Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea

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Xie A, Teodorescu M, Pegelow DF, Teodorescu MC, Gong Y, Fedie JE, Dempsey JA. Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea. J Appl Physiol 115: 22–33, 2013. First published April 18, 2013; doi:10.1152/japplphysiol.00064.2013.—To determine how the obstructive sleep apnea (OSA) patient’s pathophysiological traits predict the success of the treatment aimed at stabilization or increase in respiratory motor outputs, we studied 26 newly diagnosed OSA patients [apnea-hypopnea index (AHI) 42 ± 5 events/h with 92% of apneas obstructive] who were treated with O2 supplementation, an isocapnic rebreathing system in which CO2 was added only during hyperpnea to prevent transient hypocapnia, and a continuous rebreathing system. We also measured each patient’s controller gain below eupnea [change in minute volume/change in end-tidal PETCO2 (ΔV/ΔPETCO2)], CO2 reserve (eupnea-apnea threshold PETCO2), and plant gain (ΔPETCO2/ΔVt), as well as passive upper airway closing pressure (Pcrit). With isocapnic rebreathing, 14/26 reduced their AHI to 31 ± 6% of control (P < 0.01) (responder); 12/26 did not show significant change (nonresponder). The responders vs. nonresponders had a greater controller gain (6.5 ± 1.7 vs. 2.1 ± 0.2 l/min−1·mmHg−1, P < 0.01) and a smaller CO2 reserve (1.9 ± 0.3 vs. 4.3 ± 0.4 mmHg, P < 0.01) with no differences in Pcrit (−0.1 ± 1.2 vs. 0.2 ± 0.9 cmH2O, P > 0.05). Hypercapnic rebreathing (+4.2 ± 1 mmHg PETCO2) reduced AHI to 15 ± 4% of control (P < 0.01) in 17/21 subjects with a wide range of CO2 reserve. Hyperoxia (SaO2 ~95–98%) reduced AHI to 36 ± 11% of control in 7/19 OSA patients tested. We concluded that stabilizing central respiratory motor output via prevention of transient hypocapnia prevents most OSA in selected patients with a high chemosensitivity and a collapsible upper airway, whereas increasing respiratory motor output via moderate hypercapnia eliminates OSA in most patients with a wider range of chemosensitivity and CO2 reserve. Reducing chemosensitivity via hyperoxia had a limited and unpredictable effect on OSA.

isocapnia; hypocapnia; hyperoxia

There are several lines of evidence linking the stability of central respiratory motor output with airway obstruction during sleep. First, there are significant (albeit modest) correlations of loop gain, an estimate of control system stability, with the severity of obstructive sleep apnea (OSA) (3, 68, 78), and continuous positive-airway-pressure (CPAP) therapy reduces loop gain in many OSA patients as well as in animals (16, 57, 65). Second, central apneas or unstable breathing during sleep may result in airway obstruction at the nadir of respiratory drive in snoring subjects (1, 6, 26, 52, 66). Third, increasing or stabilizing respiratory drive or reducing chemosensitivity reduces airway resistance and/or relieves airway obstruction in some sleep apnea patients (5, 15, 28, 69). However, which OSA patients might benefit from reducing the propensity for unstable central respiratory motor output has not been adequately addressed.

Based on these background findings we hypothesized that stabilizing central respiratory motor output in OSA patents who are characterized by a combination of mild to moderate airway collapsibility (Pcrit = 0 ± 2 cmH2O) and increased controller gain (chemosensitivity) would relieve airway obstruction. To this end we determined the critical closing pressure of the upper airway (UAW), the CO2 responsiveness below eupnea (controller gain), and plant gain in newly diagnosed, untreated OSA patients. Then, in these same patients we tested the effect of three treatments on their OSA. These included preventing transient hypocapnia (via selective rebreathing during the hyperpneic phase), raising end-tidal Pco2 (PETCO2) (via continuous deadspace rebreathing) and preventing hypoxemia [via supplemental fraction of inspired O2 (FiO2)]. We found the isocapnic and especially the hypercapnic treatments to be effective in reducing OSA; these treatments were more likely to be successful in those patients with mild to moderately collapsible upper airways and high controller gains and narrowed CO2 reserves.

METHODS

Subjects. Twenty-six newly diagnosed adult patients (18–72 yr) with mild to severe OSA (AHI ≥ 10 events/h of sleep of predominantly obstructive type) were studied before receiving any treatment. Subjects were excluded if they had acute or chronic heart dysfunction or failure, cerebrovascular disease, asthma, or chronic obstructive pulmonary disease. All subjects provided written informed consent prior to participation. The experimental protocol was approved by the University of Wisconsin Center for Health Sciences Human Subjects Committee.

All subjects underwent 2–4 overnight studies in our laboratory, and each time, they reported to the laboratory in the evening (8–9 pm), having refrained from any alcohol and caffeinated beverages during or after their evening meal. Subjects deprived themselves of ~1 h of their normal sleep duration before each study night. Subjects slept with a facemask, through which they were connected to a breathing circuit that was modified for each protocol as described below.

