Effects of OSA, inhalational anesthesia, and fentanyl on the airway and ventilation of children

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Received 15 June 2001; accepted in final form 16 January 2002

Obstructive sleep apnea (OSA) describes the repetitive collapse of the upper airway during sleep. Factors that can predispose to the condition include a small upper airway size (13), and abnormal neuromuscular control (29), and there may be an inherited factor in the disease (26). During childhood, OSA is commonly associated with compromise of the airway size by adenotonsillar hypertrophy, and adenotonsillectomy is the treatment of choice (11).

Physiological abnormalities in subjects with OSA include a more collapsible upper airway compared with subjects with primary snoring or control subjects without symptoms, whether this is measured during wakefulness or natural sleep (7, 14, 17). Many adults with a diagnosis of OSA have abnormal ventilatory responses (8), and in severe cases respiratory failure encroaches into the waking state. However, compared with control subjects, the ventilatory responses for children with OSA have only been abnormal under specialized conditions (9, 16). For example, these children have diminished responses to repeated hypercapnia when awake (9) and reduced arousal in response to CO2 when asleep (14).

Sedatives and anesthetic agents are known to exacerbate abnormalities of neuromuscular and respiratory control. There is, however, little specific evidence for or against the use of sedatives and opioids in the perioperative period of children with OSA (11). To date, there are only anecdotal reports of respiratory depression in children in response to sedatives such as chloral hydrate (1) and respiratory depression of subjects with OSA, including children, in the perioperative period (27) including hypoxia (4, 5, 10, 11, 19, 25). Ostermeier et al. (24) summarized 18 cases of respiratory depression in the postoperative period for patients with OSA but included only one child, who had airway obstruction and bradycardia after chloral hydrate.

We hypothesized that, although subtle, the ventilatory control abnormalities present in children with OSA would increase their risk for respiratory depression during anesthesia. To examine whether children with OSA are more sensitive to the respiratory depressant effects of anesthesia and/or opioid analgesics compared with a control group, we measured ventilation after anesthetic induction and then repeated the measurement after an intravenous dose of fentanyl. We found that children with OSA have respiratory depression despite elevated CO2 compared with control subjects under anesthesia and that opioid analgesics compounded this, causing apnea in approximately half of the OSA group.

METHODS

Patient selection. Consecutive patients from The Children’s Hospital at Westmead (Royal Alexandra Hospital for Children) were recruited if they were undergoing adenotonsillar hypertrophy, and adenotonsillectomy is the treatment of choice (11).

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sillectomy for OSA that had been confirmed by overnight sleep study. Control subjects were children having surgery who had no symptoms of sleep disordered breathing. Questionnaires regarding symptoms of sleep breathing abnormalities were collected in all cases (2). The study was approved by the Ethics Committee of the hospital, and informed, written consent was obtained from the parents or the child, before each child’s participation in the study. For this preliminary investigation, we estimated that 18 subjects were needed in each group to show that a statistically significant effect size of one standard deviation between groups.

Questionnaire data were collected on the day of surgery. Children in the control group generally had surgery unrelated to the upper airway. Questionnaires were used to confirm that control subjects had minimal risk for OSA, and the sleep study before surgery was used to confirm the presence of OSA. Previous studies have shown that in children from the general population, rather than from a sleep unit, questionnaire responses can distinguish children who are unlikely to have OSA by using the "OSA score" (2). Any "control" subject with chronic snoring was excluded because of the inability of the questionnaire to distinguish primary snoring from OSA in children (3). Analyses were made between the groups of children with vs. without OSA.

Anesthesia and study protocol. No premedication was used. Anesthesia was induced by an inhaled mixture of 30% oxygen, 60% nitrous oxide, and 5% halothane (with remainder air), and then an intravenous cannula was inserted. The expired concentration of halothane was stabilized at 1% before the study protocol commenced (Datex AS3 Capnograph, Ohmeda, Homebush, Australia). Closing pressure was measured by using a sealed nasal mask, with the head in a neutral position and the mouth closed. Upper airway closing pressure was measured by manually occluding the mask inlet for an average of 10 spontaneous breath efforts while the anesthetist maintained the mask and head positions. The flow signal was monitored for a plateau indicating airway closure (Fig. 1). When obstruction occurred above atmospheric pressures, positive pressure was introduced into the circuit via a T piece and reservoir bag containing 30% oxygen, 60% nitrous oxide, and the percentage of halothane required to maintain a 1% expired concentration just before the test. Pressure at the mask was monitored in real time on the digital data display.

