Sustained hyperoxia stabilizes breathing in healthy individuals during NREM sleep

Susmita Chowdhuri,1,2 Prabhat Sinha,1,2 Sukanya Pranathiageswaran,1,2 and M. Safwan Badr1,2,3

1Medical Service, John D. Dingell Veterans Affairs Medical Center, 2Division of Pulmonary/Critical Care and Sleep Medicine, Department of Medicine, and 3Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan

Submitted 27 April 2010; accepted in final form 18 August 2010

Chowdhuri S, Sinha P, Pranathiageswaran S, Badr MS. Sustained hyperoxia stabilizes breathing in healthy individuals during NREM sleep. J Appl Physiol 109: 1378–1383, 2010. First published August 19, 2010; doi:10.1152/japplphysiol.00453.2010.—The present study was designed to determine whether hyperoxia would lower the hypocapnic apneic threshold (AT) during non-rapid eye movement (NREM) sleep. Nasal noninvasive mechanical ventilation was used to induce hypocapnia and subsequent central apnea in healthy subjects during stable NREM sleep. Mechanical ventilation trials were conducted under normoxic (room air) and hyperoxic conditions (inspired PO2 above 250 Torr) in a random order. The CO2 reserve was defined as the minimal change in end-tidal P CO2 (PETCO2) between eupnea and hypocapnic central apnea. The PETCO2 of the apnea closest to eupnea was designated as the AT. The hypocapnic ventilatory response was calculated as the change in ventilation below eupnea for a given change in PETCO2. In nine participants, compared with room air, exposure to hyperoxia was associated with a significant decrease in eupnic PETCO2 (37.5 ± 0.6 vs. 41.1 ± 0.6 Torr, P = 0.001), widening of the CO2 reserve (−3.8 ± 0.8 vs. −2.0 ± 0.3 Torr, P = 0.03), and a subsequent decline in AT (33.3 ± 1.2 vs. 39.0 ± 0.7 Torr, P = 0.001). The hypocapnic ventilatory response was also decreased with hyperoxia. In conclusion, 1) hyperoxia was associated with a decreased AT and an increase in the magnitude of hypocapnia required for the development of central apnea. 2) Thus hyperoxia may mitigate the effects of hypocapnia on ventilatory motor output by lowering the hypocapnic ventilatory response and lowering the resting eupnic PETCO2, thereby decreasing plant gain.

HYPXIA PROMOTES BREATHING instability during sleep by increasing the susceptibility to develop hypocapnic central apnea and periodic breathing (7, 44, 46). Similarly, episodic hypoxia increases the propensity to develop central apnea, even after the removal of the hypoxic stimulus (7). Conversely, supplemental oxygen, used as a pharmacological agent, may stabilize respiration and has been shown to reduce the frequency of central apnea in patients with heart failure (33, 39). Acute hypoxia decreased the number of apneas and percent apnea time, although the result was inconsistent (25). The effect of hypoxia on ventilation is likely biphasic, manifesting as initial hypoventilation (12), secondary to the inhibition of peripheral chemoreceptors, followed by gradual hyperpnea (4, 5, 20, 35, 40, 42).

Brief hypoxic exposure (Hyp) may also promote breathing stability during sleep. Xie et al. (46) demonstrated that brief Hyp was associated with reduced hypocapnic ventilatory response, owing to inhibition of peripheral chemosensitivity. Likewise, Wellman et al. (43) demonstrated that supplemental oxygen therapy reduced “loop” gain in patients with obstructive sleep apnea with high-loop gain, but not in those with low-loop gain. The mechanisms underlying the stabilizing effect of hyperoxia on ventilatory control during sleep remain uncertain. Therefore, the purpose of our study was to determine the physiological effect of sustained hyperoxia on the hypocapnic apneic threshold (AT) during non-rapid eye movement (NREM) sleep. We hypothesized that hyperoxia lowers the AT during NREM sleep in healthy individuals by increasing the carbon dioxide reserve.

METHODS

Participants

The Human Investigation Committees of Wayne State University School of Medicine and Detroit Veterans Affairs Medical Center approved the experimental protocols, and informed, written consent was obtained from all participants. All participants were nonsmoker healthy participants, nonsnorers, free of daytime sleepiness, and free from cardiovascular, pulmonary, neurological, or other medical disorders.