Experimental Setup

Polysomnographic methods and respiratory monitoring. Standard polysomnography technique was used to document the sleep/wake state and arousal (29). In addition, ventilation was measured with a
sleep was assessed by measuring the controller gain and plant gain and estimating the ‘CO₂ reserve’ below eupnea. Upper airway collapsibility was estimated by measuring upper airway critical closing pressure (Pcrit). Both methods have been described previously in detail (73).

Briefly, to determine controller and plant gains, a positive-pressure ventilator in the assist mode was attached to the subject through a sealed mask. CO₂ reserve was measured in a lateral posture to avoid the need for application of high levels of CPAP to stabilize the airway and breathing. Following the baseline CPAP period (usually at 4–8 cmH₂O), a transient hyperventilation was initiated in the pressure support mode to bring PETCO₂ down in steps of 1–2 mmHg to the apneic threshold (73, 75). The average PETCO₂ on the three breaths immediately preceding the apnea was taken as the apneic PICO₂ threshold. The difference between eupneic PETCO₂ during stable breathing and the apneic threshold PETCO₂ was calculated as CO₂ reserve. The controller gain was calculated as the slope of minute ventilation (ΔV) to ΔPETCO₂ from eupnea to apnea, and the plant gain was determined by the ΔVme required to decrease PETCO₂ during pressure support hyperventilation.

To determine Pcrit, the subject was connected to a modified BiPAP device (Respiricore; Murrayville, PA) that was able to deliver both negative and positive (–20 to 20 cmH₂O) pressures through a tight-fitting full facemask. Pcrit was determined by reducing airway pressure to the point of zero flow rate in each subject. Pcrit was assessed in a supine posture with the head positioned on a contoured foam pillow to ensure a constant position and neck flexion.

Zolpidem (10 mg) was given prior to bedtime to facilitate sleep and to suppress the arousability from sleep. Zolpidem at this dosage has been shown to have no significant effect on ventilation or ventilatory stability, blood gases, occlusion pressure, ventilatory responses to CO₂, or ventilatory stability (7, 12, 43, 46, 53).

Protocol for Treatment Studies

Visit 1 (split night). Subjects received isocapnic rebreathing to prevent transient hypocapnia, hypercapnic rebreathing to increase respiratory drive, and room air breathing to provide control data. The three interventions were given in a random order, and the duration of each condition was allotted about one-third of each individual’s total sleep time, as was inferred from the subject’s clinical polysomnography study (292 ± 28 min total sleep/night). A 5-min washout period was allowed for the transition between any two conditions. In addition, four subjects had two split nights with one night of room air vs. isocapnia and the other night of room air vs. hypercapnia, because their total sleep time was too short to complete the three conditions in a single night. Studies were separated by 2–15 days. To verify the findings obtained during the split night, one subject underwent an overnight with isocapnic rebreathing; another subject underwent an overnight with hypercapnic rebreathing treatment.

Visit 2. Visit 2 was used to quantify UAW collapsibility (Pcrit) and controller and plant gains and CO₂ reserve below eupnea during sleep (73).

Visit 3. After 60–90 min of room air breathing each of 19 subjects underwent a hyperoxia intervention for the reminder of their sleep period during which O₂ was supplied through the breathing valve at a flow rate sufficient to maintain SaO₂ between 95 and 98%.

Data analysis. During the treatment night, AHI, apnea index (AI), and hypopnea index (HI) were compared in the same sleep stage in the same position under conditions of room air (control), and for each treatment using one-way repeated-measures ANOVA, along with Tukey test if necessary. The eupneic VE and PETCO₂ were averaged under each condition during 3–5 min stable breathing, and the mean values were compared among control, isocapnia, and hypercapnia in the split night using one-way repeated-measures ANOVA; and compared between control and hyperoxia using paired t-test. Arousal index was also compared under the three conditions using the above-
mentioned statistical methods. For the four subjects who had two split
nights, the control values were the means of the two night room air
studies.

to assess differences in Pcrit, controller, plant and loop gains as
well as CO2 reserve between those patients who did and those who did
not respond to each treatment, we used a cutoff of a >30% reduction
in AHI below control as a meaningful treatment effect. We also
identified those patients who experienced a reduction of AHI to <10
events/h with each of the treatments as an indication of a complete
resolution of OSA. An unpaired t-test was applied to compare the
above-mentioned characteristics between the two groups. In addition,
we determined the correlation coefficient among all subjects between
reductions in AHI and the CO2 reserve, controller gain and Pcrit.

All data are expressed as means ± SE.

RESULTS

Characteristics of Subjects

We studied 26 subjects (20 men and 6 women), average age
58 ± 2 yr, body mass index (BMI) = 33 ± 1 kg/m². Based on
the results from the diagnostic overnight polysomnogram the
subjects had an average AHI of 42 ± 5 events/h of sleep, AI of
23 ± 20, and HI of 19 ± 14; 92 ± 3% of the apneas were
scored as obstructive.

Sleep Times/Respiratory Arousals

Subjects slept for similar times (88–90 min total sleep time)
and for similar durations in each sleep stage for control,
isocapnic, and hypercapnic conditions (see Fig. 2). Sleep was
predominantly in Stage I and II NREM with much shorter
periods in Stage III and REM. Transient arousals (3–15 s)
associated with a respiratory disturbance event averaged 23 ± 3
events/h under room air control, were unchanged with the
isocapnic treatment (19 ± 4) and significantly reduced with the
hypercapnic treatment (12 ± 4). Arousals not associated with
respiratory disturbance were unchanged across all conditions,
and averaged 6–7 events/h.

