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Effect of oxygen in obstructive sleep apnea: Role of loop gain

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Abstract

We compared the effect of oxygen on the apnea-hypopnea index (AHI) in 6 obstructive sleep apnea patients with a relatively high loop gain (LG) and 6 with a low LG. LG is a measure of ventilatory control stability. In the high LG group (*unstable* ventilatory control system), oxygen reduced the LG from 0.69 ± 0.18 to 0.34 ± 0.04 ($p < 0.001$) and lowered the AHI by 53 ± 33 percent ($p = 0.04$ compared to the percent reduction in the low LG group). In the low LG group (*stable* ventilatory control system), oxygen had no effect on LG (0.24 ± 0.04 on room air, 0.29 ± 0.07 on oxygen, $p = 0.73$) and very little effect on AHI (8 ± 27 percent reduction with oxygen). These data suggest that ventilatory instability is an important mechanism causing obstructive sleep apnea in some patients (those with a relatively high LG), since lowering LG with oxygen in these patients significantly reduces AHI.

1. Introduction

Recurrent upper airway collapse is the cardinal feature of obstructive sleep apnea (OSA). While a small (narrow lumen) upper airway increases the risk of collapse, other mechanisms, such as ventilatory control instability, might further increase the risk. This is because the upper airway muscles, like the diaphragm, are linked to ventilatory control. An increase in ventilatory drive activates the upper airway muscles and promotes patency (Badr et al. 1991; Badr et al. 1994), whereas a decrease in ventilatory drive relaxes the upper airway muscles and facilitates closure (Kuna et al. 1993; Badr et al. 1995). Consequently, fluctuations in ventilatory drive (due to ventilatory control instability) can lead to upper airway instability and potentially collapse at the nadir of ventilatory drive (Onal et al. 1986; Hudgel et al. 1987; Warner et al. 1987). This suggests that stabilizing the ventilatory control system might be one way to reduce the risk of upper airway collapse in patients with OSA.

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Since oxygen has well-described ventilatory stabilizing properties (primarily a reduction in peripheral chemoresponsiveness (Nielsen et al. 1952; Reite et al. 1975; Severinghaus et al. 1978; Cunningham et al. 1986; Bisgard et al. 1996; Mohan et al. 1997; Duffin et al. 2000; Simakajornboon et al. 2002)) and is easy to administer, investigators have tested its effectiveness in patients with OSA. The results have been quite variable. Of 37 subjects studied in four prior experiments (Martin et al. 1982; Smith et al. 1984; Gold et al. 1985; Gold et al. 1986), 14 exhibited a 50 % or greater reduction in apnea-hypopnea index (AHI) with oxygen. The rest, however, demonstrated little or no improvement. We believe that this is the result of varying levels of ventilatory instability in different patients. In these studies, however, subjects were not categorized using a measurement of instability. We speculate that the subjects who responded well to oxygen in these studies had an unstable ventilatory control system, and that this instability significantly contributed to their disordered breathing.

To test this, we administered oxygen to two groups of OSA patients: those with a stable ventilatory control system (control group) and those with a relatively unstable ventilatory control system (treatment group). Ventilatory instability was quantified by determining each patient's loop gain (LG). LG is an engineering term that describes the *gain* of the negative feedback *loop* that regulates ventilation. Mathematically, it is the ratio of the ventilatory response to a ventilatory disturbance. If the magnitude of the response (e.g., hyperpnea) is greater than or equal to the magnitude of the disturbance (e.g., hypopnea), then the LG ratio will be ≥ 1 and ventilation will fluctuate between hyperpnea and hypopnea/apnea (i.e., the system is highly unstable). If the LG ratio is less than 1, or near zero, then ventilation will remain stable (little to no fluctuations in breathing) in response to a disturbance (see Fig. 1).

In this study, we hypothesized that OSA patients with a high LG (unstable ventilatory control system) would exhibit a significant reduction in AHI during supplemental oxygen breathing. On the contrary, OSA patients with a low LG (stable control system) would have little or no change in AHI during oxygen administration.

2. Methods

2.1 Subject selection

For this study, we wanted to enroll OSA patients with a high LG and a separate control group of patients with a low LG. In order to define the LG ranges for the high and low groups to be studied in this protocol, we pooled LG data from 35 OSA patients previously studied in our lab. These previously studied subjects were divided into quartiles. The upper quartile had a $LG > 0.45$, and the lower quartile had a $LG < 0.30$. Thus, these values were used as cutoffs for the individuals recruited into this current protocol.

