Arousal and ventilatory responses during sleep in children with obstructive sleep apnea

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Marcus, Carole L., Janita Lutz, John L. Carroll, and Owen Bamford. Arousal and ventilatory responses during sleep in children with obstructive sleep apnea. J. Appl. Physiol. 84(6): 1926–1936, 1998.—Abnormal central regulation of upper airway muscles may contribute to the pathophysiology of the childhood obstructive sleep apnea syndrome (OSAS). We hypothesized that this was secondary to global abnormalities of ventilatory control during sleep. We therefore compared the response to chemical stimuli during sleep between prepubertal children with OSAS and controls. Patients with OSAS aroused at a higher PCO2 (58 ± 2 vs. 60 ± 5 Torr, P < 0.05); those with the highest apnea index had the highest arousal threshold (r = 0.52, P < 0.05). The hypercapnic arousal threshold decreased after treatment. For all subjects, hypoxia was a poor stimulus to arousal, whereas hypercapnia and, particularly, hypoxic hypercapnia were potent stimuli to arousal. Hypercapnia resulted in decreased upper airway obstruction in OSAS. Ventilatory responses were similar between patients with OSAS and controls; however, the sample size was small. We conclude that children with OSAS have slightly blunted arousal responses to hypercapnia. However, the overall ventilatory and arousal responses are normal in children with OSAS, indicating that a global deficit in respiratory drive is not a major factor in the etiology of childhood OSAS. Nevertheless, subtle abnormalities in ventilatory control may exist.

THE OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) is common during childhood, occurring in ~1% of preschool children (1). Complications include pulmonary hypertension, failure to thrive, developmental delay, and even sudden death. Nevertheless, despite the frequency and severity of this condition, little is known about the pathophysiology of childhood OSAS.

Childhood OSAS differs from adult OSAS in its etiology, clinical manifestations, and treatment. In children who are otherwise healthy, OSAS is assumed to be secondary to adenotonsillar hypertrophy. However, there is evidence that adenotonsillar hypertrophy is not the sole cause of OSAS, for the following reasons. 1) Children with OSAS do not have airway obstruction during wakefulness. 2) Studies have failed to show a correlation between OSAS and the degree of adenotonsillar hypertrophy (17). 3) In some children, OSAS persists after tonsillectomy and adenoidectomy; and continuous positive airway pressure (CPAP) treatment may be required (24). 4) Guilleminault (13) reported a cohort of children in whom OSAS resolved after tonsillectomy and adenoidectomy but recurred during adolescence. It is possible that children with OSAS have anatomic abnormalities in addition to adenotonsillar hypertrophy, such as an underlying narrow oropharynx. An alternative theory is that childhood obstructive apnea is not caused by anatomic abnormalities alone but also by dynamic (neuromuscular) factors affecting the upper airway. The upper airway muscles are activated by many factors, including the central nervous system ventilatory response to hypoxia and hypercapnia (32). It is therefore possible that the central ventilatory response to hypoxia and/or hypercapnia is abnormal in children with OSAS. This postulated central nervous system abnormality may result in isolated decreased upper airway motor tone or in more global abnormalities, such as depressed ventilatory or arousal responses to chemical stimuli.

Adults with OSAS often have a decreased ventilatory drive (2, 10, 29). We previously showed that children with OSAS have normal ventilatory responses during wakefulness (21). However, inasmuch as these children breathe normally when awake and have upper airway obstruction only during sleep, it is possible that they have a selective abnormality of their ventilatory drive that is limited to periods of sleep. This has not been evaluated.

Arousal from sleep is a protective response to upper airway obstruction and results from such factors as hypoxemia, hypercapnia, and increased upper airway resistance. Nevertheless, obstructive apneas with desaturation frequently do not result in cortical arousal in children (25); indeed, some children with OSAS are noted to have prolonged periods of partial upper airway obstruction without evidence of arousal (1). In addition, although the arousal response has been well characterized in infants (30, 31) and adults (3, 11, 15), no data are available regarding arousal to chemical stimuli in normal older children.

We hypothesized that children with OSAS have global abnormalities of ventilatory control during sleep. We therefore evaluated the arousal and ventilatory response to hypoxia, hypercapnia, hypoxic hypercapnia, and hyperoxia in children with OSAS compared with normal controls.

METHODS

Study Group

Prepubertal children (Tanner stage 1) with previously diagnosed OSAS secondary to adenotonsillar hypertrophy who were old enough to cooperate with testing (in general, those >4–5 yr of age) were eligible for the study. All children had been referred to the Pediatric Sleep Disorders Clinic of Johns Hopkins University for evaluation of clinically suspected OSAS. Children with craniofacial anomalies, morbid obesity [body mass index (BMI) ≥30 kg/m²], pulmonary
disease, or significant medical conditions other than OSAS were excluded from the study.