Polygraph Recordings of Isocapnic and Hypercapnic
Treatment Effects

Figure 3 shows the response to selective isocapnic treatment
in an OSA patient who is typical of those who responded
positively. Under room air control, note the cyclical apneas
with paradoxical motion of ribcage and abdomen during the
apneas. With the selective isocapnic treatment, PETCO2 was
maintained and almost all apneas were eliminated, although
some underlying instability in flow rate and VT is noticeable.
Figure 4 shows the typical patient with severe OSA who failed
to reduce AHI in response to the selective rebreathe isocapnic
treatment, but did reduce their AHI to <10 events/h with
continuous rebreathing and hypercapnia (in this case +5
mmHg PETCO2).

Effectiveness of Maintaining Isocapnia on AHI

Selective rebreathing, isocapnic trials produced no change
from room air control in the mean eupneic PETCO2 or Vσ (see
Table 1). Individual subject changes in AHI in response to
isocapnia and hypercapnia are shown for all subjects in Fig. 5
with group mean values for eupnic breathing shown in Table
1. In 14 of 26 patients the isocapnic treatment method reduced
AHI by >30% below room air control (−69 ± 6%; range −31

\begin{align*}
\text{PetCO}_2 & = 40 \\
\text{RC} & = 0 \\
\text{AB} & = -0.5 \\
\text{Airflow} & = 0.5 \\
\text{SaO}_2 & = 100 \\
\text{EEG} & = \text{electroencephalogram} \\
\text{AB} & = \text{abdominal movement} \\
\text{RC} & = \text{rib cage movement}
\end{align*}

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to −95%). Seven of these 14 “responders” reduced their AHI to <10 events/h. Mean AHI fell from 38 ± 6 to 13 ± 3 events/h, AI from 24 ± 5 to 7 ± 2/h, and HI from 14 ± 2 to 6 ± 2/h. None of the remaining 12 patients reduced their AHI >30% below control, as neither apnea nor hypopnea indexes were significantly reduced in these subjects.

**Effectiveness of Hypercapnia on AHI**

The hypercapnia achieved via continuous deadspace rebreathing caused a 4.2 ± 1 mmHg increase in eupneic PetCO2 and a 13.6 ± 3% increase in V˙E (see Table 1). All but four of the 21 subjects who received the hypercapnia treatment showed a reduction in AHI in excess of 30% below control (see Fig. 5). In these 17 responsive patients AHI was reduced by 94 ± 3% below control (range −33 to −100%), and this reduction was attributable primarily to a reduction in AI. Fourteen of these 17 patients reduced their AHI to <10 events/h. In all 14 patients who had responded significantly to the isocapnic treatment (see above), hypercapnia reduced AHI substantially further from an average of 13 ± 3 with isocapnia to 2 ± 1 events/h with hypercapnia. Of the 12 nonresponsive subjects to isocapnia, 8 showed >30% reductions in AHI with hypercapnia due to further reductions in both AI (38 ± 19%) and HI (30 ± 3%); and 3 of these 8 patients reduced their AHI to <10 events/h.

**Table 1.Effects of three treatments on eupnic breathing**

<table>
<thead>
<tr>
<th>Room Air Control for CO2 Treatments</th>
<th>Isocapnia</th>
<th>Hypercapnia</th>
<th>Room Air Control for O2 Treatment</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep time, min</td>
<td>90.7 ± 8.2</td>
<td>92.6 ± 10.0</td>
<td>86.0 ± 10.1</td>
<td>87 ± 6.1</td>
</tr>
<tr>
<td>Vt, liters</td>
<td>0.47 ± 0.16</td>
<td>0.50 ± 0.18</td>
<td>0.67 ± 0.21*</td>
<td>0.56 ± 0.04</td>
</tr>
<tr>
<td>Freq, no/min</td>
<td>15.1 ± 2.0</td>
<td>15.5 ± 2.5</td>
<td>15.2 ± 2.0</td>
<td>14.8 ± 0.6</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>7.2 ± 2.5</td>
<td>7.8 ± 2.9</td>
<td>9.8 ± 3.1*</td>
<td>8.1 ± 0.6</td>
</tr>
<tr>
<td>PETCO2</td>
<td>105.5 ± 4.8</td>
<td>109.0 ± 7.8</td>
<td>100.3 ± 5.0</td>
<td>107.4 ± 1.6</td>
</tr>
<tr>
<td>PEO2</td>
<td>40.9 ± 3.5</td>
<td>41.7 ± 3.8</td>
<td>45.1 ± 4.6*</td>
<td>45.0 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 26 for isocapnia, 21 for hypercapnia, and 19 for hypoxia. Vt, tidal volume; Freq, frequency; Vs, minute volume; PetCO2, end-tidal PO2; PetCO2, end-tidal PCO2. *P < 0.05 compared with room air and isocapnia. †P < 0.05 compared with room air.
the improvement of AHI and either Pcrit (R = 0.006; P = 0.98) or plant gain (R = 0.07, P = 0.77).