Adults greater than 20 years of age were included. Subjects were excluded if they had a history of cerebrovascular disease, congestive heart failure, renal insufficiency, or lung disease. If greater than 50 % of respiratory events were central, or if there was crescendo-decrescendo Cheyne-Stokes respiration with central apnea during clinical polysomnography (PSG), then the subject was excluded from the study. Subjects taking medications that could potentially affect respiratory drive (e.g., stimulants or sedatives, thyroid hormones, or

aspirin/ibuprofen) were not excluded so long as there was no change in dosage or frequency while enrolled in the protocol. The study was approved by the Institutional Review Board at Brigham and Women's Hospital. All subjects gave informed, written consent prior to participating.

2.2 Equipment

Clinical PSG—AHI was measured on and off oxygen. Recorded signals included: electroencephalography (EEG; C₄/A₁, C₃/A₂, O₂/A₁, O₁/A₂), left and right electrooculography (EOG), chin and leg electromyography (EMG), airflow [nasal-oral thermistor and nasal pressure (using a nasal cannula attached to a pressure transducer, PTAF2, Pro-Tech Services, Woodinville, WA)], chest plus abdominal wall motion (piezo-electric bands), EKG, arterial oxygen saturation (Model 930 Pulse-Oximeter, Respironics, Murrysville, PA), body position using a mercury gauge, and snoring using a microphone attached to the neck. All signals were collected and stored using the Alice digital PSG system (Respironics).

Research PSG—LG was also measured on and off oxygen. EEG, EOG, chin EMG, and EKG were monitored similar to the clinical PSG. Oxygen saturation was monitored at the finger (BCI, Waukesha, WI) and expired P_{CO₂} was monitored at the mask with a calibrated CO₂ analyzer (BCI). Subjects wore a nasal mask connected to a BiPAP Vision mechanical ventilator (Respironics). Mask pressure and airflow signals were obtained from the pressure transducer and the pneumotach inside the ventilator. Signals were sampled at 125 Hz and displayed on Nihon Kohden (Tokyo, Japan) and Spike 2 software (Cambridge Electronic Design, Cambridge, UK). The BiPAP Vision mechanical ventilator is capable of delivering continuous positive airway pressure (CPAP) alone or in combination with proportional assist ventilation (PAV).

PAV is a mode of ventilatory support that generates pressure at the airway opening in proportion to respiratory effort (Younes 1992; Meza et al. 1996; Meza et al. 1998; Younes et al. 2001). Using a flowmeter to detect the movement of air from the ventilator to the patient, flow and tidal volume are continuously monitored. These signals are amplified by separate gain controls: a flow assist gain control (FA) and a volume assist gain control (VA). The amplified flow and volume signals determine ventilator pressure output. FA and VA may be set equal to the resistance and elastance of the respiratory system, respectively, or they may be set to "normal" values as was done in this study. Finally, a percent assist dial is used to set the percentage of FA and VA gains used to amplify the flow and tidal volume signals. For example, if the percent assist is set at 50%, then 50% of the pressure needed to overcome the resistance and elastance of the respiratory system is supplied by the ventilator, and thus the patient needs to generate only 50% effort to produce normal tidal volumes.

With PAV, large efforts receive more assist (inspiratory pressure) than small efforts. Therefore, ventilatory responsiveness, and thereby LG, is increased by PAV. Incremental increases in PAV can raise the LG to 1 and produce periodic breathing, which allows the subject's intrinsic LG to be calculated as described below in Data Analysis. Occasionally, however, LG cannot be increased to 1 because the inspiratory pressure generated by PAV

exceeds the pressure needed to overcome the intrinsic resistive and elastic pressures of the respiratory system. As a result, the lungs continue to inflate during neural expiration until eventually elastic pressure (at high lung volumes) exceeds airway opening pressure (produced by PAV), at which point exhalation can occur. This is known as “volume runaway” and, in some patients, prevents PAV from being increased beyond a certain level. If volume runaway occurs at a lower PAV level than that needed to raise LG above 1, then periodic breathing cannot be induced. It is not unusual for this to occur in individuals with a very low LG, because the amount of PAV needed to induce instability can be quite high in these subjects. Higher LG individuals, on the other hand, by definition develop periodic breathing at relatively low PAV support, and thus volume runaway is typically not a problem.

2.3 Protocol

Clinical PSG—The room air and oxygen AHI measurements were performed on separate nights within 1 month of each other. Subjects presented to the clinical sleep laboratory at 9 pm and were asked to sleep in the supine position. The room air and oxygen studies were conducted exactly the same except for the difference in inspired gas. For the oxygen night, an initial 3 L/min of oxygen was administered via nasal cannula. If the oxygen saturation dropped below 95 % during respiratory events, then the flow rate was increased as needed to a maximum of 5 L/min.

