Effects of nasal CPAP therapy on respiratory and spontaneous arousals in infants with OSA

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McNamara, Frances, and Colin E. Sullivan. Effects of nasal CPAP therapy on respiratory and spontaneous arousals in infants with OSA. J. Appl. Physiol. 87(3): 889–896, 1999.—Obstructive sleep apnea (OSA) in infants has been shown to resolve frequently without a cortical arousal. It is unknown whether infants do not require arousal to terminate apneas or whether this is a consequence of the OSA. We studied the apnea and arousal patterns of eight infants with OSA before and after treatment with nasal continuous positive airway pressure (CPAP). These infants were age matched to eight untreated infants with OSA and eight normal infants. Polysomnographic studies were performed on each infant. We found that the majority of central and obstructive apneas were terminated without arousal in all OSA infants. After several weeks of nasal CPAP treatment, the proportion of apneas terminating with an arousal during rapid-eye-movement sleep increased in treated infants compared with untreated infants. Spontaneous arousals during rapid-eye-movement sleep were reduced in all OSA infants; however, during CPAP treatment, the spontaneous arousals increased to the normal control level. We conclude that OSA in infants possibly depresses the arousal response and treatment of these infants with nasal CPAP partially reverses this depression.

rapid-eye-movement sleep; obstructive apnea; spontaneous arousals; respiratory arousals; nasal continuous positive airway pressure

AROUSAL FROM SLEEP IS CONSIDERED to be an important response to a respiratory stimulus, allowing an individual to initiate protective reflexes that are depressed during sleep (22). Several respiratory stimuli, including hypoxia (11), hypercapnia (21), airway occlusion (9, 7), and laryngeal stimulation (29), can induce arousal from sleep and stimulate reflex respiratory changes. The arousal response has been shown to differ between different sleep states; stronger stimuli are often required to induce arousal from rapid-eye-movement (REM) sleep than from non-rapid-eye-movement (NREM) sleep (7, 21, 29).

Arousal is a prominent feature of the adult obstructive sleep apnea (OSA) syndromes (27), and the arousal threshold to upper airway occlusion and hypoxia has been demonstrated to be higher in OSA patients than in normal subjects (13). Adults with OSA can experience profound oxyhemoglobin desaturation before awakening (6), which is more severe during REM sleep (27). The potential mechanisms of the increased arousal threshold are unknown; however, it has been suggested that sleep fragmentation and repeated hypoxemia associated with OSA may be involved. Recently, it was found that the impairment of the arousal responsiveness to occlusion was partially reversed after long-term treatment with nasal CPAP (4, 5).

Previously, we have shown that the majority of obstructive and central apneas in infants and children are not resolved with an accompanying electroencephalogram (EEG) arousal (18). It was also demonstrated that infants with OSA have a reduction in the number of spontaneous arousals during REM sleep compared with normal infants. It is not known whether infants do not require arousal to resolve an obstructive event or whether, similar to adults, arousal has been depressed as a consequence of the OSA. The effects of OSA on arousability in infants during NREM and REM sleep have not been previously described.

We hypothesized that OSA in an infant is associated with a depressed arousability and that treatment of OSA would result in an increase in an infant’s arousability. Nasal continuous positive airway pressure (CPAP) therapy has been demonstrated previously to be an effective treatment for OSA in infants, preventing obstruction and reversing the associated sleep disturbances (8, 17). We examined the respiratory and spontaneous arousal patterns during overnight polysomnographic studies in infants who had OSA and required treatment with nasal-mask CPAP. We studied these infants before treatment with nasal CPAP and on the first night of CPAP withdrawal after several weeks of CPAP therapy. Their respiratory and spontaneous arousal patterns were compared with those of normal infants and infants with OSA who were not treated. We wanted to determine the effects of nasal CPAP treatment on respiratory and spontaneous arousability and whether there were any differences between NREM and REM sleep.

METHODS
Patients

Three separate groups of infants were included in the study. All of the infants studied had been referred to our sleep unit for investigation of OSA either because of a family history of sudden infant death syndrome (SIDS) or because they had experienced an apparent life-threatening event. All infants included in the study were normal on clinical examination while awake and had no anatomic or congenital abnormality.

We studied eight infants who were diagnosed with OSA from a diagnostic sleep study and were treated with nasal-
mask CPAP therapy (group I). OSA in the present study was defined as obstructive events recorded in the diagnostic study in excess of five events per hour of sleep. These infants were between 6 and 18 wk of age when they were first diagnosed with OSA. The decision to treat these infants with nasal CPAP was based on the severity of OSA. Infants were treated with nasal CPAP if their obstructive apnea index exceeded 15 apneas/h of total sleep time. Treatment with nasal CPAP was commenced within 2 wk of diagnosis. We also selected a control group of eight infants (control infants) who had undergone overnight polysomnographic studies and had normal sleep and breathing patterns. In addition, a group of eight infants who were diagnosed with OSA but were not treated with nasal CPAP was also included (group II). These infants were monitored at home with a cardiorespiratory monitor. The control and untreated groups of OSA infants were age-matched to the group I infants for the first diagnostic and a repeat diagnostic study performed ~7 wk later. The clinical characteristics of the three groups of infants are described in Table 1.