**Hypercapnia.** The middle panels in Table 2 and Fig. 6 contrast characteristics determined under control conditions for responders and nonresponders to hypercapnia. Note, that as with the isocapnic treatment, the responsive group to hypercapnia tended to have slightly higher controller gains and narrower CO2 reserves although there was considerable overlap between the two groups. Hypercapnia was more effective than isocapnia in reducing AHI in some OSA patients with relatively low controller gains and wide CO2 reserves. As a result, there was no difference in either controller gain, loop gain, plant gain, CO2 reserve or Pcrit between the responsive and the nonresponsive groups to hypercapnia. Of further note are the uniformly positive Pcrits (and holding pressures of 11–15 cmH2O) as well as relatively wide CO2 reserves in all four nonresponders to iso- or hypercapnic treatments.

**Effectiveness of Hyperoxia in Treating OSA**

Hyperoxic inhalation consistently increased end-tidal PO2 (PETO2) and maintained SaO2 between 95 and 98%, but did not affect other respiratory parameters, except for a slight (by 1 breath/min) yet significant (P < 0.05) reduction in the breathing frequency and higher PETO2/SaO2 (see Table 1). Hyperoxia did not reduce the group mean AHI significantly (room air vs. hyperoxia: 39 ± 6 vs. 34 ± 6 events/h, P = 0.25). However, as shown in Figs. 7A and 8, 7/19 subjects reduced AHI by >30% of baseline via hyperoxic inhalation (−64 ± 11%; range −100% to −32%). In these 7 subjects, AHI was reduced from 36 ± 7% during overnight room air control study or from 36 ± 11 during the same (split) night control room air breathing to 14 ± 6 events/h (P < 0.05). However, in the remaining 12 subjects, their AHI was not altered significantly (46 ± 6/h) compared with either the overnight baseline studies (52 ± 8 events/h) or the 1.45 h of room air breathing within the same split night (41 ± 8 events/h) as shown in Fig. 7B. Apnea length increased in both responders and nonresponders to hyperoxic treatment, as the average length increased from 24.1 ± 3.6 to 30.1 ± 4.3 s (P < 0.05).

As shown in the right panels of Table 1 and Fig. 6, there were no clear group differences in plant gain or Pcrit distinguishing the responsive from the nonresponsive group to hyperoxia. However, we note that all but one of the 12 nonresponsive group members tended to show a relatively low controller gain or CO2 chemoreflex slope below eupnea.

**Table 2. Control values for subjects who were responsive and nonresponsive to isocapnic, hypercapnic, and hyperoxic treatments**

<table>
<thead>
<tr>
<th></th>
<th>To Isocapnia</th>
<th>To Hypercapnia</th>
<th>To Hyperoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>14 (3F + 11M)</td>
<td>12 (3F + 9M)</td>
<td>17 (5F + 12M)</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td>59 ± 2</td>
<td>58 ± 3</td>
<td>58 ± 2</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>33 ± 2</td>
<td>34 ± 2</td>
<td>33 ± 2</td>
</tr>
<tr>
<td><strong>AHI, no/h</strong></td>
<td>38 ± 6</td>
<td>48 ± 8</td>
<td>34 ± 4</td>
</tr>
<tr>
<td><strong>CA/total apnea, %</strong></td>
<td>10.9 ± 3.7</td>
<td>3.9 ± 2.8</td>
<td>9.5 ± 3.2</td>
</tr>
<tr>
<td><strong>AHI range, min-max</strong></td>
<td>12–92</td>
<td>12–93</td>
<td>12–57</td>
</tr>
<tr>
<td><strong>Mean SaO2</strong></td>
<td>93 ± 1</td>
<td>91 ± 1</td>
<td>93 ± 1</td>
</tr>
<tr>
<td><strong>Controller gain, 1· min⁻¹·mmHg⁻¹</strong></td>
<td>6.5 ± 1.7</td>
<td>2.1 ± 0.2**</td>
<td>4.5 ± 1.2</td>
</tr>
<tr>
<td><strong>Plant gain, mmHg·1· min⁻¹·min⁻¹</strong></td>
<td>0.33 ± 0.06</td>
<td>0.29 ± 0.04</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td><strong>CO2 reserve, mmHg</strong></td>
<td>1.9 ± 0.3</td>
<td>4.3 ± 0.4**</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td><strong>Pcrit, cmH2O</strong></td>
<td>−0.1 ± 1.2</td>
<td>(3 to −8)</td>
<td>−0.6 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. Responsive group, apnea-hypopnea index (AHI) reduced by 30% of baseline value or more in response to isocapnic rebreathing (31 ± 6% of control) or hypercapnia (15 ± 4% of control) or hyperoxia (36 ± 11% of control); Nonresponsive group, the reduction in AHI was <30% of baseline during isocapnic rebreathing (112 ± 10% of control) or hypercapnia (98 ± 8% of control) or hyperoxia (149 ± 21% of control). BMI, body mass index; CA, central apnea; CO2 reserve, the proximity between eupneic PETCO2 and apneic threshold PETCO2. Pcrit, critical closing pressure.
Overnight vs. Split Night

The AHI under control, air-breathing conditions averaged 35/26 events/h for the overnight polysomnography study (5.2 ± 0.8 h) and 42/23 for the shorter split night (1.5 ± 0.1 h) (P = 0.10). The control AHI magnitude was significantly correlated among subjects between overnight and split night sessions (r = 0.66, P < 0.01).