Research PSG—Room air and oxygen LG measurements were attempted in a single night, although usually a second night was needed. Oxygen was added to the nasal mask at 4 L/min and adjusted to keep the $S_{a_{O_2}}$ 95%. Subjects slept in the supine position for the entire study. Once stable NREM sleep was achieved, CPAP was adjusted to eliminate any flattening in the inspiratory flow pattern. A maximum volume limit of twice the subject’s baseline tidal volume was used to prevent awakening from PAV amplification of occasional large efforts (e.g., sigh). Next, PAV was increased to approximately 50 % assist for 5 minutes. If periodic breathing was not observed, PAV was incremented to slightly higher levels every 3 to 5 minutes. At each level not associated with periodic breathing, a tidal volume amplification factor (VTAF) was measured 3 to 5 times by abruptly lowering the percent assist to zero for one breath (Younes et al. 2001). VTAF is the ratio of assisted tidal volume to unassisted tidal volume and is used for calculating LG (see Data Analysis). The PAV manipulations ended after sustained periodic breathing or volume runaway occurred.

If awakening occurred during the PAV increase, the percent assist was decreased back to zero until stable sleep resumed. We then increased PAV over several minutes back to the percent assist achieved prior to awakening. Thereafter, PAV was raised in small increments as described above (with VTAF’s being measured at each assist level not associated with periodic breathing). If at any time cycling ventilation occurred without an adequate number of preceding VTAF measurements, the percent assist was decreased by 5–10 % to measure VTAF’s during stable breathing. We then increased the percent assist back to the level associated with periodic breathing as confirmation.

2.4 Data Analysis

Apneas and hypopneas were scored according to American Academy of Sleep Medicine recommendations (AASM 1999). However, oxygen desaturation criteria were not used for scoring events. Central and mixed events were scored when there was an absence of respiratory effort throughout (central) or in the early portion (mixed) of an apnea. Cheyne-Stokes respiration was defined as a crescendo-decrescendo breathing pattern with central apnea at the nadir. AHI (number of apneas and hypopneas per hour of sleep) was calculated from supine, NREM sleep only. Apnea and hypopnea length were determined from the time at which flow decreased below 50 % of baseline until the event ended.

LG was calculated from the average VTAF of the highest assist level achieved prior to the development of periodic breathing or volume runaway (Younes et al. 2001). VTAF is a measure of PAV amplification of the subject's intrinsic LG ($LG_{intrinsic}$). Thus, the total LG on PAV (LG_{PAV}) is the product of $LG_{intrinsic}$ and VTAF ($LG_{PAV} = LG_{intrinsic} \cdot VTAF$). At the lowest PAV level associated with periodic breathing, $LG_{PAV} = 1$. Thus, $LG_{intrinsic}$ is calculated as the reciprocal of VTAF. If LG_{PAV} could not be brought to 1 due to volume runaway ($LG_{intrinsic} \cdot VTAF < 1$), $LG_{intrinsic}$ was assigned a "less than" value. Periodic breathing was defined as at least 4 cycles of a crescendo-decrescendo pattern in flow and VT (nadir VT < 30 % of peak VT). Cycles were excluded if they contained arousals (> 3 seconds of > 8 Hz EEG activity).

2.5 Statistics

Three sets of comparisons were made. First, baseline (room air) variables were compared between the high and low LG groups to determine if there were significant differences between them. This was done using a non-parametric test (Wilcoxon rank sum test). Second, the effect of oxygen on measured variables *within* each group was compared using the Wilcoxon sign rank test. Third, to compare the effect of oxygen *between* groups, the change (absolute difference) in each variable was compared between groups using the Wilcoxon rank sum test. For AHI, the percent change, rather than the absolute difference, was compared. To deal with paired censored observations (i.e., LG values that were "less than"), survival methods for clustered data were used (Lee et al. 1992). To implement this method, we subtracted LG values from 1 so that less than values became greater than values (or right censored). The data were analyzed by specifying the COVS(AGGREGATE) option in the SAS PHREG procedure to compute the robust sandwich covariance matrix. All statistics were performed using SAS 9.1 software (Cary, NC). Results are reported as means $\pm$ standard deviations. The less than sign was ignored when averaging LG values. A $p < 0.05$ was considered significant.

3. Results

We performed 43 LG measurements to obtain 12 individuals that fit into either the high or low LG group (6 in each group). Each of the 12 participants underwent 3–4 separate study nights. Thus, a total of 77 sleep studies were performed. Two of the high LG subjects did not participate in the LG re-measurement on oxygen. One subject was given 5 mg of zolpidem on each of the study nights. Two subjects took 81 mg of aspirin daily and were not

instructed to discontinue this for the study. Two subjects in the high LG group and one in the low LG group did not use CPAP at home. All others were compliant CPAP users by history.