Control children were recruited from the families of hospital staff members. All control children were healthy, had no symptoms of OSAS, and had not undergone adenotonsillectomy, tonsillectomy, or other airway surgery. Some control children had a history of mild, intermittent snoring, but none snored loudly or continuously.

Informed consent was obtained from the parents/legal guardians of each child, and assent was obtained from the child. The study was approved by the Institutional Review Board of Johns Hopkins University.

Study Design

All children underwent baseline polysomnography to confirm their diagnosis. Then, on a separate night, ventilatory and arousal responses during sleep were evaluated. The height and weight of each child were determined at the time of polysomnography, and growth percentiles were obtained using standard growth charts (National Center for Health Statistics, adapted by Ross Laboratories). Children were considered obese if their weight was >120% of their ideal weight for height. The BMI was defined as the weight in kilograms divided by the square of the height in meters. Patients with OSAS were treated by tonsillectomy and adenotonsillectomy per standard clinical practice, this being the primary treatment for childhood OSAS. In those subjects undergoing surgery who consented to reevaluation, polysomnography was repeated 6–10 wk postoperatively and ventilatory and arousal responses were tested again. In one patient with OSAS and abnormal arousal responses, testing of ventilatory and arousal responses was repeated 6 mo after surgery. Arousal and Ventilatory Response Testing

Arousal and ventilatory responses were measured on a separate night. EEG, electrooculograms, EMG, chest wall motion, SpO2, and oximeter pulse waveform were measured as previously described. Because many of the children with adenotonsillar hypertrophy breathed through their mouth, subjects wore oronasal masks. We found that an adult CPAP mask (Respironics, Murrysville, PA; size large or large narrow, with a Comfort Flap) would cover the child’s nose and mouth snugly. The mask was attached to a heated pneumotachometer (Hans Rudolph, Kansas City, MO) and transducer (Validyne Engineering, Northridge, CA) and then a T circuit, through which room air flowed at a constant rate of 20 l/min. The pneumotachometer was calibrated with a rotameter. PETCO2 was measured via a port in the mask with an infrared capnometer (Ametek, Paoli, PA). During the latter part of the study a transcutaneous monitor became available, and transcutaneous PO2 and PCO2 were measured as a safety backup (Radiometer, Paramus, NJ). The mask was checked for leaks periodically throughout the study and whenever the patient aroused or changed positions or the shape of the flow or PETCO2 waveforms changed. The patient was considered to have a flow-limited pattern of breathing when airflow failed to increase, despite increasing respiratory effort. The characteristic waveform pattern, which has been described previously (6, 22), consists of increasing inspiratory flow followed by a midinspiratory plateau.

Ventilatory responses were tested by introducing test gases into the respiratory circuit at a constant rate. During these trials the room air bias flow was adjusted so that there was no change in the total flow through the circuit. For the hypoxic challenge a constant flow of N2 was introduced into the circuit at 10 l/min until SpO2 fell to 75%, the patient aroused, or for a maximum of 3 min. The response to hyperoxia was assessed by introducing N2 and CO2 until SpO2 reached 90% in association with hypoxia. The response was considered a hypoxic/hypercapnic challenge if the patient aroused, or for a maximum of 3 min. PETCO2 tended to increase gradually over the first 30–45 s and then stabilize. A combined hypoxic/hypercapnic trial was performed by introducing N2 and CO2 until SpO2 fell to 75%, Pco2 reached 65 Torr, the patient aroused, or for a maximum of 3 min. PETCO2 tended to increase gradually over the first 30–45 s and then stabilize. A combined hypoxic/hypercapnic trial was performed by introducing N2 and CO2 until SpO2 fell to 75%, Pco2 reached 65 Torr, the patient aroused, or for a maximum of 3 min. The response to hyperoxia was assessed by introducing O2 at 5 l/min until the patient aroused or for a maximum of 3 min. Between challenges the subject breathed room air for a
minimum of 15 min after the return of $\text{SpO}_2$ and $\text{PETCO}_2$ to baseline. Challenges were initially performed in slow-wave sleep (SWS); when possible, they were repeated during stage 2 and rapid-eye-movement (REM) sleep. For each type of challenge, one trial was attempted in each sleep stage. Challenges were not initiated during periods of obstruction. However, some obstructive apneas did occur during challenges. A pediatrician was in constant attendance at the bedside, and the patient's heart rate, respiration, and gas exchange were closely monitored.