In the one subject with overnight isocapnic treatment the AHI was reduced from 74 (control night) to 15 events/h, which compared favorably with the split night trial (115 min study time), with reductions in AHI from 92 to 30 events/h (AI: from 71 to 16 event/h). Similarly, for the single subject with overnight hypercapnic treatment, AHI fell from 52 to 18 events/h (AI 46 to 8 events/h) for the overnight studies, compared with reductions from 47 to 0 events/h for AHI (24 to 0 event/h for AI) for the split night study (99 min).

DISCUSSION

Our study was aimed at 1) evaluating the effects of stabilizing or increasing central respiratory motor output and of reducing chemoreflex gain on OSA in newly diagnosed, untreated patients; and 2) determining whether certain characteristics of passive airway collapsibility and control system gains would be predictive of treatment success. There were three major findings. First, stabilization of respiratory motor output through selective isocapnic rebreathing limited to the transient hyperpneic phase, reduced OSA substantially in those patients with a high controller gain and a narrowed CO2 reserve. Second, enhancement of respiratory motor output via continuous hypercapnia (achieved via continuous dead space rebreathing) was effective in reducing obstructive apneas in the vast majority of OSA patients (17/21) with a wide range of chemoreflex gains and upper airway collapsibility. Third, hyperoxia (SaO2 95–98%) showed a mixed outcome in terms of its effect on the frequency of obstructive apneas/hypopneas (7 of 19 patients reduced AHI by >30%) but had a consistent effect in prolonging apnea length. Finally, in a minority of OSA patients (4/26) maintaining isocapnia or creating hypercapnia or hyperoxia were all ineffective at reducing OSA. These findings have implications for evaluating the potential contributions of controller gain and both the stability and magnitude of respiratory motor output to the pathogenesis and treatment of OSA.

Limitations

There were advantages as well as limitations to our experimental design which, for almost all patients, compared control,
room air breathing conditions to each of the three treatments within three separate nights of sleep. On the one hand, this approach avoided night to night variability in sleep-disordered breathing and its determinants and allowed us to assess the consistency of any treatment effects on the transition from room air controls to each of the treatments and also upon return to control conditions. Our design also compared treatment vs. controls under similar conditions of sleep posture and sleep state, which ruled out any contributions of these variables to the observed treatment effects on airway obstruction. On the other hand it is well documented that within-night variability of sleep-disordered breathing and/or upper airway resistance can also be significant in OSA patients and cannot always be explained by variations in posture or sleep stage. Indeed, some OSA patients have significant periods with no or few episodes of obstructive apneas or transient arousals (76, 79). So, by limiting our observations of each treatment effect to only 1.5–2 h of sleep, we have not achieved an ideal design for quantifying treatment effects on AHI. This would require an additional session of observations over an entire night (or more) of sleep for each treatment. These additional nights of study were not a realistic goal for this initial study in the great majority of our newly diagnosed, untreated OSA patients, who were awaiting assignment to CPAP treatment. For now we can only point out that the diagnostic polysomnography night revealed that our OSA patients, especially those with AHI > 40, tended to have cyclical obstructive apneic episodes fairly consistently throughout the great majority of the night. Importantly, their AHI indexes under control, room air breathing conditions were significantly correlated and comparable in magnitude over the course of the entire polysomnography night vs. during the shorter periods in the split night. We attribute the higher average AHI during the split night to the requirement for a supine sleeping position during this sleep session (see below). We also note the close

Fig. 7. PSG records from two representative subjects during room air vs hyperoxia. A: room air vs. hyperoxia in one subject/responder. B: room air vs. hyperoxia in one subject/nonresponder. Repetitive obstructive apneas were noted in both A and B. In A, apneas and hypopneas were eliminated by hyperoxia; while in B, the apneas were persistent despite the high FiO2 and SaO2. Note in B, apnea length was increased by hyperoxic inhalation.
studies using CO2 administration in patients with congestive hypercapnic treatments, per se, were unable to accurately evaluate the effects of the iso- or apparatus and its potentially disruptive effect on sleep state, we the supine position. Because of the discomfort created by the chograph and its use required our patients to sleep primarily in isocapnia was equipped with a solenoid valve and pneumota-

trials of 5 to 6 h each vs. the split night studies. Between control vs. treatment were made between overnight reducing AHI in two of our OSA patients when comparisons agreement achieved for isocapnic or hypercapnic treatments on nonrespiratory arousals and significant reductions in transient arousals associated with respiratory disturbances during the hypercapnic rebreathing with no change during the isocapnic treatment.

The primary variable used to assess the effectiveness of the three interventions was the change in AHI. If the AHI was reduced by \( \geq 30\% \) of baseline value in response to hyperoxia.

agreement achieved for isocapnic or hypercapnic treatments on reducing AHI in two of our OSA patients when comparisons between control vs. treatment were made between overnight trials of 5 to 6 h each vs. the split night studies.