Breathing Circuit

Each participant was connected to the breathing circuit via a nasal mask. An appropriate-sized, airtight silicone nasal mask (Respironics, Murrysville, PA) was glued to the face to prevent mask leaks. The mask was connected to a Plateau Exhalation Valve (Respironics, Pittsburgh, PA), via a heated pneumotachometer. The valve, which provides a continuous leak path in the breathing circuit and serves as an exhaust vent, was connected to the inspiratory line. Participants were restricted to nasal breathing by placing tape over the mouth. During the mechanical ventilation (MV), protocol hyperventilation was achieved using a pressure support ventilator [bilevel positive airway pressure (PAP) machine; Resmed Sullivan VPAP II ST-A] for which the minimum allowable continuous PAP was 2 cmH2O. Gases were introduced from external sources connected to the inspiratory line. During the Hyp, participants breathed inspired O2 fraction (FiO2) of >35% from a 100% FiO2 gas source connected to the inspiratory line to keep inspired PO2 (PiO2) ≥ 250 Torr, whereas, during sham exposure (sham), participants breathed only room air introduced into the inspiratory line from a separate source.

Measurements

Electroencephalograms, electrooculograms, and chin electromyograms were recorded using the International 10–20 system of electrode placement (electroencephalogram: C3-A2 and C4-A1; electrooculogram, O-A2). Inspiratory airflow was measured by a heated pneumotachometer (model 3700A, Hans Rudolph, Kansas City, MO) attached to a RSS 100 HR Research Pneumotach System. The tidal volume (VT) was obtained from the electronic integration of the flow.
Arterial O2 saturation (SaO2) was measured by a pulse oximeter (Biox PA) from tubing placed in the nares via a port in the nasal mask.

The hypopharyngeal position was obtained by advancing the catheter tip for 2 cm after it disappeared behind the tongue. End-tidal Pco2 (Petco2) readings were obtained continuously by an infrared analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA) from tubing placed in the nares via a port in the nasal mask. Arterial O2 saturation (SaO2) was measured by a pulse oximeter (Biox 3700, Ohmeda). Petco2 was sampled continuously by an infrared analyzer (model CD-3A, AEI Technologies) via tubing attached to a port on the nasal mask. The signals were displayed on a polygraph recorder (Grass model 15, Astro-Med, West Warwick, RI) and recorded using Powerlab data-acquisition software (AD Instruments, Colorado Springs, CO) for detailed analysis.

Experimental Protocol

Overview. Hyperventilation via nasal MV was induced under conditions of Hyp or sham in random order in nine participants. Simple randomization was performed using a random table; the participants were blinded to the order of condition. Study participants were instructed to limit total sleep time to a maximum of 5 h on the night preceding the study. Two participants who did not maintain stable sleep on the first night repeated their respective experimental studies with zolpidem 5 mg before the study, to allow interrupted sleep. Participants assumed the supine position for the entire experimental protocol that was conducted during stable NREM sleep; hence, all trials were conducted while they were in stable stage 2 or stage 3 sleep. During Hyp, MV was conducted with continuous flow of oxygen, while the PIO2 was continuously monitored to keep PIO2 at 2 cmH2O throughout MV. MV was terminated after 3 min by returning the inspiratory PAP to the baseline expiratory PAP of 2 cmH2O. The ensuing hypocapnia resulted in either a hypopnea or central apnea. If an apnea was not induced, hyperventilation trials were repeated until apnea was induced. Central apnea was defined as an expiratory time ≥5 s. This methodology has been previously described (7, 31, 32, 47). A compressed polygraph segment, obtained from a participant in stage 2 sleep, before and during sustained hyperoxia, is shown in Fig. 1. The MV protocol was repeated on a second night under the alternate condition, Hyp or sham, in the nine participants.

Data Analysis

Sustained hyperoxia before MV. Data recorded during exposure to hyperoxia in the 10 participants before MV was used for analysis only if it was measured during stable NREM sleep. Inspired VT, inspiration time, total breath time, breathing frequency, minute ventilation (Vt), Petco2, inspired end-tidal Pco2, SaO2, supraglottic pressure, and upper airway resistance (RuA) were calculated breath by breath. RuA was computed using pressure-flow loops plotted for every breath; this methodology has been described previously (6, 34). For each variable, an average value was computed during the control room air period and during later hyperoxia period (sustained hyperoxia), just before the onset of MV protocol. The variables outlined above were averaged using 14 ± 4 (mean ± SD) breaths during control room air and using 5 breaths just before the onset of MV protocol (sustained hyperoxia, Table 1).