### Data Analysis

The steady-state hypercapnic response was calculated by measuring the slope of the mean minute ventilation ($\dot{V}_E$) vs. $\text{PETCO}_2$, during the last 30 s of hypercapnia compared with baseline. Because the time to arousal was variable, with many subjects arousing before $\text{PETCO}_2$ reached 100 Torr, inasmuch as these subjects were not considered physiologically important. Six children were excluded from analysis if they remained unaroused at $\text{PETCO}_2$ levels greater than 100 Torr.

### Study Population

Fifteen children with OSAS and 10 controls were studied. It was necessary to study a larger number of OSAS patients than controls because all challenges could not always be performed in OSAS patients because of the presence of frequent obstructive apneas. Subject characteristics are shown in Table 1. Control subjects were slightly older than OSAS patients. However, a difference of 1 yr in this prepubertal, school-aged cohort was not considered physiologically important. Six children with OSAS and one control were classified as obese ($P = 0.05$). One child with OSAS had been born prematurely. One control had a history of mild asthma, for which he occasionally received albuterol, but he did not require medication for some time. Another control had a history of attention deficit disorder but was not on medication at the time of study.

### Polysomnography

Polysomnography results are outlined in Table 1. The children had moderate-to-severe OSAS by pediatric standards (1). Three of the children with OSAS had predominantly obstructive hypoventilation (i.e., snoring associated with retractions, paradoxical respiration, and hypercapnia) (1), rather than complete obstructive apneas. No control child had apnea, desaturation, or hyperventilation.

#### Table 1. Population characteristics and polysomnography results

<table>
<thead>
<tr>
<th></th>
<th>OSAS (n = 15)</th>
<th>Control (n = 10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>8 (53)</td>
<td>5 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>128 ± 13</td>
<td>135 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>32 ± 13</td>
<td>34 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.9 ± 5.0</td>
<td>18.5 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>86 ± 7</td>
<td>87 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>REM sleep time, %TST</td>
<td>21 ± 3</td>
<td>17 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Apnea index, %/h</td>
<td>12 ± 11</td>
<td>0 ± 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0-35</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Peak $\text{PETCO}_2$, Torr</td>
<td>53 ± 4</td>
<td>49 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48-61</td>
<td>42-53</td>
<td></td>
</tr>
<tr>
<td>Duration of hypoventilation, $\text{PETCO}_2 &gt; 50$ Torr as %TST</td>
<td>14 ± 18</td>
<td>0 ± 0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0-47</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>$\text{SpO}_2$, %</td>
<td>78 ± 17</td>
<td>95 ± 3</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>39-96</td>
<td>90-98</td>
<td></td>
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</tbody>
</table>

Values are means ± SD unless otherwise specified. OSAS, obstructive sleep apnea syndrome; BMI, body mass index; REM, rapid eye movement; TST, total sleep time; $\text{SpO}_2$, arterial $O_2$ saturation; $\text{PETCO}_2$, end-tidal $CO_2$; NS, not significant. * Some patients had obstructive hypoventilation rather than cyclic obstructive apneas and, therefore, had low apnea indexes.
Arousal Responses

Arousal responses to the various stimuli are shown in Fig. 1 and Table 2. Approximately one-fourth of subjects aroused in response to hypoxia, whereas all subjects aroused in response to hypercapnia. As expected, arousal rarely occurred in response to hypoxia. There was no difference in the proportion of OSAS patients who aroused in response to any of the stimuli compared with controls.

Arousal threshold. There was no difference in the time to arousal in response to hypoxia or the level of \( \text{SpO}_2 \), at which arousal occurred between patients with OSAS and controls. This held true when either method of calculating the arousal threshold was used. However, there was a difference in the arousal threshold to hypercapnia. Patients with OSAS aroused at a higher PCO\(_2\), during the hypercapnic and hypoxic hypercapnic challenges, than the controls (Table 2). There was no significant difference in the time to arousal in response to hypercapnia.

Response to hypoxic hypercapnia. When exposed to hypoxic hypercapnia, control subjects aroused more quickly and at a lower PET\(_{CO_2}\) than when exposed to hypercapnia alone (Fig. 2, Table 2). Patients with OSAS showed a similar trend, which did not reach statistical significance. The method of calculating the arousal threshold did not alter the significance of the results. In most subjects, little desaturation had occurred by the time of arousal: \( \text{SpO}_2 \) at the time of arousal was 94 ± 4% for hypoxic hypercapnia compared with 98 ± 2% for hypercapnia alone. Arousal did not occur on three of the hypoxic hypercapnic trials (1 control child did not arouse during stage 2 or SWS, and 1 child with OSAS did not arouse during REM sleep). However, this was because of the safety precautions used: some trials were terminated when \( \text{SpO}_2 \) reached 75%, even though PET\(_{CO_2}\) had not yet increased to 65 Torr.