Anesthesia was then deepened, and an uncuffed endotracheal tube (ETT) or laryngeal mask was inserted to provide an unobstructed airway. Laryngeal mask airway (LMA) was used in 14 (61%) of the 23 control cases and 1 (7%) of the 13 children with OSA. Expired halothane concentration was then stabilized again at 1%, and minute ventilation and end-tidal CO2 (Datex AS3 Capnograph) were digitally recorded (Amlab, Sydney, Australia). An intravenous injection of 0.5 μg/kg of fentanyl was given; then these measurements of ventilation were repeated. End-tidal CO2 at baseline was calculated as the mean plateau value over 9.6 ± 1.9 min (range of 4.6–13.3).

Signal acquisition, calibration, and measurement of ventilation. For the purpose of this study, real-time signals for CO2 and flow were acquired directly from analog outputs of the Datex AS3. Pressure signals were acquired in real time by using a Validyne DP45-28 pressure transducer and CD101 carrier demodulator. All signals were digitized by using a signal processor (Amlab International). The pressure range of the DP45-28 is ±0.6 to 90 in H2O full scale, with accuracy ±0.25% at full scale. The Validyne carrier demodulator (CD101) has a linearity of ±0.05%. The specifications of the Datex AS3 are a range of 0–10% for CO2, with accuracy of ±0.2 vol%, rise time of 360 ms, and sample rate of 200 ml/min. When the same sampling tubing, flow rate, and Datex AS3 were used, the measured delay in our circuit (with relation to the other data) to a step change in CO2 was 2.2 s.

Flow measurements were made by use of a Datex (AS3) and either the Pedi-lite or D-lite sensor. The Pedi-lite sensor, which has a range of 0.25 ml/min to 25 l/min and a dead space of 2.5 ml, was used for patients weighing 3–30 kg. The D-lite sensor has a range of 1.5–100 l/min and dead space of 9.5 ml and was used for children >20 kg. Because either sensor was suitable for children weighing 20–30 kg, the choice between the two was made on the basis of other children in the same recording session.

All equipment was allowed to stabilize thermally for 30 min before calibration and subsequent data collection. A two-point calibration was made before each test, using 0 and 10 l/min flow rates and taking the sampling rate of the CO2 analyzer into account. Signals for flow and for pressure were checked by using a calibration analyzer (RT-200, Timeter Instrument, Allied Healthcare Products, St. Louis, MO). The Timeter calibration analyzer (Timeter RT200) is a traceable

![Fig. 1. Raw data demonstrating the method used to determine closing pressure in a subject with obstructive sleep apnea (OSA). Absence of flow was confirmed in the 1st trace (top), whereas airway pressure is shown in the 2nd (bottom). The pressure at which the airway collapsed was measured at −3.2 cmH2O.](http://jap.physiology.org/Downloadedfrom)
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reference instrument, serial no. S17F, with pressure resolution of 0.1 cmH₂O and accuracy of ±0.5% of the reading. The same instrument was used for flow calibration, with resolution of 0.1 l/min and accuracy of ±1% of the reading.

The Amlab (Amlab International) is a commercially available digital signal processor with an accuracy of 0.0001%. Data were acquired at a sampling frequency of 100 Hz. The Amlab processor was calibrated to read the same as the RT-200 calibration analyzer. The CO₂ signal was calibrated by using the Datex Quick Cal calibration gas (at 5 and 0% CO₂) with the Amlab digital signal processor then calibrated to read the same values. Real-time, calibrated data were stored in digital format by using Amlab data acquisition software and then exported for further analysis. Signal analysis was performed by Anadat (RHT-Infodat, Montreal, PQ, Canada), which is another commercially available digital signal analysis package. This software package includes a program for deriving respiratory variables on a breath-by-breath basis from the calibrated flow signal (Abreath, V 5.2, RITT-Infodat). The output variables include minute ventilation, tidal volume (Vt), respiratory frequency, and inspiratory (Ti) and expiratory breath times. Minute ventilation was corrected for body weight (ml·kg⁻¹·min⁻¹) to account for the large variability in age and weight of the children being studied.

Sleep studies. All overnight polysomnograms (sleep studies) were performed in the Sleep Unit of the Children’s Hospital at Westmead, in the usual manner for the unit. Briefly, conditions were adapted to approximate the child’s usual sleep habits, and studies commenced at the child’s usual bedtime. Sleep staging was performed with a minimum of five channels, and respiratory analysis utilized a minimum of seven variables.

