The effects of hypoxia on load compensation during sustained incremental resistive loading in patients with obstructive sleep apnea

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Submitted 22 December 2005; accepted in final form 26 March 2007

Obstructive Sleep Apnea (OSA) is a common disorder that affects 2–4% of the adult population (34). It is characterized by recurrent partial and complete upper airway obstruction during sleep associated with reduction or cessation of airflow. Airway occlusion leads to a period of hypoxia, and increasing inspiratory effort against the obstructed airway frequently culminates in a brief arousal that helps to restore airway patency. In severe cases, this cycle is repeated hundreds of times per night. Increased daytime sleepiness is a common symptom of untreated OSA, and patients with OSA have also been shown to have significantly impaired neuropsychological functioning (2). The improvement of these deficits with continuous positive airway pressure (CPAP) treatment suggest that they are a consequence of OSA (14, 15).

Maintenance of ventilation in the face of an added resistive load is an important compensatory mechanism in a number of respiratory disorders, including OSA. Patients with OSA show impaired perception of added resistive loads compared with normal controls (22, 30), and they have abnormal compensatory responses to inspiratory resistive loading when awake (17, 27). Reversal of these deficits with CPAP treatment again suggests that they are a consequence of OSA, although similar abnormalities in non-OSA offspring of OSA parents suggest that an underlying abnormality of ventilatory control may play some part in the etiology of OSA (26). Patients with OSA have been shown to have abnormal late respiratory-related evoked potential responses (1, 16), suggesting that a cortical deficit may be at least partly responsible for some of these abnormalities.

Hypoxia is a neurocognitive depressant that is thought to be responsible for some of the negative consequences of OSA. Our group has recently demonstrated that sustained hypoxia impairs components of cortical respiratory sensory processing (12) and blunts perception of the magnitude of externally applied inspiratory resistive loads in both normal (24) and asthmatic subjects (13). These changes may be secondary to the elaboration of inhibitory neuromodulators that may also be responsible for depressed neurocognitive functioning during hypoxia (7) and ventilatory depression both during and for at least 15 min after sustained hypoxia (10, 11). The effects of sustained hypoxia on load compensation responses in patients with OSA have not been systematically studied previously.

In the present study, we compared the ventilatory responses in OSA patients and control subjects during a 12-min period of incrementally increasing inspiratory resistive loading. Both groups were studied at baseline (after 30 min of normoxia) and then again after a 30-min period of hypoxic preconditioning. Subjects were studied after, rather than during, hypoxia to determine the load dependence of decompensation responses. The loading protocol of six incremental resistive loads was used to assess load responses across a wide range of loads and also to determine the load dependence of decompensation responses. We postulated that chronic repetitive nocturnal respiratory
loading and hypoxemia in patients with OSA would impair responses to loading at baseline and render subjects more vulnerable to the depressant effects of further hypoxia. Specifically, we hypothesized that OSA patients would demonstrate impaired ventilatory compensation during acute resistive loading compared with non-OSA controls and that these abnormalities would be exaggerated following sustained hypoxia.

METHODS

Subject selection. Ten newly diagnosed OSA patients gave written informed consent to participate in the study. All had polysomnographically confirmed severe OSA [respiratory disturbance index (RDI) ≥30 events/h]. Patients had never used CPAP or had any other treatment for OSA. Ten sex-matched healthy subjects with no history of snoring or daytime sleepiness were recruited as controls. All had significant OSA excluded with overnight polysomnography (RDI ≤ 15 events/h). Sleep studies were scored by an experienced sleep technician with sleep stage, arousals, and respiratory events scored using standard criteria (2, 3, 28). In both groups, subjective daytime sleepiness was assessed using the Epworth Sleepiness Scale (19). All participants were nonsmokers and were free of significant cardiopulmonary disease. The study was approved by the Daw Park Repatriation General Hospital Human Research and Ethics Committee.

Study design. The study was a within-subjects (hypoxia effects) and between-groups (patients vs. controls) design. After an initial visit where demographic and lung function data were obtained to ensure normal lung function (Jaeger CompactLab using version 4.52 Jlab software, Viasys Healthcare, Hoechberg, Germany), subjects returned for the main experimental visit. During this visit, ventilatory parameters were measured during incremental resistive loading following two gas conditions, isocapnic hypoxia and normoxia. A period of at least 90 min was allowed between the hypoxic and the normoxic trials, and the order of the two conditions was randomized for each subject. Subjects were blinded to which gas condition they were receiving.