Effect of sleep stage on arousal. In normal subjects, arousal occurred less during SWS than in other stages. No normal subject aroused to hypoxia during SWS (P < 0.02 compared with other sleep stages). OSAS patients showed a similar trend but did not reach statistical significance. In controls the time to hypercapnic arousal was longer during SWS than stage 2. REM sleep values were similar to stage 2 values, but there were fewer REM sleep trials, and this was not significant. In patients with OSAS there was no significant difference between SWS and other stages. There was no significant difference in the level of PCO\(_2\) at which arousal occurred among the different stages for controls or OSAS patients, inasmuch as most subjects had reached a steady state before arousal.

Variability of arousal responses. There was considerable intrapatient variability in hypoxic arousal responses in this study (Fig. 3). Approximately one-half of OSAS patients and control subjects never aroused in response to hypoxemia; the others aroused on some but not all trials. Only one subject aroused on all three hypoxic trials. All subjects aroused in response to hypercapnia. Each patient was studied only once during each sleep stage, and the arousal threshold was shown to be affected by sleep stage. Therefore, the study design did not allow us to directly assess the intrapatient variability for hypercapnic arousal. Figure 3 shows the lowest and highest PET\(_{CO_2}\) at arousal for each individual.

Ventilatory Responses

The ventilatory responses to hypoxia and hypercapnia are shown in Figs. 4 and 5. Because ventilatory responses could not be measured during periods of obstruction, fewer successful challenges were performed in the OSAS group. There were no differences in ventilatory responses between patients with OSAS and controls. The 95% confidence intervals were −0.03 to 0.07 l·min\(^{-1}\)·%SpO\(_2\)\(^{-1}\) for hypoxia and −0.05 to 0.11 l·min\(^{-1}\)·Torr PET\(_{CO_2}\)\(^{-1}\) for hypercapnia. To minimize the effect of partial airway obstruction, ventilatory responses were also compared during SWS, when the least amount of obstruction occurs (9). There were no significant differences in the hypoxic or hypercapnic responses between the two groups during SWS [hypoxic response: −0.16 ± 0.08 and −0.10 ± 0.1 l·min\(^{-1}\)·%SpO\(_2\)\(^{-1}\) for controls (n = 10) and OSAS patients (n = 9), respectively; hypercapnic response: 0.24 ± 0.14 and 0.20 ± 0.09 l·min\(^{-1}\)·Torr PET\(_{CO_2}\)\(^{-1}\) for controls (n = 8) and OSAS patients (n = 11), respectively]. Two subjects (1 OSAS patient and 1 control) developed periodic breathing when returned to normoxia after hypoxic challenges.

Hypoxia. Patients with OSAS and controls showed a similar response to hypoxia: Ve fell to 91.5 ± 11.7% of baseline in OSAS patients and to 94.7 ± 8.9% in controls (P = NS).
Hypoxic hypercapnia. Successful pairs of hypercapnic and hypoxic hypercapnic challenges could be performed in only seven trials in controls and two trials in OSAS patients. The small number of trials was partly because fewer trials were attempted, inasmuch as patients were often wide awake and had difficulty settling down after the hypercapnic trials and, in OSAS patients, because they tended to have obstructions during at least one part of the challenge. For control subjects, there was a trend to a higher ventilatory response with the combined challenge: slope of hypercapnic response of $0.243 \pm 0.189$ and $0.052 \pm 0.074$ l·min$^{-1}$·Torr PETCO$_2^{-1}$ for combined and hypercapnic challenge, respectively, at the same degree of hypercapnia ($P < 0.05$). The response in the OSAS patients was variable; one OSAS patient had a higher response to the combined challenge than to hypercapnia alone ($0.391$ vs. $0.063$ l·min$^{-1}$·Torr PETCO$_2^{-1}$), whereas the other had a lower response ($0.195$ vs. $0.211$ l·min$^{-1}$·Torr PETCO$_2^{-1}$).

Effect of body size on ventilatory responses. Body size can affect ventilatory responses. However, size was similar between patients with OSAS and controls (Table 1). When hypoxic and hypercapnic ventilatory responses were corrected for body surface area, there were no significant differences between the two groups.