The mask we used for selective rebreathing to maintain isocapnia was equipped with a solenoid valve and pneumotachograph and its use required our patients to sleep primarily in the supine position. Because of the discomfort created by the apparatus and its potentially disruptive effect on sleep state, we were unable to accurately evaluate the effects of the iso- or hypercapnic treatments, per se, on sleep efficiency. Previous studies using CO2 administration in patients with congestive heart failure have shown that elimination of central apnea and periodic breathing may (42) or may not (62, 63) eliminate or significantly reduce the prevalence of transient arousals associated with disordered breathing events. Our findings showed no effect of iso- or hypercapnic treatments on nonrespiratory arousals and significant reductions in transient arousals associated with respiratory disturbances during the hypercapnic rebreathing with no change during the isocapnic treatment.

The primary variable used to assess the effectiveness of the three interventions was the change in AHI. If the AHI was reduced by \( \geq 30\% \) of the baseline level, we considered this to be a meaningful alleviation of the patient’s OSA because it corresponds to changes found via the use of compliant CPAP treatment in patients with moderate OSA (54). The biological basis for this standard, however, needs to be further verified. We also point out that half of our “responsive” patients to isocapnia and all but two of our responders to hypercapnea reduced their AHI to <10 events/h. Further, even if we had used a cut-off of a 50% reduction in AHI to designate responders vs. nonresponders to isocapnia, the responders (10 subjects now) would still have been separated by a high controller gain (7.6 ± 2.1 vs. 2.4 ± 0.3, \( P < 0.01 \)) and narrower CO2 reserve (1.8 ± 0.4 vs. 3.9 ± 0.4, \( P < 0.01 \)).

Finally, we note that two of our OSA patients had highly negative Pcrits of \(-7 \) to \(-8\) cmH2O, which we confirmed with repeated measures upon reducing airway pressure to achieve absolute zero flow conditions. One of these patients was our mildest OSA patient (with only 12 AHI) who had a high controller gain (5.7 l·min\(^{-1}\)·mmHg\(^{-1}\) ) and small CO2 reserve (1.5 mmHg), but the other had an AHI of 47 and AI of 23 and with isocapnic treatment reduced his AHI and HI by more than 70%. We are puzzled by this finding and can only refer to the comprehensive study of Kirkness et al. (37) who observed that 5 of 150 OSA patients with AHI > 10 showed Pcrit values more negative than \(-5\) cmH2O.

Determinants of Propensity for Central Respiratory Instability

Although specific mechanisms will vary across the various conditions of sleep-induced breathing instability, in general the major determinants of central respiratory motor output instability include enhanced chemoreceptor sensitivities (\( \Delta V\text{E} / \Delta Pa\text{CO2},\) controller gain), gas exchange efficiency (\( \DeltaPa\text{CO2} / \Delta V\text{E},\) plant gain) and/or mixing gain (i.e., circulatory delay from lungs to chemoreceptors) (10, 17, 36, 44). Indirect estimates for assessing loop gain, or the risk of ventilatory instability, have included the ratio of ventilatory decline to ventilatory response achieved via variations in airway pressure with CPAP (67) or a proportional assist ventilator (49), pseudorandom binary stimulation using inspired CO2 (19) and mathematical models of the patient’s spontaneous, sinusoidal periodic patterns (44, 58). Our method for estimating controller and plant gains (between eupnea and apnea) used assist control, positive pressure ventilation to gradually reduce PcritCO2 in a stepwise fashion in the sleeping patient until the apneic threshold and periodic breathing were achieved. The PcritCO2 reduction resulting from the corresponding increase in Ve to reach the apneic threshold provided an estimate of the control system plant gain. The slope of the ventilatory decline between eupnea and apnea was assumed to be linear and provided an estimate of controller gain below eupnea; and this slope also likely reflected the gain above eupnea as well, although this has not been directly tested (51, 75). In turn, these measurements allow calculation of what we have termed the “CO2 reserve” or the proximity of the eupneic PaCO2 to apneic threshold PaCO2, which reflects the magnitude of the controller and plant gains.

We emphasize that it is not the apneic threshold or even the CO2 reserve, by themselves, that cause instability; rather it is the controller and plant gains which are responsible for system instability as well as for dictating alterations in the apneic threshold and the CO2 reserve (13, 17, 44, 51, 67). Thus these gains and the CO2 reserve are interdependent, and we think it
is important to consider all three of these parameters when assessing the propensity for instability. For example, according to classic linear control theory (35, 36) a small ventilatory disturbance in the face of high controller and/or plant gains can initiate ventilatory oscillations, but this theory no longer applies once apnea (and a limit cycle) occurs. Apneas then introduce potential perpetrators of transient arousals, ventilatory overshoots and continued ventilatory oscillations because of the marked synergistic effects on respiratory motor output and sensory input to the central nervous system produced by changes in chemoreceptor stimuli. These apneas, per se, are then important mediators of ventilatory instability, and we believe it is instructive to quantify their determinants in terms of PCO2 threshold and the CO2 reserve below spontaneous eupnea.