Main experimental visit. Subjects arrived at 10:00 AM after a light breakfast and having abstained from alcohol and caffeine for the previous 24 h. All measurements were obtained with the subjects lying supine on a bed with one pillow. EEG monitoring was undertaken to confirm wakefulness for the duration of the study period (C3-A2, Compumedics S-series, Abbotsford, Victoria, Australia). A nasal mask (Gel mask, Respironics, Murraysville, PA) with unidirectional valves (series 2600, Hans Rudolph, Kansas City, MO) was fitted and held in place with an adjustable head strap. Breath-by-breath ventilation was measured with a pneumotachograph (Jaeger, Viasys Healthcare) attached to the mask and differential pressure transducer (model PT36, Jaeger, Viasys Healthcare). End-tidal PCO₂ (PETCO₂) was measured (model 602-3, POET II monitor, Criticare Systems, Viasys Healthcare) attached to the mask and differential pressure transducer (series 2600, Hans Rudolph, Kansas City, MO) was achieved using a device described previously (24). Briefly, the device consisted of two concentric tubes, the innermost having had segments removed and replaced with filter paper. An internal plunger was moved to alter the area of paper through which subjects inspired, thus altering the inspiratory resistance. Loading commenced 2 min following the end of the gas period. Six incremental resistive loads (11.7 ± 0.1, 16.1 ± 0.2, 20.9 ± 0.3, 30.0 ± 0.5, 45.8 ± 0.9, and 98.4 ± 3.2 cmH₂O·l⁻¹·s⁻¹) were applied sequentially, commencing at end expiration and remaining for a duration of 2 min each. Following the sixth load, the load was removed, and subjects were allowed to breathe room air for 1 min before data collection was concluded.

Measurement of ventilatory parameters. Minute ventilation (V̇E), tidal volume (Vt), inspiratory time (Ti), expiratory time (Te), total breathing time (Ttot), breathing frequency (fB), peak inspiratory pressure (PIP), peak inspiratory flow (PIF), PetCO₂, and SaO₂ were measured on a breath-by-breath basis both before loading and throughout the loading period. Mean values for each parameter were then calculated for every 30-s period during the baseline period and for each 2-min load period. These mean values were then compared in the statistical analysis. In addition, the first five breaths of each loading period were analyzed individually looking for time-dependent effects within each load.

Data analysis and statistical procedures. Anthropometric and sleep study data were compared between patients and controls using two-sample Student’s t-tests. Comparison of ventilatory parameters at baseline and maximal loading was undertaken using Student’s t-tests. Ventilatory parameters during the loading period were compared using ANOVA for repeated measures (SPSS v12.1, SPSS, Chicago, IL). Post hoc comparison of ventilatory parameters between the initial and subsequent loads was undertaken using t-tests with the Bonferroni adjustment method. For all comparisons, P < 0.05 was considered significant. Data are presented as means ± SE or 95% confidence interval.

RESULTS

Subject and control baseline anthropometric, lung function, and sleep data are presented in Table 1.

Gas period. During normoxia, SaO₂ was not significantly different between controls and OSA patients (Table 2). During hypoxia trials, SaO₂ declined rapidly within the first 5 min and

<table>
<thead>
<tr>
<th>Table 1. Patient and control characteristics</th>
<th>Patients (n = 10)</th>
<th>Controls (n = 10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric variables</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, yr</td>
<td>52.5 ± 3.2</td>
<td>43.9 ± 4.0</td>
<td>0.112</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>7/3</td>
<td>7/3</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>35.5 ± 2.2</td>
<td>29.1 ± 0.9</td>
<td>0.018</td>
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<tr>
<td>Lung function</td>
<td></td>
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<tr>
<td>FEV₁, %predicted</td>
<td>105.1 ± 2.9</td>
<td>95.1 ± 3.7</td>
<td>0.047</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>98.2 ± 3.1</td>
<td>95.7 ± 4.5</td>
<td>0.652</td>
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<tr>
<td>Sleep variables</td>
<td></td>
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<td></td>
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<tr>
<td>ESS</td>
<td>10.3 ± 1.6</td>
<td>7.4 ± 2.2</td>
<td>0.318</td>
</tr>
<tr>
<td>RDI, events/h</td>
<td>59.5 ± 7.3</td>
<td>8.6 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AI, arousals/h</td>
<td>45.3 ± 7.6</td>
<td>13.4 ± 1.3</td>
<td>0.002</td>
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<tr>
<td>SaO₂ nadir</td>
<td>74.6 ± 3.8</td>
<td>92.3 ± 1.5</td>
<td>0.001</td>
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</tbody>
</table>

Values are means ± SE; n, no. of subjects; FEV₁, forced expired volume in 1 s; FVC, forced vital capacity; ESS, Epworth sleepiness score; RDI, Respiratory disturbance index; AI, arousal index; SaO₂, arterial oxygen saturation.
was not significantly different between controls and OSA patients during the remaining gas period (Table 2). Isocapnic conditions were maintained during hypoxia, and mean PetCO2 was not significantly different between groups under either gas condition (Table 2). With hypoxia, both groups showed a similar ventilatory response with an initial increase in Vt followed by a roll-off after ~5 min to a level intermediate between the initial peak and the previous baseline level (Fig. 1).