Baseline (room air) variables for each group are displayed in Table 1. Except for 1 female in the high LG group, all subjects were male. The high LG group was younger, required less CPAP to eliminate flow limitation, and had a higher P_{CO_2} asleep than the low LG group. There were no differences in BMI or oxygen saturation. The frequency and length of respiratory events, as well as the percentage of central and mixed apneas, were not different between groups. LG was 0.62 ± 0.18 in the high group and 0.24 ± 0.05 in the low group ($p = 0.004$).

3.1 Between group comparisons of the effect of oxygen

The percent reduction in AHI in the high LG group (53 ± 33 percent) was significantly greater than in the low LG group (8 ± 27 percent, $p = 0.04$) (Fig. 2). There was a greater increase in apnea-hypopnea length in the high LG group ($p = 0.04$) (Fig. 3A). However, events were initially shorter in the high LG group. When they increased with oxygen, they became similar in length to the low LG group. The decrease in the percentage of central and mixed events with oxygen administration was not different between groups ($p = 0.42$) (Fig. 3B), and there were no differences in the change in P_{CO_2} ($p = 0.83$). The reduction in LG was significantly greater in the high LG group ($p < 0.0001$) (Fig. 4). We did not perform a correlation analysis between the change in LG and the change in AHI because the low LG group exhibited no significant change in LG, and there were insufficient numbers to test this in the high LG group.

3.2 Effect of oxygen in the high LG group

During standard PSG, similar amounts of supine NREM sleep were observed on and off oxygen (218 ± 63 minutes versus 216 ± 45 minutes, respectively). Supplemental oxygen significantly increased the Sa_{O_2} during wakefulness (from $95 \pm 1\%$ to $98 \pm 1\%$, $p = 0.03$), the minimum Sa_{O_2} during sleep (from $79 \pm 5\%$ to $91 \pm 4\%$, $p = 0.03$), and the mean desaturation during respiratory events (from $87 \pm 5\%$ to $95 \pm 2\%$, $p = 0.03$). In the high LG group, AHI decreased from 63 ± 34 episodes/hr to 34 ± 30 episodes/hr ($p = 0.03$). Apnea-hypopnea length increased from 23 ± 3 seconds to 29 ± 3 seconds ($p = 0.06$) (Fig. 3A), and the percentage of central and mixed events decreased from 14 ± 15 percent to 3 ± 4 percent ($p = 0.06$) (Fig. 3B).

In the PAV studies, eupneic P_{CO_2} did not change with oxygen administration (44.1 ± 2.3 mmHg* on air versus 43.5 ± 2.4 mmHg on oxygen, $p = 0.25$). Fig. 5 shows tracings from four high LG subjects. In the left column is room air breathing at the PAV level associated with periodic breathing. In the right column is oxygen breathing at a similar PAV level as the corresponding tracing on the left. The ventilatory pattern completely regularizes in tracings A and D. While ventilation is still variable during oxygen breathing in tracings B

*Calculated from the four individuals who had LG measured on oxygen.

and C, there is no crescendo-decrescendo periodicity. Rather, the variations are mostly random and thus probably due to PAV amplification of physiologic variability rather than a high LG. Indeed, LG decreased substantially in the high LG group (from $0.69 \pm 0.18^*$ to less than 0.34 ± 0.04 , $p < 0.001$) (Fig. 4).

3.3 Effect of oxygen in the low LG group

Similar amounts of supine NREM sleep were observed on and off oxygen during the standard PSG (253 ± 27 minutes versus 235 ± 35 minutes, respectively). Supplemental oxygen significantly increased the Sa_{O_2} during wakefulness (from $95 \pm 2\%$ to $98 \pm 1\%$, $p = 0.03$), the minimum Sa_{O_2} during sleep (from $81 \pm 8\%$ to $91 \pm 5\%$, $p = 0.03$), and the mean desaturation during respiratory events (from $91 \pm 6\%$ to $96 \pm 2\%$, $p = 0.03$). There was no significant change in AHI on oxygen (44 ± 34 episodes/hr on air, 37 ± 28 episodes/hr on oxygen, $p = 0.44$). Apnea-hypopnea length did not change with oxygen administration (Fig. 3A), and the percentage of central and mixed events decreased but was not statistically significant (Fig. 3B).

During the PAV nights, end-tidal P_{CO_2} was similar on and off oxygen (39.5 ± 2.1 mmHg on air versus 39.0 ± 2.5 mmHg on oxygen, $p = 0.53$). We also observed no significant change in LG with oxygen: it was less than 0.24 ± 0.04 on room air, and it remained less than 0.29 ± 0.07 during oxygen breathing ($p = 0.73$) (Fig. 4).