Sleep staging was derived from electroencephalogram (EEG; C3/A2 O2/A1), electrooculogram (left outer canthus/A2, and right outer canthus/A1), and submental electromyogram. Electrocardiogram was included. Respiratory effort was recorded by use of inductance plethysmography and surface electromyogram of the diaphragm. Plethysmography included abdominal, thoracic, and sum (Respirtrace, Non-Invasive Monitoring Systems, Miami Beach, FL). Apneas and adequacy of ventilation were recorded through airflow, oxygen saturation (SaO₂), and transcutaneous CO₂ (TcPCO₂). Airflow was recorded via nasal oxygen cannulas (intermediate infant nasal cannula, no. 1615, Salter Labs, Arvin, CA) connected to a pressure transducer with or without thermister recording because airflow measurement provides more reliable detection of respiratory events in OSA (21). Respiratory events were analyzed by using a combination of airflow and Respirtrace (15). Gas measurements were made transcutaneously by using SaO₂ (Ohmeda Biox 3700e pulse oximeter, Datex-Ohmeda, Homebush, Australia) and TcPCO₂ (TINA TCM3, Radiometer, Denmark).

Sleep study data were acquired on a digital system (Compumedics, Melbourne, Australia) and analyzed for sleep stages and the frequency and severity of apneas and hypopneas. Respiratory events were considered significant if they lasted ≥2 respiratory cycles, based on the respiratory rate of the preceding minute, and they were associated with SaO₂ desaturation of ≥3% and/or they were terminated by an arousal. Treatment is generally recommended by our clinicians if the respiratory disturbance index (RDI) exceeds ≥5 respiratory events per hour and includes obstructive events. Full arousals were defined as an abrupt shift in EEG for ≥1 s, with the exception of an occurrence of a spindle to indicate arousal, because of the risk that spindles occurring as a normal part of sleep could be incorrectly marked as respiratory-related events. Movement arousals were defined as disturbances on ≥2 independent channels with EEG remaining unaffected for at least 1 s. The primary outcome measure of the sleep study was the apnea index (number of all apneas per hour of sleep time). The obstructive apnea index (number of mixed or obstructive apneas and hypopneas per hour of sleep time) and RDI (number of apnea and hypopnea per hour of sleep time, including central apnea, and sleep stage-specific indexes) were also recorded. Other outputs included the arousal index (number of all arousal types per hour of sleep time), TcPCO₂ (mean and range), heart rate (mean and range), and SaO₂ (mean, range, and number of desaturations >2, >4, and >5% per hour of sleep time). All measurements of SaO₂ were made after the study had been reviewed and movement artifact had been excluded.

Statistical analyses. Multivariate analysis or repeated-measures ANOVA (SPSS version 10.0.5, Chicago, IL) were used to analyze differences between the two groups and the responses to fentanyl. Group comparisons were made by assuming equal variance. A χ² analysis was used to assess the difference in incidence of central apnea after fentanyl. Results are shown as means ± SD unless otherwise stated. A P value of <0.05 was considered statistically significant. Subgroup analyses for groups with diagnoses in addition to OSA were not performed because of the small sample size in this study.

RESULTS

At the end of the data collection period, a total of 42 children had participated in the study. Results are presented for 38 children (13 with OSA and 25 age-matched control subjects). Two OSA cases were excluded from the analysis, one because the sleep study showed partial airway obstruction but no apnea and the other because the sleep study was undertaken in another center, so sleep state and respiratory analyses (to confirm the presence of OSA) were not available. Two control cases were excluded because they had a history of chronic snoring. The OSA scores of the groups were −3.2 ± 0.5 (−3.8 to −1.7) and 2.0 ± 1.8 (−0.3 to 4.0) (P < 0.001, control vs. OSA, respectively). Thus questionnaires completed for all control cases confirmed that the children did not snore or snored occasionally and did not have other sleep breathing problems. All children used as control subjects had OSA scores low enough to exclude OSA, and all children with OSA fell into the range in which sleep studies would be recommended (2).