How Can the Concepts of Plant Gain and CO2 Reserve Be Applied To Explain How Raising FiCO2 Diminishes or Removes Instability in Central Respiratory Motor Output?

As inspired PCO2 (PICO2) increases and the PICO2 to alveolar Pco2 (Paco2) gradient is reduced, each liter of alveolar ventilation excretes less net CO2, amounting to a rightward shift and reduced slope of the isometabolic curve relating Paco2 to alveolar ventilation (V̇A) (35, 36, 44). So, theoretically at least, the stabilizing effect of increased PICO2 appears to result from two related mechanisms. First, plant gain is reduced, requiring a much greater increase in alveolar ventilation for a given reduction in Paco2. This influence of reduced plant gain is equivalent to the stabilization and apnea-reducing effects of a pharmacologically induced hyperventilation and hypocapnia (31, 51). Second, with elevations in FiCO2, the operating levels of Paco2, and ventilation rise further above the apneic threshold, thereby widening the CO2 reserve. In our experiments, we would expect both is- and hypercapnia protocols to provide a stabilizing effect on central respiratory motor output. That is, 1) with isocapnia, an augmented PICO2 reduced plant gain; and 2) with hypercapnia, an even greater stabilizing effect on central respiratory motor output will occur as the PICO2 to Paco2 gradient would be further reduced and the raised Paco2 is moved further away from the apneic threshold.

Central Instability and CO2 Effects on OSA

We observed that the selective rebreathe isocapnic treatment conditions, which prevented the cyclical reductions in PetCO2 commensurate with transient ventilatory overshoots, were effective in significantly reducing AHI below air-breathing control in some of the OSA patients, whereas continuous rebreathing and hypercapnia were effective in eliminating OSA in almost all patients. What might explain the effectiveness and relative effectiveness of these two types of manipulations of CO2?

First, we think the available evidence in sleeping animals and humans supports a significant role for transient reductions in Paco2 as critical mediators of central apneas and periodicities during NREM sleep. Supportive evidence includes the apneas and periodicities achieved via transient hypocapnic hyperpneas elicited via either assisted mechanical ventilation (24, 49, 51, 61, 75) or following airway occlusion (11, 30). These post hyperpnea central apneas are prevented via control-ling PetCO2 at or very near eucapnic levels (8, 21, 51) or by carotid chemoreceptor denervation (9, 50). Pressure support-assisted hyperpneas with raised Vt and with PetCO2 controlled at normocapnic levels will, by themselves, also elicit significant neuromechanical inhibition of diaphragm EMG (and Pdi) amplitude but without significant TE prolongation or apnea (55, 72). Second, it has also been demonstrated that hypocapnic-induced central periodicities or apneas will precipitate upper airway narrowing and/or obstruction at the nadir of respiratory drive in subjects with airways susceptible to collapse (6, 27, 40, 59, 66). Third, in snorers with elevated upper airway resistance during air breathing, hypercapnia induced via increased FiCO2 reduced upper airway resistance during sleep (4, 5, 48). This effect of hypercapnia on reducing airway resistance is consistent with its reported stimulating effect on the recruitment of hypoglossal motor nerve activity and on airway dilator muscle EMG. Some human and animal data support a linear CO2 driven recruitment of the diaphragm as opposed to a highly nonlinear, threshold-like response of upper airway muscle EMG to increased chemoreceptor stimuli (23, 25, 41, 45).

We believe our present findings in OSA patients are explained by these fundamental concepts which combine chemoreflex/controller gain effects on central instability, together with substantial variability in chemosensitivity among patients in their CO2-dependent recruitment of upper airway as well as respiratory pump muscles. Accordingly, we would attribute our isocapnic treatment effects of reducing OSA to maintaining a stable central respiratory motor output, presumably to both the chest wall and upper airway musculature. Most of the OSA patients who responded positively to this isocapnic “stabilizing” treatment had collapsible airways (passive Pcrit = 0.1 ± 1.2 cmH2O and CPAP holding pressures > 10 cmH2O) in combination with a relatively high chemoreflex controller gain to reduced Paco2 below eupnea, resulting in an abnormally narrowed CO2 reserve. Those patients who failed to reduce their OSA significantly with maintained isocapnia had levels of passive Pcrit equivalent to those of the responsive group, but they had controller gains that were substantially lower and CO2 reserves that were more than double those of the responsive group.

We interpret these group differences to mean 1) that high controller gain leading to central control instability was a more important underlying mechanism contributing to OSA in the responsive group vs. the nonresponsive group; and 2) that a raised Paco2 not only stabilized any underlying central periodicity but importantly, added a powerful recruitment of both chest wall and upper airway dilators which raised Vt significantly and completely or near completely eliminated airway obstruction in almost all patients.

Classification of Pathophysiological Traits and Treatment Outcomes

We believe our findings illustrate the importance of classifying patients to select treatments aimed at control system stability and/or upper airway muscle recruitment which might be effective in diminishing obstructive events. However, there are other important characteristics that are known to influence the propensity for cyclical obstructive apneas that we have not considered. These mechanisms include individual differences in the ability to effectively recruit upper airway dilators during...
reductions. In this comprehensive study the authors attributed with about half of the patients showing greater than 30% over a 1-wk period resulted in a 50% reduction in median AHI, OSA patients (who were already undergoing CPAP treatment) of acetazolamide administered in relatively high doses to 13.