4. Discussion

Our primary aim in this study was to determine if OSA patients with high LG exhibit a greater reduction in AHI than patients with a low LG when oxygen was administered. The major findings were:

1. Oxygen breathing reduced the AHI substantially in OSA patients with high LG but not in patients with a low LG.
2. Supplemental oxygen effectively reduced the LG in patients with a high LG but had little effect in those with a low LG.

4.1 Role of ventilatory instability in OSA

Several studies have examined the relationship between ventilatory instability and OSA. Early studies measuring hypoxic and hypercapnic ventilatory responses (i.e., chemosensitivity) in OSA patients were conflicting (Garay et al. 1981; Lopata et al. 1982; Benlloch et al. 1995; Appelberg et al. 1997; Wilcox et al. 1998). However, more recent studies, in which the total LG was measured, suggest that OSA patients as a group have a more unstable system than normal individuals. Using random pulses of inspired CO_2 to stimulate the feedback loop, Hudgel and colleagues found a higher awake LG in OSA patients compared to controls (Hudgel et al. 1998). Similarly, Younes showed that individuals with severe OSA exhibit periodic breathing at lower levels of PAV than mild OSA patients (Younes et al. 2001), and that OSA patients in general have increased chemoresponsiveness (Younes et al. 2007). Our lab has also measured the relationship between LG and AHI in patients with varying degrees of upper airway collapsibility. We

found a significant correlation between these variables in patients with a pharyngeal closing pressure near 0 cmH₂O (Wellman et al. 2004), indicating the importance of upper airway anatomy in relationship to LG. Lastly, Asyali and colleagues (Asyali et al. 2002) used a minimal model of ventilatory control to estimate LG from esophageal pressure fluctuations in response to an arousal stimulus. While they found no significant difference in steady state LG between OSA patients and controls, the OSA group exhibited more oscillatory response dynamics.

While these studies suggest an association between ventilatory control instability and OSA, they do not necessarily demonstrate a cause-and-effect relationship. Thus, it is not clear whether the levels of instability observed in OSA patients are physiologically important. In our experiment, we lowered LG with supplemental oxygen and showed a significant improvement in apnea severity in a subgroup of patients. This, we believe, is compelling evidence that LG plays a causal role in these individuals.

This is supported by a recent theoretical study by Longobardo et al (Longobardo et al. 2008). These investigators examined the role of LG in producing obstructive sleep apnea using a theoretical model. The model contained equations describing the neurochemical control of breathing, changes in alertness, and upper airway collapsibility. They found that an increased LG caused obstructive apneas when the upper airway was “moderately” collapsible, and that lowering the LG with supplemental oxygen eliminated the obstruction. This effect was less apparent when the airway was made more collapsible, which could explain why we did not observe more complete resolution of OSA in our study.

4.2 Can oxygen stabilize the upper airway?

Studies demonstrating a link between ventilatory instability and fluctuating upper airway mechanics did so by producing substantial ventilatory instability, i.e., LG was raised to > 1 and periodic breathing was induced (Onal et al. 1986; Hudgel et al. 1987; Warner et al. 1987). In this study, we were interested in determining whether a LG of approximately 0.50 (which would not produce frank periodic breathing but is typical of what we find in “high” LG OSA patients) could potentially have an effect on upper airway mechanics. More importantly, we wanted to know if reducing the LG by 0.30 or 0.40 points (as we observed on oxygen) would be sufficient to stabilize the airway. Our results suggest that it is, at least part of the time.

To further investigate the plausibility of our findings, we simulated a model of respiratory control (Khoo et al. 1982) to: 1) determine if the amplitude of fluctuations in ventilatory drive (following, say, an obstructive hypopnea) in a typical high LG OSA patient (LG = 0.5–0.6) could reasonably be expected to influence upper airway mechanics; 2) verify our observation that supplemental oxygen reduces LG by 0.30–0.40 points in a high LG OSA patient; and 3) determine if such a reduction in LG could “dampen” fluctuations in ventilatory drive enough to stabilize the upper airway. We chose to simulate the model developed by Khoo because it is well-established, and because the equations can be solved analytically for a particular LG. The model equations and parameters used in the simulation are provided in the Appendix.