The nature of our recruitment meant that these children were characteristic of our sleep unit population, including 50% with an associated diagnosis likely to increase their risk for OSA (28). These diagnoses included Down syndrome (n = 3), Charge syndrome (n = 1), obesity (n = 1), and cerebral palsy (n = 1), with the remainder having no associated abnormalities other than enlarged tonsils and adenoids. Surgical procedures being undertaken in the control group included herniotomy (n = 3), hydrocele (n = 4), circumcision (n = 5), orchidopexy (n = 4), cholecystectomy (n = 1), other urological surgery (n = 2), burns (n = 1), excision of lip cyst (n = 1), adenoidectomy (n = 1), and

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insertion of grommets (middle ear drainage, \( n = 1 \)). Three were reported to have asthma, and one was born prematurely.

There was a male predominance in both OSA and control groups (78.3 vs. 69.2\% boys, control and OSA, respectively). The mean age of the subjects was 4.0 ± 2.2 and 5.3 ± 4.0 yr in the OSA and control groups, respectively. The proportion of obese subjects was 30 and 23\% in the control and OSA groups, respectively, with obesity defined as weight >95th percentile for age and gender according to World Health Organization reference values (31). As a group, the control subjects tended to be on a higher weight percentile (Table 1).

The median obstructive apnea index of the OSA group was 30.6 (mean 21.7, SD 15.9, range 4.5–67 obstructive events per hour of sleep time). Details of the sleep studies are shown in Table 2.

Respiratory measurements. Closing pressures were higher in children with OSA (2.2 vs. −14.2 cmH\(_2\)O, OSA vs. control, respectively, \( P < 0.001 \); Fig. 2A). Closing pressures also correlated with RDI, \( R^2 = 0.58, P < 0.005 \), excluding one extreme outlier (case 10, 1 of 3 children with Down syndrome, who had a high closing pressure of 12 cmH\(_2\)O, but relatively low RDI of 13.2 h\(^{-1} \); Fig. 2B).

During spontaneous breathing, at baseline and after anesthetic induction, end-tidal P\( CO_2 \) was elevated in the OSA group (49.3 ± 5.6 vs. 42.1 ± 4.9 Torr, OSA vs. control, respectively, \( P < 0.001 \)). Despite this, minute

### Table 1. Group characteristics at baseline of children with OSA and age-matched control subjects

<table>
<thead>
<tr>
<th></th>
<th>OSA</th>
<th>Control</th>
<th>t-Test</th>
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<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Gender, M:F (%Boys)</td>
<td>9.4(69)</td>
<td>18.5(78)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>4.0 ± 2.2</td>
<td>5.3 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Weight percentile mean</td>
<td>54 ± 34</td>
<td>79 ± 28</td>
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</tr>
<tr>
<td>ORDI</td>
<td>22.3 ± 14.0</td>
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</table>

Values are means ± SD. OSA, obstructive sleep apnea; M, male; F, female, ORDI, obstructive apnea/hypopnea index; NS, not significant.

### Table 2. Indexes of the overnight sleep studies

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<th>Age, yr</th>
<th>Case</th>
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<th>ORDI</th>
<th>REM OAI</th>
<th>Mean</th>
<th>Min</th>
<th>Desaturation Episodes</th>
<th>Av Desat</th>
<th>CO(_2)</th>
<th>Study CO(_2)</th>
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<td>416.7 135.1 93.5 5.4</td>
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| RDI, respiratory disturbance hypopnea index; REM OAI, obstructive apnea index (events per hour) during rapid eye movement sleep; Sa\(_{O_2}\), mean min, and mean minimum \( O_2 \) saturation recorded during the sleep study, respectively; >2\%, >4\%, and >5\% = number of desaturation episodes of 2, 4, and 5% or more, respectively; Av Desat, average desaturation following a respiratory event; CO\(_2\) low, high, and range, minimum, maximum, and range of transcutaneous CO\(_2\) values (maximum minimum) during sleep, respectively; BL, baseline. *Subjects who had central apnea with fentanyl. T&A, adnontoisillar hypertrophy; DS, Down syndrome; Charge, charge association; CP, cerebral palsy.
ventilation (corrected for weight) was lower in children with OSA (115.5 ± 81.6 vs. 158.7 ± 81.6 ml·kg⁻¹·min⁻¹, OSA vs. control, respectively, \( P = 0.02 \); Table 3). The \( T_I/T_{tot} \) ratio was lower in children with OSA at baseline with an unloaded upper airway (0.32 ± 0.01 vs. 0.37 ± 0.01s, OSA vs. control, respectively, \( P < 0.001 \)). Other respiratory parameters were not different between the OSA and control subjects at baseline. Measurements included \( V_t \) [4.7 ± 2.8 vs. 4.7 ± 2.7 ml·kg⁻¹·min⁻¹, OSA vs. control, respectively, not significant (NS)], inspiratory flow (11.7 ± 9.0 vs. 13.0 ± 9.6 l/s, OSA vs. control, respectively, NS), and respiratory frequency (34.8 ± 11.1 vs. 37.8 ± 10.1 min⁻¹, OSA vs. control, respectively, NS).