**Ventilatory changes during inspiratory resistive loading.** During the loading period, there was no significant change in SaO2 or PetCO2 in either group. With increasing load, there was a significant fall in Vt in both OSA patients (P = 0.003) and controls (P < 0.001), and a significant increase in Ti in both OSA patients (P = 0.006) and controls (P = 0.003) (Fig. 2). PIF declined significantly in both OSA patients and controls throughout the loading period (P = 0.006 and < 0.001, respectively) (Fig. 3). During loading there was a reduction in both Te and an increase in Ttot in both groups, but these changes were not statistically significant. In the control group, Vt showed a significant change with increasing load (P = 0.02), with an initial increase followed by a subsequent decline irrespective of gas condition (Fig. 2). In contrast, OSA patients maintained Vt at a level similar to baseline with no significant change despite increasing load (P = 0.656; Fig. 2). Post hoc analysis did not suggest a specific load at which ventilatory parameters tended to become significantly abnormal compared with baseline. Breath-by-breath analysis of the first five breaths of each load period did not reveal any major time-dependent effects within each load.

Ventilatory responses following hypoxia were not significantly different between the two groups. In both groups following hypoxia, Vt and Fb were significantly increased when compared with normoxia during loading (P < 0.001 for both) (Fig. 2). This was accompanied by a trend toward a reduction in Ti following hypoxia in both groups (P = 0.052) but no significant change in Vr (P = 0.572; Fig. 2).

**DISCUSSION**

This is the first study to compare load compensation responses between OSA patients and a non-OSA control group under both hypoxic and normoxic conditions. As such, it provides key insights into the ability of OSA subjects to compensate for sustained high-magnitude loads and into the acute effects of hypoxia on load compensation in these groups. In addition, this is the first study of this type where both full polysomnography and pulmonary function testing has been performed on both OSA patients and controls to fully characterize both groups.

The main findings of this study were, first, that the changes in ventilation during incremental resistive loading were not significantly different between OSA patients and controls. These results suggest that, despite previously demonstrated abnormalities of load compensation, OSA patients do not show a significant impairment of ventilatory response when confronted with sustained high-level resistive loading. Second, following exposure to 30 min of hypoxia, ventilatory responses were not significantly different between the two groups, suggesting that OSA patients do not have an increased susceptibility to hypoxia. Indeed, in both groups, Vt was significantly greater following hypoxia during resistive loading, suggesting that rather than blunt the ventilatory response to loading hypoxia serves to enhance it.

Our main finding was that Vt significantly declined during incremental resistive loading but that this decline was not significantly different between OSA patients and controls. In both groups, the reduction in ventilation arose as a result of a change in breathing pattern, with a prolongation of Ti and a reduction in PIF. This suggests that both groups are sacrificing inspiratory airflow to compensate for increasing inspiratory resistance. Contrary to our expectations, ventilatory responses in OSA patients were not impaired at baseline, and they were not significantly affected by prior exposure to hypoxia. This is an important clinical observation because it demonstrates for the first time that OSA patients are capable of maintaining ventilation even when confronted with high levels of upper

**Table 2. Mean SaO2, and PetCO2, during gas period**

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<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Normoxia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>97.6±0.7</td>
<td>79.8±0.2*</td>
</tr>
<tr>
<td>PetCO2, Torr</td>
<td>41.4±1.1</td>
<td>41.5±1.1</td>
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Values are means ± SE of 30-s values between 10 and 30 min of gas period. *p < 0.001 for gas effect.

**Fig. 1.** Minute ventilation (Vt) during the 30-min gas period for controls (A) and obstructive sleep apnea (OSA) patients (B). Data points represent 30-s means ± SE.
airway resistance, such as would be experienced during nocturnal airway obstruction.