Figure 6 shows the results of the model simulation. In part A, the model is breathing room air and has a LG of 0.57. We disturbed the ventilatory control system with a typical “obstructive hypopnea” by reducing ventilation from the baseline level to 2 L/min for 23 seconds. At the termination of the hypopnea, the figure shows that ventilation overshoots to 33 L/min due to the build up in ventilatory drive (dotted line). The subsequent undershoot decreases to 0.67 L/min. As a result, significant upper airway obstruction might occur if, for instance, the airway tends to collapse when ventilatory drive to the muscles drops below 1 L/min. Figure 6B is the same model as figure 6A except oxygen has been added. This decreases the LG from 0.57 to 0.17. Note that there is virtually no undershoot following the hypopnea, despite the fact that it lasts 6 seconds longer than the hypopnea in part A (experimentally, we found a 6 second increase in apnea-hypopnea length during oxygen administration). Even if oxygen only reduced the LG to 0.29, (Fig. 6C), the ventilatory drive is still prevented from dropping below the critical threshold of 1 L/min for this example. Obviously, this threshold depends upon on the anatomy/collapsibility of the individual upper airway. Nevertheless, this simulation makes it plausible that a LG of 0.57 is probably high enough to produce clinically significant changes in upper airway mechanics, and that a reduction in LG of a few tenths of a point might be sufficient to stabilize the upper airway.

4.3 Limitations

We did not measure upper airway anatomy/collapsibility in this study. It is possible that the lack of improvement in the low LG group, in whom a greater amount of CPAP was required, could be due to a more collapsible airway such that changes in LG were not physiologically important. However, CPAP requirement is an imprecise measure of collapsibility, and since we also found no change in LG in this group, we think it is unlikely that greater collapsibility was the reason for the poorer response.

It would also have been ideal to better match for age in the two groups. However, this would have required us to screen a much larger number of subjects. Also, we have recently shown that LG is quite low in elderly individuals (Wellman et al. 2007), and therefore it is not surprising that the low LG group was slightly older.

Lastly, it could be argued that the reduction in AHI in the high LG group was simply due to a lengthening of respiratory events, and thus the perceived improvement is misleading. However, if an individual had, on average, a 23 second apnea followed by an approximately 23 second hyperpnea (i.e., one event every 46 seconds), then the AHI would be 78 if the individual cycled continuously. Lengthening the apneas by 6 seconds, such that events now occurred every 58 seconds, would decrease the AHI to 62 (a 21 % reduction). As we observed a much larger reduction than this, we believe the improvement in OSA was not simply related to an increase in apnea length.

4.4 Conclusion

In summary, we have shown that supplemental oxygen reduces LG and improves the AHI in OSA patients with an unstable ventilatory control system. In contrast, patients with an inherently stable system are relatively unaffected by oxygen. This could explain the variable response to oxygen observed in previous studies. Our findings also suggest a cause-and-

effect relationship between ventilatory instability and OSA *at the levels of instability we find in OSA patients*. Thus, a LG of ~ 0.50 , while it does not produce frank instability per se, is probably an important contributor to the development of sleep related upper airway obstruction, and reducing it to ~ 0.20 with supplemental oxygen may significantly decrease the number of disordered breathing events. In the future, further characterization of the different mechanisms leading to OSA in individual patients might allow us to reduce the AHI even further in select populations. This would require intense physiologic investigation and/or simpler methods for quantifying the different pathophysiologic mechanisms.

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Appendix: Model of respiratory control {Khoo, 1982#2108}

Glossary of terms

Ca_{CO_2}, Ca_{O_2}	concentration of CO ₂ and O ₂ in arterial blood, ml/ml
Cv_{CO_2}, Cv_{O_2}	concentration of CO ₂ and O ₂ in venous blood, ml/ml
$\dot{V}D, \dot{V}A, \dot{V}E$	dead space, alveolar, and expired ventilation, L/sec
$\dot{V}P, \dot{V}C$	peripheral and central contributions to ventilation, L/min
$\dot{Q}$	cardiac output, L/sec
V_{CO_2}, V_{O_2}	lung storage volume for CO ₂ and O ₂ , L
PI_{CO_2}, PI_{O_2}	partial pressure of inspired CO ₂ and O ₂ , mmHg
Pa_{CO_2}, Pa_{O_2}	partial pressure of arterial CO ₂ and O ₂ , mmHg
$\dot{V}_{CO_2}, \dot{V}_{O_2}$	metabolic production rate for CO ₂ and consumption rate for O ₂ , L/sec
Vt_{CO_2}, Vt_{O_2}	body tissue storage volume for CO ₂ , L
K_{CO_2}	slope of the CO ₂ dissociation curve, mmHg ⁻¹
τ_P, τ_C	peripheral and central circulation delays, sec
τ_h, τ_a	mixing time constants for the heart and arteries, sec
GP, GC	peripheral and central controller gains, L/sec/mmHg
IP, IC	peripheral and central apnea thresholds for CO ₂ , mmHg
Pb_{CO_2}	partial pressure of CO ₂ in the brain compartment, mmHg
$\dot{Q}_b$	brain blood flow, L/sec
Vb	volume of brain tissue compartment, L
$\dot{V}b_{CO_2}$	metabolic production rate for CO ₂ in the brain compartment, L/sec