**Response to fentanyl.** A single intravenous dose of fentanyl induced depression of respiratory parameters in all children (Tables 3 and 4). Complete apnea was induced in 6 of 13 children with OSA (46%) but only 1 of the 23 control children (5%, \( \chi^2 P < 0.001 \)), with no spontaneous respiratory efforts for 3.7 ± 4.0 min (range from 30 s to 11.5 min). Assisted ventilation was provided during the apneic period. All children with a baseline end-tidal \( PCO_2 \) >50 Torr had central apnea after fentanyl. The control subject who experienced apnea had a spontaneous \( PCO_2 \) of 45.7 Torr, and no other diagnosis that would explain the predisposition to apnea. Neither the degree of respiratory depression nor the occurrence of apnea after fentanyl was affected by the presence of another diagnosis. Although numbers were small, the proportion of children with abnormalities was not different in the apneic group (3/6 = 50%) compared with the study group (6/13 = 46%). Apnea indexes on the sleep study were not predictive of fentanyl-induced apnea (Table 2).

After fentanyl, group differences in respiratory parameters remained consistent with the baseline data. For example, end-tidal \( PCO_2 \) levels were higher in children with OSA than in control children (55.4 ± 2.8 vs. 48.7 ± 1.4 Torr in OSA vs. control, respectively, \( P < 0.02 \)), and the \( T_I/T_{tot} \) ratio was lower in children with OSA (0.25 vs. 0.30, OSA vs. control, respectively, \( P = 0.01 \)). The respiratory rate after fentanyl was not different in children with OSA compared with control subjects (23.4 ± 9.6 vs. 24.6 ± 11.4 min⁻¹ in OSA vs. control, NS). There was a trend for respiratory rate as a proportion of baseline to be lower in children with OSA compared with control subjects (63.7 vs. 78.6%, \( P = 0.06 \)).

**Relative effects of OSA vs. fentanyl.** Two-way ANOVA showed that the respiratory depressant effects of fentanyl were present for all children but not different between groups (OSA vs. control). Differences attributable to fentanyl are shown in Table 4. For example, minute ventilation fell in all children (159.4 ± 57.4 vs. 114.5 ± 55.9 ml·kg⁻¹·min⁻¹ before vs. after fentanyl, \( P < 0.01 \)) and spontaneous \( CO_2 \) levels increased. Figure 3 illustrates the change in end-tidal \( PCO_2 \) for control and OSA subjects, before vs. after fentanyl. Figure 4 shows minute ventilation as combined data for both groups, before vs. after fentanyl.

Two-way ANOVA showed that, overall, the \( T_i \) was not different between groups (0.71 ± 0.09 vs. 0.69 ± 0.03, OSA vs. control, NS). In addition, \( T_i \) did not change significantly before vs. after administration of fentanyl (0.69 ± 0.06 vs. 0.71 ± 0.03, NS). Multivariate analyses were also performed for inspiratory drive.
Fig. 4. Minute ventilation (V") of all subjects at baseline (after induction with inhalational anesthetic) compared with anesthetic plus fentanyl. Values for control and OSA subjects were combined because the effect of fentanyl was independent of the effect of diagnostic category. See text for statistical analyses.

(VT/TI) and showed that fentanyl had a significant effect (14.7 ± 1.9 vs. 12.6 ± 2.0 ml/kg before vs. after fentanyl, P = 0.03), but no effect was attributable to OSA (11.9 ± 3.1 vs. 15.4 ± 3.3 ml/kg, OSA vs. control, NS), and there was no interaction between the two. When minute ventilation was normalized to end-tidal PCO2, the differences in minute ventilation between the diagnostic groups (OSA vs. control) and fentanyl (before vs. after) were independently significant. Thus respiratory depression was present in children with OSA (2.7 ± 1.3 vs. 4.2 ± 4.3 ml·kg⁻¹·min⁻¹·Torr CO2⁻¹, OSA vs. control, P = 0.01) and in the presence of fentanyl (4.5 ± 4.3 vs. 2.7 ± 2.2 ml·kg⁻¹·min⁻¹·Torr CO2⁻¹, before vs. after, P = 0.004).