These results contrast with previous researchers who have found load compensation responses to be impaired in OSA patients compared with controls. Rajagopal et al. (27) found that $V_t$ during CO$_2$ rebreathing was significantly reduced during fairly low-level resistive loading (12 cmH$_2$O·l$^{-1}$·s) in OSA patients compared with controls, whereas Greenberg et al. (17) found that $V_t$ was significantly reduced during a 15- to 20-min period of inspiratory loading at 18 cmH$_2$O·l$^{-1}$·s. A possible reason for the difference between these results and ours is the loading protocol we employed. Rather than presenting a fixed moderate-level load that remained constant over a set period during which stable ventilation could be assessed, we elected to use an incremental loading protocol with very high levels of resistance reached by the final load. The main reasons for this were to assess load compensation across a wide range of loads and also to determine the load dependence of decompensation responses. Certainly ventilation was reasonably well maintained for the first three loads, following which there was a decline as resistive load increased. However, this response was similar in controls and OSA patients, suggesting that, using this protocol, the two groups behaved in a similar fashion with respect to overall ventilation.
Alternatively, the failure to demonstrate a difference in ventilatory responses between subjects and controls may reflect the characteristics of our control group. Despite our efforts to recruit a control group free from OSA, the mean RDI (8.6) was above that which is currently considered normal (<5). Although the control group was thus arguably not normal, we believe that it still provides a valid comparison with the study group, which had a higher mean RDI (59.5) than is often seen in studies of this type. However, it is possible that our results may have therefore underestimated the differences between the two groups.

It is also possible that differences between our results and those of previous researchers may be due, at least in part, to methodological differences. In the study by Rajagopal et al. (27), eight OSA patients were compared with eight controls matched for age, sex, weight, and height. Although not significantly different, mean forced vital capacity was lower in the OSA group by 660 ml, implying a relative restrictive deficit in the OSA subjects that may have reduced ventilatory compensation in this group. Similarly, in the study by Greenberg et al. (17), pulmonary function tests were only performed in OSA subjects and not in controls, and underlying pulmonary impairment may have influenced the ventilatory responses in the OSA group. In addition, the OSA patients were significantly older than the control group, another possible cause of impaired loading responses.

We did find some subtle differences in individual respiratory variables that may indicate contrasting responses to loading between the OSA patients and controls. In normal individuals, sustained inspiratory loading generally results in an augmentation of VT, which, along with a prolongation of Ti and reduced F0, serves to maintain VT near baseline levels (6, 18, 33). This response was seen in the control group during loading with an initial increase in VT followed by a later decline, presumably as compensatory mechanisms were overwhelmed by increasing load. In contrast, in the OSA group VT did not significantly change during the loading period. Although this may reflect a difference in loading response between the two groups, this result may be due to inadequate matching of subjects and controls. Despite every effort to match the two groups, the OSA group had a significantly greater mean body mass index (BMI), and this may have impaired the normal VT response to loading in this group. Massive obesity is associated with a reduced resting VT (29), and in normal subjects in whom obesity is simulated with external chest loading, the VT response during exercise is blunted compared with unloaded controls (31). However, we did not find a difference in resting ventilatory parameters between OSA patients and controls, and furthermore, the increased BMI in the OSA group was not associated with any demonstrable impairment of resting lung function. We thus believe that it is unlikely that obesity had a significant influence on the ventilatory responses during loading but accept it as a possible confounding factor.

Contrary to our expectations, we did not demonstrate a significant negative effect of hypoxia on ventilation during loading in either group. Hypoxia is a neurocognitive depressant that has been shown to have a number of negative effects on respiratory sensation and control (10–12, 24), and we had therefore expected that, in this study, prior exposure to hypoxia would impair ventilatory responses to inspiratory loading. The lack of negative effect may reflect the underlying mechanisms that mediate ventilation during loading, including intrinsic properties of the chest wall and ventilatory apparatus (9, 35), local neural reflexes (4, 5), chemoreflex activity (8, 25), and conscious mechanisms (32, 33). Within the central nervous system there appears to be a rostral to caudal vulnerability to hypoxia (23). It is possible therefore that cortical activities such as load perception may be more sensitive to the inhibitory effects of hypoxia than the more peripheral mechanisms involved in load compensation.

The reason for the increase in ventilation in both groups during loading following hypoxia is not immediately apparent. To our knowledge, ventilatory responses to loading following hypoxia have not been previously assessed, although Kelsen et al. (20) demonstrated an enhanced ventilatory response to flow-resistive loading during hypoxia. This was believed to be due to an increase in respiratory efferent activity to maintain or even enhance ventilation, and it may be that our results reflect a similar phenomenon.

**Implications.** In summary, we have demonstrated that OSA patients have the ability to mount a similar ventilatory response to controls when confronted with high-level incremental resistive loading. These results suggest that OSA patients do not have a clinically significant underlying abnormality of load compensation, particularly when confronted with high levels of upper airway resistance such as are frequently encountered in OSA patients during sleep. Furthermore, neither OSA patients nor controls showed a significant decline in load compensation after hypoxic preconditioning, suggesting that, unlike other aspects of ventilatory function, load compensation is relatively impervious to the effects of hypoxia.

Fig. 3. Peak inspiratory flow (PIF) vs. PIP during loading. Data points represent mean values for each 2-min load period ± SE.
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GRANTS
This work was supported by the National Health and Medical Research Council of Australia.

REFERENCES