Model Equations

Lung compartment:

$$\begin{aligned}\frac{dPa_{CO_2}}{dt} &= \frac{863\dot{Q}}{V_{CO_2}} (Cv_{CO_2} - Ca_{CO_2}) + \frac{PI_{CO_2} - Pa_{CO_2}}{V_{CO_2}} \dot{V}A \\ \frac{dPa_{O_2}}{dt} &= \frac{863\dot{Q}}{V_{O_2}} (Cv_{O_2} - Ca_{O_2}) + \frac{PI_{O_2} - Pa_{O_2}}{V_{O_2}} \dot{V}A \\ \dot{V}A &= \dot{V}E - \dot{V}D\end{aligned}$$

Body tissue compartment:

$$\begin{aligned}\frac{dCv_{CO_2}}{dt} &= \frac{\dot{Q}}{Vt_{CO_2}} (Ca_{CO_2} - Cv_{CO_2}) + \frac{\dot{V}_{CO_2}}{Vt_{CO_2}} \\ \frac{dCv_{O_2}}{dt} &= \frac{\dot{Q}}{Vt_{O_2}} (Ca_{O_2} - Cv_{O_2}) - \frac{\dot{V}_{O_2}}{Vt_{O_2}}\end{aligned}$$

CO₂ and O₂ dissociation curves:

$$\begin{aligned}Ca_{CO_2} &= K_{CO_2} Pa_{CO_2} + 0.244 \\ Ca_{O_2} &= 0.00025 Pa_{O_2} + 0.1728 \quad (70 < Pa_{O_2}) \\ &= 0.00067 Pa_{O_2} + 0.1434 \quad (55 < Pa_{O_2} < 70) \\ &= 0.00211 Pa_{O_2} + 0.0662 \quad (35 < Pa_{O_2} < 55)\end{aligned}$$

Circulatory mixing and delay:

$$\begin{aligned}\tau_1 \tau_2 \frac{d^2 Pa_{CO_2}^x}{dt^2} + (\tau_1 + \tau_2) \frac{dPa_{CO_2}^x}{dt} + Pa_{CO_2}^x &= Pa_{CO_2}(t - \tau_x) \\ \tau_1 \tau_2 \frac{d^2 Pa_{O_2}^x}{dt^2} + (\tau_1 + \tau_2) \frac{dPa_{O_2}^x}{dt} + Pa_{O_2}^x &= Pa_{O_2}(t - \tau_x)\end{aligned}$$

where x represents P for the peripheral circulation and C for the central circulation.

Peripheral and central controllers:

$$\begin{aligned}\dot{V}P &= GP e^{-0.05 Pa_{O_2}^P} (Pa_{CO_2}^P - Ip) \\ \frac{dPb_{CO_2}}{dt} &= \frac{\dot{Q}b}{\dot{V}b} (Pa_{CO_2}^C - Pb_{CO_2}) + \frac{\dot{V}b_{CO_2}}{K_{CO_2} \dot{V}b} \\ \dot{V}C &= GC \left(Pb_{CO_2} - \frac{\dot{V}b_{CO_2}}{\dot{Q}b K_{CO_2}} - IC \right) \\ \dot{V}E &= \dot{V}P + \dot{V}C\end{aligned}$$

Parameter values used in the model simulation

	Normoxia	Hyperoxia
$\dot{V}_D$, L/sec	0.03	0.03

	Normoxia	Hyperoxia
$\dot{Q}$, L/sec	0.1	0.1
V_{CO_2} , L	3.2	3.2
PI_{CO_2} , mmHg	0	0
V_{O_2} , L	2.5	2.5
PI_{O_2} , mmHg	150	200
Vt_{CO_2} , L	15	15
$\dot{V}_{CO_2}$, L/sec	0.0035	0.0035
Vt_{O_2} , L	6	6
$\dot{V}_{O_2}$, L/sec	0.005	0.005
τ_p , sec	6.1	6.1
τ_c , sec	7.1	7.1
τ_1 , sec	1	1
τ_2 , sec	2	2
GP , L/sec/mmHg	0.504	0.504
GC , L/sec/mmHg	0.015	0.015
IP , mmHg	35.5	35.5
IC , mmHg	44.5	44.5
$\dot{Q}_b$, L/sec	0.025	0.025
V_b , L	1.4	1.4
$\dot{V}_b$, L/sec	0.00075	0.00075
Loop gain*	0.57	0.17

* Loop gain at the frequency associated with a 180 degree phase angle.