MV protocol. Sleep staging (1) and scoring of arousals (38) was performed using standard criteria, analyzing trials with stable NREM sleep. We analyzed MV trials accompanied by a stable stage N2 or N3 sleep state for both Hyp and sham conditions. During the control period, five breaths recorded immediately at the onset of MV protocol were averaged. Likewise, during the MV period, the last five mechanically ventilated breaths before the return to baseline expiratory PAP were averaged. The data analysis methodology has been previously described (7, 31, 32, 47). The AT was defined as the Petco2 that demarcated the central apnea closest to the eupneic Petco2. The CO2 reserve was defined as the change in Petco2 between eupneic Petco2 (control) and AT Petco2 (ΔPetco2). In addition, "hypocapnic ventilatory response" was defined as the change in Vt between control and
Table 1. Results of grouped data for timing, ventilation, and resistance during room air control and sustained hyperoxia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Sustained Hyperoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti, s</td>
<td>2.1 ± 0.1</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>Te, s</td>
<td>2.2 ± 0.1</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>14.6 ± 0.8</td>
<td>15.0 ± 0.8</td>
</tr>
<tr>
<td>PetCO2, Torr</td>
<td>41.5 ± 0.8</td>
<td>39.1 ± 0.8†</td>
</tr>
<tr>
<td>VT, liter</td>
<td>0.436 ± 0.03</td>
<td>0.507 ± 0.03*</td>
</tr>
<tr>
<td>Vi, l/min</td>
<td>6.2 ± 0.5</td>
<td>7.5 ± 0.6*</td>
</tr>
<tr>
<td>RUA, l·s⁻¹·cmH₂O⁻¹</td>
<td>9.7 ± 1.1</td>
<td>7.1 ± 1.3</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>96.5 ± 1.1</td>
<td>98.8 ± 0.6†</td>
</tr>
<tr>
<td>FIO₂, %</td>
<td>20.1 ± 0.8</td>
<td>74.2 ± 9.7‡</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 subjects (see test for details). Ti, inspiratory time; Te, expiratory time; f, frequency of breathing; PetCO2, end-tidal PCO2 level; VT, tidal volume; Vi, minute ventilation; RUA, upper airway resistance; SaO2, oxygen saturation; FIO2, fraction of inspired O2.

Results of grouped data for timing, ventilation, and resistance during room air control and sustained hyperoxia. Table 1 summarizes the results noted during control room air and sustained hyperoxia before onset of MV protocol. There was a significant increase in Vi, with a corresponding significant drop in PetCO2, during exposure to sustained hyperoxia, before the onset of MV protocol. Thus the lower PetCO2 observed during hyperoxia was likely a result of increased Vi upon exposure to sustained hyperoxia. A representative example of hyperventilation during sustained hyperoxia is shown in Fig. 1.

MV Protocol

In the nine participants who completed the MV protocol, the eupneic Vi during Hyp was significantly higher than Vi during sham exposure (7.2 ± 0.6 vs. 5.9 ± 0.9 l/min; P < 0.05), with a correspondingly lower eupneic PetCO2 during Hyp than during sham exposure (37.6 ± 0.6 vs. 41.1 ± 0.6 Torr; P = 0.001). The CO2 reserve was significantly larger during Hyp exposure relative to sham exposure (-3.8 ± 0.8 vs. -2.0 ± 0.3 Torr; P = 0.03) (Fig. 2A). Subsequently, the AT was significantly lower during Hyp relative to the sham study (33.3 ± 1.2 vs. 39.0 ± 0.7 Torr; P = 0.001) (Fig. 2A). This was associated with a significant decline in the hypocapnic ventilatory response under Hyp vs. sham conditions (2.5 ± 0.5 vs. 3.7 ± 0.5 l·min⁻¹·Torr⁻¹; P = 0.008, Fig. 2B).