Effect of sleep stage on ventilatory responses. In controls the hypoxic ventilatory response was lower during REM sleep than during SWS: slope of hypoxic response of $-0.157 \pm 0.76$, $-0.125 \pm 0.047$, and $-0.039 \pm 0.052$ l·min$^{-1}$·%SpO$_2^{-1}$ in SWS, stage 2, and REM sleep, respectively ($P < 0.05$).

### Table 2. Arousal data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th></th>
<th>OSAS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Arousals/trials, n (%)</td>
<td>7/27 (26)</td>
<td>3/10 (30)</td>
<td>0/10 (0$^a$)</td>
<td>4/7 (57)</td>
<td>7/33 (21)</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td>Time, s</td>
<td>34 ± 15</td>
<td>40 ± 18</td>
<td>30 ± 14</td>
<td>26 ± 10</td>
<td>26 ± 12</td>
<td>18</td>
</tr>
<tr>
<td>SpO$_2$, %</td>
<td>88 ± 13</td>
<td>82 ± 19</td>
<td>89 ± 12</td>
<td>90 ± 9</td>
<td>89 ± 11</td>
<td>91</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Arousals/trials, n (%)</td>
<td>24/24 (100)</td>
<td>10/10 (100)</td>
<td>9/9 (100)</td>
<td>5/5 (100)</td>
<td>36/36 (100)</td>
<td>11/11 (100)</td>
</tr>
<tr>
<td>Time, s</td>
<td>51 ± 31</td>
<td>36 ± 12</td>
<td>74 ± 39$^p$</td>
<td>38 ± 13</td>
<td>61 ± 43</td>
<td>64 ± 59</td>
</tr>
<tr>
<td>PETCO$_2$, Torr</td>
<td>58 ± 2</td>
<td>58 ± 3</td>
<td>59 ± 3</td>
<td>57 ± 1</td>
<td>60 ± 5$^p$</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>Hypoxic/hypercapnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousals/trials, n (%)</td>
<td>17/19 (90)</td>
<td>7/8 (88)</td>
<td>7/8 (88)</td>
<td>3/3 (100)</td>
<td>19/20 (95)</td>
<td>8/8 (100)</td>
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<tr>
<td>Time, s</td>
<td>23 ± 6$^a$</td>
<td>24 ± 6</td>
<td>25 ± 7</td>
<td>18 ± 1</td>
<td>29 ± 6$^b$</td>
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<td>54 ± 6</td>
<td>49 ± 4</td>
<td>58 ± 5$^c$</td>
<td>59 ± 7</td>
</tr>
<tr>
<td>SpO$_2$, %</td>
<td>95 ± 4</td>
<td>96 ± 2</td>
<td>93 ± 5</td>
<td>97 ± 3</td>
<td>93 ± 4$^d$</td>
<td>96 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SD unless otherwise specified. Data are shown only for subjects who aroused. SWS, slow wave sleep. $^aP < 0.02$ for SWS vs. other stages (controls only); $^bP < 0.05$ for SWS vs. other stages (controls only); $^cP < 0.05$ for OSAS vs. controls; $^dP < 0.005$ for hypoxic hypercapnia vs. hypercapnia (controls only); $^eP < 0.001$ for OSAS vs. controls.

![Fig. 2. Time to arousal (left) and end-tidal PCO$_2$ (PETCO$_2$) at which arousal occurred (right) for subjects exposed to hypercapnia (CO$_2$) or hypoxic hypercapnia (N$_2$/CO$_2$).](http://jap.physiology.org/ Downloaded from http://jap.physiology.org/)

Control subjects; ○, OSAS patients. Three trials in which subjects did not arouse are not shown. Time to arousal and PET$_{CO_2}$ at arousal were lower when subjects breathed N$_2$/CO$_2$ than when they breathed CO$_2$ alone ($P < 0.002$ for both).
slope of 0.241 ± 0.140, 0.125 ± 0.084, and 0.071 ± 0.077 l·min⁻¹·Torr PETCO2⁻¹ in SWS, stage 2, and REM sleep, respectively (P = NS). Because the patients with OSAS obstructed most during REM sleep, too few REM sleep trials were performed to allow for statistical analysis. Hyperoxic responses did not differ among different sleep stages for OSAS patients or controls.