DISCUSSION

We examined the effects of opioids on ventilatory parameters of children with proven OSA in the common clinical context of an inhalational anesthetic and found respiratory depression in children with OSA. After the airway was secured, children with OSA had reduced minute ventilation and elevated CO2 in the presence of inhalational anesthesia, compared with control subjects. The addition of an opioid analgesic (fentanyl) led to central apnea in approximately half of the OSA group.

Although questionnaires can distinguish control subjects from children with possible or likely OSA, sleep studies are necessary to confirm the presence of OSA once a child is identified as symptomatic of OSA (2). Carroll et al. (3) found a one in four chance of misdiagnosis (positive and negative) of OSA once children presented to a sleep unit; therefore, all children in the present study had OSA proven by an overnight sleep study. The OSA scores of our OSA group reflect the characteristics of a sleep-unit population. Other clinical characteristics were also consistent with the population of our pediatric sleep unit; that is, children with moderate to severe disease often have an associated clinical condition (28). We deliberately recruited such an unselected group, to ensure that the results would be applicable to clinical populations in general. Because our ventilatory measurements were made after bypassing the upper airway, the presence of anatomic abnormalities would not be expected to confound the measured outcomes.

Upper airway closing pressures were above atmospheric levels in 8 of 13 (62%) of the OSA subjects when measured under anesthesia. This highlights the ready collapsibility of the airway of children with confirmed OSA, under routine inhalational anesthesia (6, 11, 13), which is important if anesthesia is to be introduced for any routine procedure in this group of patients. In this study, no muscle paralysis or local anesthetic was used, and the children were breathing spontaneously. According to standard procedure for this measurement, if the airway collapses above atmospheric pressure, positive pressure was introduced into the circuit (14). The closing pressure values below atmosphere likely reflected some component of upper airway muscle activity (6, 13). Closing pressures measured above atmosphere, for children with OSA and after introduction of positive pressure into the circuit, were likely to have been biased toward a passive airway (no muscle activity) through muscle relaxation (13). The interactions of muscle activity, airway resistance, and airway size are complex. Henke (12) demonstrated that upper airway muscles have no significant role in maintaining patency in nonsnoring young adults, suggesting that the recruitment of upper airway muscles in subjects with OSA is a response to inspiratory load and/or hypercapnia. Thus the conditions for upper airway muscle activity may have differed between the OSA and control groups, with the bias introduced by a positive-pressure environment possibly leading to additional loss of upper airway muscle activity in OSA subjects at the time of measurement. As far as we are aware, this is the first documentation of closing pressures during inhalational anesthetic, without muscle relaxant, for adults or children with and without OSA.

A new finding of this study was that respiratory depression was present in children with OSA after anesthetic induction, compared with control subjects, at baseline. We were not able to determine the mechanism underlying this difference, and it may be due to abnormal airway responsiveness, to abnormal respiratory control mechanisms, or to a combination of both. The profile of abnormalities in children with OSA was similar to that seen in the control subjects after fentanyl. Elevation of PCO2 and lower minute ventilation compared with control subjects suggests that there was a central component to the respiratory depression that we observed in the OSA group. Inspiratory loading may induce similar respiratory changes but would usually also prolong Tl, which was not observed in the OSA group. Respiratory control abnormalities appear to be subtle in children with OSA, and one previous study showed that children rapidly reduce minute ventilation in response to an upper airway load (18).
Previously documented respiratory abnormalities in children with OSA include failure to arouse from sleep in response to high CO\textsubscript{2}, depression of responses to CO\textsubscript{2} when the stimulus is cyclical (9, 16), and tolerance of higher CO\textsubscript{2} levels under anesthesia. The pattern of respiratory depression for children with OSA in this study, compared with control subjects, included depression of baseline ventilation and the occurrence of apnea after fentanyl. Similar changes to those we observed in our baseline measurements have been noted in adults in response to the opiate \mu-receptor (23), including the finding of a shorter Ti, which was present in children with OSA under anesthetic and was consistent before and after fentanyl. This altered pattern of ventilation, with shorter Ti, has been previously observed in children with OSA after repeated hypercapnia (9). In our study, an artificial airway bypassed any upper airway obstruction, and there had been no prior chemical stimulus (e.g., CO\textsubscript{2}) when this shift in ventilatory pattern was first observed; the airway was kept patent during the test period, excluding the brief occlusion used to measure airway closing pressure.