RESULTS

Nine participants, (4 men and 5 women) completed the MV protocol of the study, age 23.6 ± 3.8 yr, body mass index 23.6 ± 3.0 kg/m², and neck circumference 34.2 ± 4.3 cm (means ± SD), while an additional participant completed only the baseline hyperoxia portion of the study, but was not able to maintain stable sleep during the MV protocol. Of the five women, four were studied in the follicular phase of their menstrual cycle, per reported date of menses; however, data on the fifth female participant was missing. The characteristics of the group of 10 was not different from the group that underwent MV protocol, five men and five women, age 23.4 ± 3.5 yr, body mass index 23.9 ± 3.0 kg/m², and neck circumference 34.4 ± 4.1 cm.

Baseline Sustained Hyperoxia

Sustained hyperoxia, before onset of MV protocol, was maintained for 21.9 ± 16.7 min (mean ± SD) in 10 participants. Table 1 summarizes the results noted during control room air and sustained hyperoxia before onset of MV protocol. There was a significant increase in Vi, with a corresponding significant drop in PetCO2, during exposure to sustained hyperoxia, before the onset of MV protocol. Thus the lower PetCO2 observed during hyperoxia was likely a result of increased Vi upon exposure to sustained hyperoxia. A representative example of hyperventilation during sustained hyperoxia is shown in Fig. 1.
HYPEROXIA AND APNEIC THRESHOLD DURING SLEEP

DISCUSSION

Our study demonstrated several novel findings regarding the effect of hyperoxia on the control of breathing during NREM sleep. 1) Sustained hyperoxia resulted in hyperventilation manifesting by increased V1 and a corresponding decrease in PETCO2. 2) Sustained hyperoxia was associated with a decline in the hypocapnic ventilatory response, a widened CO2 reserve, and reduced AT.

**Hyperoxic Hyperventilation**

We noted that sustained hyperoxia resulted in hyperventilation, manifesting as increased V1 and reduced PETCO2. Hyperoxia is defined as the level of PO2 inspired that produces a neural tissue PO2 greater than while breathing normobaric air (PO2 > 160 Torr) (10, 27, 28). Multiple animal and human studies have shown hyperoxic hyperventilation, after an initial transient hypoventilation (3, 4, 5, 8, 17, 26, 42). The initial hyperventilation (15, 42), due to peripheral chemoreceptor inhibition, has not been demonstrated consistently (5, 15, 17, 20, 26, 42). Subsequent hyperventilation is likely of central origin (15, 20, 42) and manifests as increased V1, commencing within 5 min of hyperoxia, and may be associated with an augmented hypercapnic response (20). Conversely, recent evidence in a canine model (36) showed that there is interdependence of peripheral and central chemoreceptors, and, in fact, the gain of the central chemoreceptors seems to be very dependent on the peripheral chemoreceptor activity (36). In our study, we observed an increase in V1 after at least 10–15 min of hyperoxia, suggesting that the central chemoreceptors have been activated. Whether the peripheral chemoreceptor had an additive, hyperadditive, or hypoadditive effect (14) in our model cannot be determined from our protocol.

There are several potential mechanisms underlying hyperoxic hyperventilation. Hyperoxia may result in increased brain tissue PCO2 via cerebral vasoconstriction (19) or the Haldane effect (22). Alternatively, hyperoxia may have a direct stimulatory effect on chemosensitive respiratory neurons (11, 27, 28, 29). For example, Mulkey et al. (28) demonstrated that hyperoxia was associated with increased production of reactive oxygen species and increased firing rate of central CO2 chemoreceptors in the solitary complex neurons of the dorsocaudal medulla oblongata. Our findings are consistent with the aforementioned studies by demonstrating the presence of hyperoxic hyperventilation in sleeping humans. The potential mechanisms of hyperoxic hyperventilation in sleeping humans are not addressed by our study.

**Hyperoxia and Susceptibility to Hypocapnic Central Apnea**

We noted that hyperoxia mitigated the propensity to develop central apnea during sleep. Potential contributing factors include background increased ventilatory motor output, chemoreflex sensitivity, and sleep state stability. Our findings are consistent with previous studies demonstrating a salutary effect of increased ventilatory motor output on breathing stability, as evidenced by widened CO2 reserve following central chemoreceptor stimulation with metabolic acidosis, or stimulation of the peripheral chemoreceptor with almitrine (30). Sustained hyperoxia may increase ventilatory motor output by cerebral vasoconstriction, either via direct effect of hyperoxia or a consequence of arterial hypocapnia. The net effect is reduced CO2 washout, elevated brain tissue PCO2, and increased H+ in the medulla (14).