Changes in breathing pattern in response to chemical stimuli. Changes in the pattern of breathing in response to the chemical stimuli were assessed. There were no significant differences in the slopes of Ti, respiratory rate, Vt/Ti, or Ti/Tt between OSAS patients and controls. However, patients with OSAS showed a greater change in the slope of the flow response to hypercapnia than controls: 21 ± 20 vs. 8 ± 8 ml·s⁻¹·Torr PETCO2⁻¹. There was no significant difference in the flow response to hypoxia. Patients with OSAS also showed a larger decrease in Ti in response to hypercapnia than controls: -0.013 ± 0.013 vs. -0.001 ± 0.009 s/Torr PETCO2 (P < 0.002).

Fig. 3. Left: percentage of hypoxic trials in which each individual subject aroused. Right: lowest and highest PETCO2 at arousal for each subject. Control subjects; O, OSAS patients. Data are not shown for subjects in whom only 1 successful trial was performed.

Fig. 4. Slope of hypoxic ventilatory response (HOVR) for each trial for normal controls and OSAS patients. SpO2, arterial O2 saturation. Group means are represented by horizontal bars. There were no significant differences between OSAS patients and controls.

Fig. 5. Slope of hypercapnic ventilatory response (HCVR) for each trial for normal controls and OSAS patients. Group means are represented by horizontal bars. There were no significant differences between OSAS patients and controls.
Effect of CO₂ on airflow in patients with OSAS. In response to CO₂, many patients with OSAS had a change in flow waveform from a flow-limited pattern (i.e., failure of airflow to increase, despite increasing respiratory effort) to a non-flow-limited pattern (Fig. 6). This was associated with an increase in flow and occurred in the absence of arousal. The change in airflow pattern developed over the first few breaths of hypercapnia and was not seen in patients who aroused rapidly (i.e., during the first 3 breaths after CO₂ administration). Excluding those trials in which baseline flow limitation was absent and those trials in which subjects aroused during the first three breaths of hypercapnia, we found that the flow pattern became non-flow-limited with CO₂ administration in 28 of 31 (90%) trials. In the OSAS patients, obstructive apneas occurred frequently during the baseline period or as PETCO₂ began its initial rise. However, obstructive apneas rarely occurred during hypercapnia.

Relationship Between Severity of OSAS and Arousal and Ventilatory Responses

The degree of polysomnographic abnormalities was compared with the arousal threshold and ventilatory responses for the children with OSAS. Those patients with the highest apnea index had the highest arousal threshold to CO₂ (r = 0.52, P < 0.05). There was no significant correlation between ventilatory responses or arousal thresholds and the SpO₂ nadir, duration of desaturation, peak PETCO₂, or duration of hypventilation.

Postoperative Results

Six patients with OSAS underwent repeat testing 81 ±50 days after tonsillectomy and adenoidectomy (Table 3). As expected, patients gained weight postoperatively. OSAS resolved in five patients. The sixth patient, who had obstructive hypoventilation, did not improve (Fig. 7). There was a significant decrease in the hypercapnic arousal threshold postoperatively (P < 0.05; Table 3). When the one patient with persistent OSAS was excluded from analysis, this became even more significant (P < 0.02). One child (a 6-yr-old obese boy; Fig. 7, filled circle) with a marked decrease in arousal threshold 2 mo postoperatively was reevaluated 6 mo postoperatively. Time to arousal to hypercapnia fell from 102 s preoperatively to 34 ±2 s postoperatively and 22 ±6 s postoperatively. PETCO₂ at arousal fell from 67 to 56 to 49 Torr, respectively. This patient did not arouse to hypoxia on any of three trials preoperatively but aroused on one of three trials 2 mo postoperatively and one of three trials 6 mo postoperatively. The change in ventilatory responses could not be evaluated in this patient, inasmuch as he had frequent obstructive apneas during the preoperative trials. For the group as a whole, there were no significant differences in ventilatory responses postoperatively.

DISCUSSION

This study has shown that children with OSAS have blunted arousal responses to hypercapnia, although the difference between OSAS patients and controls was small. No difference was found in ventilatory responses between patients with OSAS and controls, although the sample size may have been too small to detect this. In addition, this study has shown that, in children with OSAS, breathing an elevated inspired PCO₂ (PICO₂) resulted in decreased airway obstruction. These results suggest that a deficit in the global ventilatory drive is not a major factor in the pathogenesis of childhood OSAS, although more subtle or dynamic defects in ventilatory control may play a role. In addition, the normal arousal responses to chemical stimuli in prepubertal children have been characterized.

Polysomnographic Characteristics

The patients studied had moderate-to-severe OSAS by pediatric standards. Children with OSAS tend to have fewer complete obstructive apneas than adults with OSAS (1). Instead, they frequently have partial airway obstruction, associated with hypercapnia and hypoxemia. Several of the patients in this study demonstrated this pattern of obstructive hypoventilation (snoring associated with retractions, paradoxical respiration, and hypercapnia) (1), rather than complete obstructive apneas.