Children with OSA appear to have specific sensitivity to opioids. The respiratory depression caused by the opioids was marked in children with OSA under anesthesia. The low dose of opioid (fentanyl) used in this study caused equivalent respiratory depression in all children, whether or not they had OSA, but precipitated central apnea in 46% of the OSA group. Consistent with this, the best predictor for opioid-induced central apnea was that the child had elevated end-tidal PCO\textsubscript{2} to levels $>50$ Torr during spontaneous breathing after anesthetic induction. The depression of respiration in the OSA group was independent of that caused by fentanyl, although the features of the respiratory depression for children with OSA at baseline were similar to those caused by 0.1 \mu g/kg of fentanyl in the control subjects.

Limitations of the study. Minute ventilation was measured in this study, but only after the children had had their airway secured. We did not examine for further changes in upper airway responsiveness in the presence of hypoxia or hyperoxia. It remains possible that differences in upper airway load, upper airway responses, and/or the responses to relative hyperoxia in the presence of an anesthetic contributed to the differences observed between the groups.

LMAs were used for the majority of control subjects in this study, whereas ETTs were used for the majority of subjects with OSA. This raises a number of issues, including 1) possible differences in the resistive load of the two circuits, 2) ventilatory responses to stimulation of the larynx vs. the supraglottic region, 3) activity of the larynx affecting the ventilatory responses, and 4) possible leak around an uncuffed endotracheal tube.

Ventilation was measured after the airway was secured, but it remains possible that the difference in resistance of the LMA vs. ETT circuits contributed to the differences observed at baseline. We measured and found a small difference in the resistive loads of the two systems. At 6 l/min, the fresh gas flow used during the studies, the pressure drop across the LMA was 0.1 cmH\textsubscript{2}O, compared with 0.5 cmH\textsubscript{2}O for the ETT. One previous study examined the effects of resistive load in children with OSA (18). An inspiratory resistive load of 15 cmH\textsubscript{2}O (30 times greater than our measured load) was required before there was a 30% reduction in minute ventilation in that study. In the present series, the OSA group had a 37% reduction in minute ventilation compared with the control subjects.

It is possible that LMAs would precipitate different respiratory reflex responses to ETTs. Previous studies have compared the reflex responses induced by laryngeal vs. tracheal stimulation with water, CO\textsubscript{2}, or cool air and found no difference (20, 22). Responses to supraglottic and glottic stimulation are also equivalent (20, 22). Activity of the larynx would only influence the responses of children for whom an LMA was used, because dilatation of the larynx would be expected at higher CO\textsubscript{2} values. However, this effect would have most influence in the control group, whereas higher CO\textsubscript{2} values were observed in the group with OSA.

Although uncuffed ETTs were used, the possibility of leak affecting the ventilatory measurements was minimized by the fact that they were made during spontaneous (i.e., negative inspiratory pressure) ventilation. A leak around the ETT would not be expected to affect the CO\textsubscript{2} levels measured but may have affected the measurement of minute ventilation.

The sampling rate of the CO\textsubscript{2} analyzer was relatively high for the size of the children being studied. However, the calibration for all flow measurements accounted for and should have eliminated any change in flow rates attributable to this sampling. The sampling rate of the analyzer may have introduced a small systematic error into our studies, and no additional correction was added for this after the data were acquired. This would not have affected the direction, although it may have had a slight effect on the magnitude of the differences we observed.

Summary and clinical relevance. We studied children with OSA in the common clinical environment of inhalational anesthesia. In this setting, we found that children with OSA have respiratory depression compared with age-matched control subjects when breathing spontaneously under anesthetic with the upper airway secured. Further studies would be required to elucidate the relative contribution of respiratory control and/or upper airway abnormalities to this response. A small dose of opioids caused additional respiratory depression. Thus, in the presence of inhalational anesthesia and an ETT, fentanyl led to central apnea requiring respiratory support in 46% of children with OSA. We conclude that children with OSA are particularly sensitive to respiratory depression caused by opioids.

The authors thank the parents and children who participated in the study. We also thank Dr. Roland de la Eva and Sara Cooper for assistance with patient recruitment, the staff of the Read Sleep Unit for performing the overnight sleep studies, and Kellie Tinworth for assistance with preparation of the manuscript.
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