia (HH) in 10 men compared to 10 women. Note that expiratory resistance increased during hypocapnic hypoxia in both men and women groups (*$p<0.05$), but there was no gender difference ($p=NS$).

Table 1

Subjects Characteristics

	Hypocapnic	Isocapnic
N	21	12
Age (year)	27.2±5.1	27.0±4.3
BMI (Kg/m^2)	23.7±4.7	24.2±4.5
Gender (F/M)	10/11	3/9
NC (cm)	35.5±4.4	37.0±3.4
Nadir SpO_2 (%)	84.8±1.7	84.7±1.9
Baseline $P_{ET}CO_2$ (mmHg)	42.2±4.7	40.8±3.5
Hypoxia $P_{ET}CO_2$ (mmHg)	39.7±3.7	41.2±2.4

All data Mean ±SD

NC, neck circumference; BMI, body mass index; SpO_2, pulse oximetry; $P_{ET}CO_2$, end tidal CO_2.

Table 2

Ventilatory Parameters

	Hypocapnic		Isocapnic	
	Control	**Hypoxia**	**Control**	**Hypoxia**
V_I (L/min)	6.9±0.3*	8.9±0.5	6.8±1.0*	8.1±0.5
V_T (L)	0.43±0.0*	0.55±0.0	0.46±0.0*	0.55±0.0
F_B (B/min)	16.0±0.5	16.3±0.5	14.9±0.9	14.8±0.8
T_I (sec)	1.72±0.1	1.67±0.1	1.92±0.1	1.81±0.1
T_E (sec)	2.68±0.2‡	2.08±0.1	2.80±0.3‡	2.37±0.2
T_I/T_{TOT}	0.45±0.0	0.45±0.0	0.46±0.0	0.43±0.0
V_T/T_I (L/sec)	0.25±0.0*	0.33±0.0	0.25±0.0*	0.31±0.0

V_I, inspiratory minute ventilation; V_T, tidal volume; F_B, breathing frequency; T_I, inspiratory time; T_E, expiratory time; T_I/T_{TOT}, inspiratory time/total breath duration; V_T/T_I, mean inspiratory flow.

* $p<0.05$ for control vs. hypoxia;

‡ $p=0.05$ for control vs. hypoxia