Most recently, Edwards et al. (15) showed that administration numbers of OSA patients with mixed effects (56, 60, 64, 71). Failure patients (31, 70) and has also been used in small effective in treating most central apneas in congestive heart failure patients (31, 70) and was effective in a smaller percentage of patients and in some cases even increased the occurrence of obstructive apneas (and increased apnea length) (18, 26, 69). Wellman et al. (69) reported that supplemental O2 sufficient to maintain SaO2 ~98% improved obstructive events significantly in half of his sample of 12 OSA patients and only in those patients with a high loop gain. Similarly, 7 of 19 of our patients reduced their OSA > 30% when we maintained SaO2 in the 95–98% range and 5 of the 7 also responded positively to the isocapnic treatment. However, unlike our isocapnic treatment, we were unable to predict treatment success with hyperoxia based on the patient’s baseline plant or controller gains or CO2 reserve or Pcrit. Perhaps we might have increased predictive power of this treatment if we had also measured any change or lack thereof in controller and plant gains with the use of hyperoxia rather than depending strictly on our measurements of these characteristics under air breathing control conditions. We note that our isocapnia and especially the hypercapnia treatments were more effective in reducing AHI than hyperoxia in the same OSA patients and we speculate that this difference is attributable to 1) a greater reduction in plant gain with the isocapnic treatment than in controller gain with hyperoxia; and/or 2) a greater stimulatory role facilitating upper airway patency for the isocapnic and especially the hypercapnic treatments vs. the hyperoxic treatment, which may even have reduced central motor output to upper airway dilator muscles.

Effects of Maintaining SaO2 > 95% Via Supplemental O2

Acute hyperoxia, even in healthy nonapneic subjects, will reduce chemoreflex controller gain for CO2 and widen the CO2 reserve (51, 74). Furthermore, carotid body denervation in canines will prevent apnea and periodic breathing induced via transient ventilatory overshoot and hypocapnia (9, 50). Accordingly, preventing intermittent hypoxemia via supplemental O2 administration has been shown to reduce many, but not all, central apneas and periodicities in most congestive heart failure patients with Cheyne-Stokes respiration (18, 22, 32, 42). However, with OSA, hyperoxia had relatively minor effects on AHI and was effective in a smaller percentage of patients and in some cases even increased the occurrence of obstructive apneas (and increased apnea length) (18, 26, 69). Wellman et al. (69) has reported that supplemental O2 sufficient to maintain SaO2 ~98% improved obstructive events significantly in half of his sample of 12 OSA patients and only in those patients with a high loop gain. Similarly, 7 of 19 of our patients reduced their OSA > 30% when we maintained SaO2 in the 95–98% range and 5 of the 7 also responded positively to the isocapnic treatment. However, unlike our isocapnic treatment, we were unable to predict treatment success with hyperoxia based on the patient’s baseline plant or controller gains or CO2 reserve or Pcrit. Perhaps we might have increased predictive power of this treatment if we had also measured any change or lack thereof in controller and plant gains with the use of hyperoxia rather than depending strictly on our measurements of these characteristics under air breathing control conditions. We note that our isocapnia and especially the hypercapnia treatments were more effective in reducing AHI than hyperoxia in the same OSA patients and we speculate that this difference is attributable to 1) a greater reduction in plant gain with the isocapnic treatment than in controller gain with hyperoxia; and/or 2) a greater stimulatory role facilitating upper airway patency for the isocapnic and especially the hypercapnic treatments vs. the hyperoxic treatment, which may even have reduced central motor output to upper airway dilator muscles.

Conclusions

With respect to the effects of preventing transient hypocapnia on OSA, our findings are consistent with an important role for high chemoreflex gain, unstable central respiratory motor output, and narrowed CO2 reserve in both the pathogenesis and treatment of OSA in a significant number of patients with collapsible airways. At the same time these findings also show
that not all OSA patients have increased chemoreceptor gain, and unstable central respiratory motor output as major influences underlying their cyclical OSA; accordingly, treatments aimed specifically at reducing controller and/or plant gain and thereby stabilizing central respiratory motor output are unlikely to be successful in the majority of severe OSA patients. Additional findings demonstrated that the use of continuous moderate hypercapnia was highly effective in the treatment of airway obstruction, apparently acting by both stabilizing central motor output as well as recruiting upper airway dilator musculature. Exactly how exogenous CO2 or, more likely, some pharmacological means of safely augmenting central respiratory motor output without increasing chemoreflex controller gain might be used in the treatment of OSA remains to be determined.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: A.X., D.F.P., and J.A.D. conception and design of research; A.X., D.F.P., and J.A.D. performed experiments; A.X., M.C.T., Y.G., and J.E.F. analyzed data; A.X. and J.A.D. interpreted results of experiments; A.X. prepared figures; A.X. drafted manuscript; M.T., M.C.T., and J.A.D. edited and revised manuscript; J.A.D. approved final version of manuscript.

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