Arousal

This study found that children with OSAS had slightly elevated hypercapnic arousal thresholds, which
decreased after treatment. Patients with OSAS aroused at a higher PCO2 during hypercapnia and hypoxic hypercapnia than controls. The hypercapnic threshold correlated with the severity of OSAS, as shown by the apnea index. In contrast to controls, hypercapnic arousal in OSAS patients did not show a state-specific response. Children with OSAS are frequently hypercapnic during sleep (1). Although this study showed no direct correlation between arousal thresholds and the degree of hypercapnia during baseline polysomnography, it is possible that habituation to chronic, intermittent hypercapnia resulted in secondary blunting of arousal responses. This theory is supported by the decrease in the hypercapnic arousal threshold after treatment. In control children, hypoxic hypercapnia resulted in arousal at a lower PCO2 than hypercapnia alone. This was not seen in the OSAS patients, perhaps because these patients routinely develop hypoxic hypercapnia during obstructive episodes.

This study also provides important information on normal arousal to respiratory stimuli in this age group. Although arousal has been studied extensively in infants and adults, few data are available regarding arousal to respiratory stimuli in prepubertal children (20). The present study provides data for this intermediate age group. This study demonstrated that hypoxia (to the degree used in the study) is a poor stimulus to arousal, which occurred in only one-fourth of trials. The percentage of subjects arousing to hypoxia is slightly less than that reported for other age groups. Arousals occurred in 32% of trials in normal infants (31). Adults are more likely to arouse to hypoxia, with arousal occurring on 42–54% of trials (3, 11), although the response is variable (3, 11, 15). The decreased arousal to hypoxia in children is consistent with the general increase in arousal threshold in children compared with adults (5). The present study found considerable intraindividual variability in the arousal response. This has been reported for adults (3).

In contrast to hypoxia, hypercapnia was a potent stimulus to arousal, resulting in arousal in all subjects. This is similar to findings in other age groups. Normal infants (30) and adults (8, 15), as well as children (20) and adolescents (18), arouse to hypercapnia. However, the arousal threshold was higher in the prepubertal children than in other age groups: PETCO2 of 59 ± 5 Torr compared with 52 Torr in infants (30), 46 Torr in adolescents (18), and 49 Torr in adults (15).

The arousal threshold was lower for hypercapnia combined with hypoxia than for hypercapnia alone. Teleologically, this makes sense. In the setting of asphyxia the most effective response to the resultant hypoxic hypercapnia is to arouse and remove the cause of the asphyxia, whereas, in a situation of pure hypoxia, arousal is less important. Isolated hypercapnia is unlikely to occur in the natural state. As expected, hyperoxia was rarely associated with arousal. Therefore, hyperoxia served as a control challenge by demonstrating that adjustments to the gas mixtures per se did not cause arousal.

### Ventilatory Drive

The ventilatory responses to hypoxia, hypercapnia, and hyperoxia were similar between children with...
In patients with OSAS the administration of CO₂ elevated PICO₂ resulted in improved airflow is consis-
temperary oscillations (19). The fact that breathing an
cal stimuli to the brain, thereby decreasing the gain of
reduction in obstructive apneas and change in inspira-
tional airflow pattern were probably due to activation of
the number of obstructive apneas. We (22) and others
(6) previously showed that flow-limited respiration can
be recognized by the characteristic flow waveform
pattern, rather than by use of invasive measures of
respiratory effort, such as esophageal balloons. The
reduction in obstructive apneas and change in inspira-
tory airflow pattern were probably due to activation of
the central nervous system by CO₂, resulting in aug-
mented upper airway muscle activity (16, 32). This is
supported by a greater increase in inspiratory flow in
the patients with OSAS than in the controls, associated
with a decrease in Ti but no change in overall Ve. An-
other potential mechanism for the reduction in
apneas is that PICO₂ diminished fluctuations in chemi-
cal stimuli to the brain, thereby decreasing the gain of
the respiratory controller and reducing central nervous
system oscillations (19). The fact that breathing an
elevated PICO₂ resulted in improved airflow is consis-
tent with the theory that dynamic factors and not just
anatomic factors are important in the pathogenesis of
childhood OSAS.