We observed that hypocapnic chemoreflex sensitivity declined during hyperoxia, as measured by the reduced ventilatory change for a given change in PETCO2. Our findings with sustained hyperoxia are similar to previous studies demonstrating reduced CO2 sensitivity following transient Hyp exposure (9, 46). Thus hyperoxia likely blunted the peripheral responsiveness to hypocapnia, resulting in lower hypocapnic ventilatory response.

Widening of the CO2 reserve may be due to plant factors, which dampen the magnitude of hypocapnia for a given increase in ventilation. The development of hyperoxic hyperventilation and the concomitant decrease in eupneic PETCO2 also suggest reduced “plant gain” (13), as a greater change in V1 is required for a given decrease in eupneic PETCO2 (Fig. 3, see legend).

**Physiological Significance**

Our findings provide a mechanistic explanation for the reported therapeutic effect of supplemental oxygen in patients with central sleep apnea, associated with high altitude (4), congestive heart failure, and idiopathic central apnea (16, 18, 33, 39). Potential mechanisms include decreased plant gain or reduced CO2 chemoreflex sensitivity (17, 25, 46). Our findings are consistent with both mechanisms, as well as increased baseline ventilatory motor output, due to increased cerebral tissue PCO2 or direct hyperoxic stimulation, producing a sustained increase in ventilation in our study. This widened the CO2 reserve by lowering the eupneic CO2, thus stabilizing respiratory control. Thus the aggregate effects of hyperoxia promoted breathing stability during NREM sleep. This may provide a therapeutic pathway for treating central sleep apnea.

![Fig. 3. Schematic representation of the relationship between minute ventilation (V1) and PETCO2, along the isometabolic curve. Note decreased eupneic PETCO2 with hyperoxia (X), compared with sham exposure (Y), indicative of decreased plant gain. There is also a decrease in the slope of V1/C02 with hyperoxia (solid line) compared with sham (dashed line), confirming a decline in the hypocapnic ventilatory responsiveness upon exposure to hyperoxia. The arrows indicate CO2 reserve during the two exposure conditions: greater magnitude of CO2 reserve with hyperoxia (solid arrow) compared with sham room air exposure (dashed arrow). Points A and B represent AT during hyperoxia and sham, respectively.](http://jap.physiology.org/DownloadedFrom)
However, long-term safety and efficacy have not been established, given the potential for production of reactive oxygen species upon prolonged oxygen use in patients with central apnea and no evidence of hypoxemia.

Methodological Considerations

Sleep state instability may influence the AT and the hypocapnic ventilatory response; however, we analyzed trials with stable sleep state only. To achieve natural unaided sleep, we implemented moderate sleep curtailment on the night preceding the experimental protocol. Our own experience and published literature (37) demonstrate no adverse effect of moderate sleep curtailment in healthy humans on ventilatory control. In addition, study participants underwent similar sleep curtailment for both the hyperoxia and sham studies. Zolpidem was used to stabilize sleep in two individuals. It has no effect on ventilation or breathing stability and has been used by other investigators in similar studies (2, 46). Additionally, MV may induce neuromuscular inhibition if large VT (>200% of euapnic VT) were applied (21). Likewise, any volume effect on ventilatory control would manifest under both hyperoxia and sham nights. It is also possible that a reduction in RQ may unload the upper airway and thereby increase airflow and V̇̇I with reduced end-tidal CO₂ levels (34) with hyperoxia; however, the effect of hyperoxia on RQ was not significant (Table 1), indicating that this was not a contributing factor to the observed findings. Additionally, Mahamed et al. (23) suggested that a decline in metabolism during sleep produces a decrease in plant gain and thereby a significant overnight reduction in chemoreflex thresholds and stable breathing in non-obstructive sleep apnea subjects. While this may have been a possibility in our study, the effect of reduced metabolism would have been a contributing factor during both hyperoxia and sham exposures and would not explain the overall decrease in chemoreflex thresholds and stable breathing in non-obstructive sleep apnea subjects.

In conclusion, hyperoxia stabilizes breathing in healthy individuals during NREM sleep by stimulating hyperventilation, consequently widening the CO₂ reserve.

GRANTS

This work was supported by the Department of Veterans Affairs and the National Heart, Lung, and Blood Institute.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