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Figure 1.

LG is the ventilatory response to disturbance ratio. A. Example of a LG of 0.72. The ventilatory control system is disturbed with a transient reduction in ventilation (a). This produces a response (b) in the opposite direction that is 72 % as large as the disturbance. The next response (c) will also be 72 % as large as (b), etc. Thus, a LG of 0.72 produces transient fluctuations in ventilation, but ventilation eventually returns to baseline. B. A LG of 1 will produce a response that is equal in magnitude to the disturbance. Ventilation, therefore, oscillates without returning to baseline. The system in B is highly unstable. The closer LG is to zero, the smaller the fluctuations in ventilation, and thus the more stable the system.

Figure 2.

Percent reduction in AHI in the high and low LG groups. Oxygen reduced the AHI from 63 ± 34 episodes/hr to 34 ± 30 episodes/hr in the high LG group (53 ± 33 % reduction) and from 44 ± 34 episodes/hr to 37 ± 28 episodes/hr in the low LG group (8 ± 27 % reduction).-, Mean value for each group.

Figure 3.

Effect of oxygen on the length and type (central or mixed) of respiratory events. Diagrams on the left are the high LG group, and diagrams on the right are the low LG group. A. Supplemental oxygen prolonged apneas and hypopneas more in the high LG group than the low LG group. B. There was a non-significant decrease in the percentage of central and mixed events. —, Mean value for each group.

Figure 4.

Effect of oxygen on LG. Oxygen significantly reduced the LG in subjects with a high LG but had little effect in the low LG group.—, Mean value for each group.

Figure 5.

Stabilization of the ventilatory pattern with oxygen. Three-minute tracings of tidal volume (V_T , liters) and oxygen saturation (SaO_2) are shown for four high LG subjects who had LG measurements on and off oxygen. Figures on the left are room air breathing at the PAV level associated with periodic breathing. Figures on the right are oxygen breathing at the same, or slightly higher, PAV level as the corresponding figure on the left, i.e., the subject's LG is amplified to the same extent in both tracings. Subject A and D breathed more regularly when oxygen was administered. The respiratory rate was substantially slower in subject A

(right figure). Subject B and C continued to exhibit variability during oxygen breathing, but the variations were non-periodic.

Figure 6.

Simulated obstructive hypopnea in a “high” LG OSA patient breathing room air (A) and supplemental oxygen (B and C). In all three tracings, the hypopnea was simulated by reducing ventilation (solid line) to 2 L/min for several seconds. Ventilatory drive (dotted line) is plotted on the same axes as ventilation. During the obstructive event, ventilatory drive increases until, after 20–30 seconds, the airway opens and ventilation increases to match the ventilatory demand, i.e., the solid line “catches up” with the dotted line. The arrowhead in each diagram marks the nadir ventilatory drive at which the airway is most susceptible to collapse. A. The LG is 0.57 and there is a 23 second obstructive hypopnea. These are similar to the values we observed in the high LG group. Note that, following the hypopnea, there is a large overshoot that leads to an undershoot to 0.67 L/min (arrowhead). Such a reduction in ventilatory drive to the upper airway muscles would likely cause obstruction in a susceptible person. B. The situation is different when LG has been lowered to 0.17 by supplemental oxygen. Here, the hypopnea lasts 29 seconds (similar to the increase in hypopnea length that we observed). Despite the longer event, there is only a small overshoot and virtually no undershoot. Thus, the airway would likely remain stable at this LG level. C. Even if the LG could only be lowered to 0.29 with oxygen, a prolonged (29

second) hypopnea would produce an undershoot in ventilatory drive of 2.9 L/min (arrowhead), which is still significantly greater than the nadir of 0.67 L/min above.

Table 1

Room air values in the high and low loop gain groups

	High LG group	Low LG group	p value
Sex, male/female	5/1	6/0	ns
Age, years	45 ± 8	57 ± 9	0.04
BMI, kg/m ²	32 ± 3	30 ± 3	ns
LG, dimensionless	0.62 ± 0.18	0.24 ± 0.04	0.004
CPAP, cm H ₂ O	9 ± 2	12 ± 1	0.01
AHI, episodes/hr	63 ± 34	44 ± 34	ns
% Centrals or Mixed	14 ± 15	7 ± 10	ns
Apnea Length, sec	23 ± 31	27 ± 4	ns
Awake Sa _{O₂} , %	95 ± 1	95 ± 2	ns
Minimum Sa _{O₂} , %	79 ± 5	81 ± 8	ns
Mean Desat, %	87 ± 5	91 ± 6	ns
P _{CO₂} , mmHg	43 ± 2	40 ± 2	0.01