Previous studies in adults showed that hypoxic and
hypercapnic ventilatory responses are greater during
wakefulness than during sleep and are lowest during
REM sleep (3, 8, 15). The reasons for the diminished
ventilatory responses during sleep compared with wake-
fulness are unclear. It may be due to a decrease in
central drive. However, it is also possible that the
mechanical changes associated with sleep, such as the
increase in upper airway resistance, result in de-
creased respiratory system output, despite an intact
drive (26). In the present study, rebreathing techniqu-
es were not used. It is therefore not possible to compare
these data with previous pediatric normative data in
the literature regarding responses during wakefulness.
Although only a few trials could be successfully com-
pleted during REM sleep, we found a trend for lower
ventilatory responses during REM than during non-
REM sleep.

It is commonly thought that the administration of
supplemental O₂ to children with OSAS can suppress
the ventilatory drive, thereby causing prolonged apnea. However, we found that hyperoxia resulted in only a
minor decrease in ventilation. This confirms clinical
studies (23). Nevertheless, this study does not rule out
the possibility that individual children with OSAS may
have a marked ventilatory depression in response to
supplemental O₂.

Limitation of Methods

The number of subjects in this study was small. Obstruc-
tive sleep apnea is relatively uncommon in this
age group, particularly in children old enough to cooper-
ate with wearing a facemask. On the basis of this study,
we cannot definitively exclude the possibility that
individual patients with OSAS have abnormal ventila-
tory responses, and additional studies should be per-
formed. However, we believe that the data from this
study are consistent with the theory that most children
with OSAS have a grossly normal ventilatory drive.

We elected to use the standard American Sleep
Disorders Association criteria for arousal (28). Al-
though other definitions of arousal, including shorter
duration, have been used for children, there are no data
to support use of a particular method. We evaluated
cortical arousal only, i.e., arousals associated with EEG
changes (28), inasmuch as pathological effects of noncor-
tical arousals have not been demonstrated.

The evaluation of ventilatory responses was compli-
cated by the presence of obstructive apnea. To prevent
obstruction from confounding the data, arousals that
were temporally associated with obstructive apneas
were discounted. Similarly, if the patient obstructed
during the performance of a ventilatory challenge, the
ventilatory response was discounted. In patients who
obstructed frequently, this resulted in a limitation to
the number of challenges that could successfully be
performed. This was a particular problem during REM
sleep, when obstructive apnea occurred most com-
monly. More hypercapnic trials could be performed
than hypoxic trials, because the inspired CO₂ regular-
ized breathing and reduced obstruction. The presence
of obstruction may have resulted in exclusion of the
most severe patients, although, at a minimum, chal-
lenges could usually be performed in SWS.

It is possible that ventilatory response measurements
were inaccurate in the patients with obstructive
apnea because of partial upper airway collapse and
resultant decreased Ve in the presence of an intact
ventilatory drive. Therefore, trials during SWS were
analyzed separately, inasmuch as obstruction is infre-
dent during this stage (9). Nevertheless, it is possible
that ventilatory drive was underestimated in the OSAS
patients.

Ventilatory response measurements can be affect-
ed by the rate of change of the stimulus intensity.
in this study we used steady-state rather than rebre-
tathing techniques. Although the same stimulus was
presented to each subject, factors such as the rate and depth of ventilation resulted in variable rates of hypoxia/hypercapnia. This may have resulted in a bias against finding true differences between groups.

Our protocol was not designed to evaluate arousal and ventilatory responses during periods of obstructive apnea. Dynamic changes in ventilatory drive, with an acute decrease in central drive occurring simultaneously with upper airway obstruction, are possible in children with OSAS. This theory could not be tested with our methods.

Significance of This Study

This study has shown that children with OSAS have slightly elevated arousal thresholds to hypercapnia and that the arousal threshold correlates with the severity of OSAS. The decrease in arousal threshold after treatment suggests that this blunted arousal threshold is secondary to OSAS. Patients with OSAS and controls appear to have similar ventilatory responses to chemical stimuli, although further study is needed. It is therefore unlikely that a global decrease in ventilatory drive plays a major role in the etiology of childhood obstructive sleep apnea syndrome. Nevertheless, it is possible that subtle defects in respiratory control are present in children with OSAS. Although many children have adenotonsillar hypertrophy, few develop OSAS, and previous studies have failed to show a correlation between anatomic measurements and OSAS in children. This suggests that dynamic factors, as well as structural factors, play a role in the pathophysiology of the disease. This theory is supported by the fact that an elevated $P_{\text{CO}_2}$ resulted in decreased airway obstruction. Potential abnormalities in children with OSAS include a decreased ventilatory drive in response to increased airway load and decreased activation of the upper airway muscles by the central nervous system. Further study is needed to delineate the pathophysiology of this disease.

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