Polysomnographic Monitoring

Each infant underwent overnight polysomnographic recordings. The polysomnographic data were recorded on a Grass (model 8) 12-channel EEG polygraph recorder (Grass Instrument, Quincy, MA). In each patient, sleep was monitored with two channels of EEG (C3-A2, O2-A1, 10–20 international placement system), two channels of electrocardiogram, and submental electromyogram (EMG). Diaphragm (EMGdia) and abdominal EMG were also measured. The electrocardiogram was measured continuously. Pulse oximetry with the use of a foot probe was measured continuously as an indication of arterial oxyhemoglobin saturation (Ohmeda Biox 3700E, Denver, CO). Transcutaneous CO₂ was measured continuously with a transcutaneous probe (TCM3, Radiometer, Copenhagen, Denmark) as an indication of arterial partial pressure of CO₂. Airflow was monitored by using small infant nasal prongs that were placed in the infant’s nostrils and then attached to a pressure transducer (DP103, Validyne, Northridge, CA). Chest wall and abdominal movements were measured by using inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY.). The optimal level of CPAP pressure was the level that minimized obstructive events and did not increase the CO₂ level or the length of central apneas.

Table 1. Clinical characteristics of OSA and control infants

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Control</th>
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<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/3</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38.5 ± 0.9</td>
<td>37.9 ± 1.4</td>
<td>40.1 ± 0.5</td>
</tr>
<tr>
<td>Age, wk</td>
<td>10.8 ± 1.3</td>
<td>10.3 ± 1.1</td>
<td>10.0 ± 1.3</td>
</tr>
<tr>
<td>CPAP study</td>
<td>11.4 ± 1.3</td>
<td>17.6 ± 2.3</td>
<td>17.1 ± 1.8</td>
</tr>
<tr>
<td>Study 1</td>
<td>17.6 ± 2.3</td>
<td>19.1 ± 1.8</td>
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</table>

Values are means ± SE for the treatment group of infants with obstructive sleep apnea (OSA) (group I) the untreated infants with OSA (group II), and the control infants (control). n, No. of infants. M/F, male/female; CPAP PD, continuous positive airway pressure pressure determination. There were no significant differences in any of the variables among the 3 groups of infants.

Analysis

Each polysomnographic study was scored, and 60-s epochs of recording were assigned as either NREM sleep, REM sleep, or awake according to established criteria for neonates and infants (1, 23). NREM sleep was further subdivided into light sleep equivalent to stage 1–2 NREM and slow-wave sleep equivalent to stage 3–4 NREM sleep. The total time in each sleep state and the proportion of total sleep time spent in stage 1–2 NREM, slow-wave sleep, and REM sleep were calculated. All apneas were scored on each study. An apnea was defined as a cessation of respiration for the duration of at least two respiratory cycles, which was ~3 s in the infants studied. Apneas were classified as central when there was an absence of airflow, EMGdia, and Respitrace movements. Obstructive apneas were scored if there was an absence of airflow and continued EMGdia bursts and deflections from the Respitrace. An apnea was classified as mixed if it involved a central and obstructive component. The number of central, mixed, and obstructive apneas was summed during each study. For the purpose of analysis, mixed and obstructive apneas were combined and are referred to as obstructive apneas. An apnea index (apneas/h) was calculated for central, obstructive, and total apneas during NREM and REM sleep for each study.

Arousals were scored according to EEG, EMG, and behavioral criteria, similar to those outlined by our previous findings (18). An arousal was defined as an abrupt change in the EEG to alpha frequencies (8–13 Hz) or frequencies >16 Hz for a minimum of 1 s. During REM sleep, arousals were scored if the change in EEG was accompanied by an increase in the amplitude of the submental EMG signal. The arousals were then classified as either respiratory or spontaneous. A
Table 2. Apnea and sleep variables in OSA and control infants

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>CPAP</th>
<th>Group II</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td>Study 1</td>
<td>Study 2</td>
<td>Study 1</td>
<td>Study 2</td>
</tr>
<tr>
<td>NREM sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central apnea, apneas/h</td>
<td>36.1 ± 8.6</td>
<td>26.3 ± 7.4</td>
<td>12.0 ± 1.7</td>
<td>27.5 ± 7.2</td>
</tr>
<tr>
<td>Obstructive apnea, apneas/h</td>
<td>22.2 ± 8.8</td>
<td>10.6 ± 2.6*</td>
<td>0.3 ± 0.1</td>
<td>6.6 ± 2.2</td>
</tr>
<tr>
<td>% I/II NREM</td>
<td>44.0 ± 1.9</td>
<td>40.4 ± 3.3</td>
<td>31.5 ± 1.3</td>
<td>44.4 ± 3.4</td>
</tr>
<tr>
<td>REM sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central apnea, apneas/h</td>
<td>32.9 ± 8.1</td>
<td>38.2 ± 8.2</td>
<td>24.2 ± 4.7</td>
<td>45.1 ± 9.3</td>
</tr>
<tr>
<td>Obstructive apnea, apneas/h</td>
<td>51.8 ± 16.3</td>
<td>25.7 ± 7.2*</td>
<td>1.1 ± 0.5</td>
<td>29.4 ± 12.8</td>
</tr>
<tr>
<td>% REM sleep</td>
<td>16.2 ± 1.6</td>
<td>18.5 ± 1.9</td>
<td>27.8 ± 1.5</td>
<td>15.9 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SE for infants with OSA treated with nasal CPAP (group I), infants with OSA who were not treated (group II), and control infants. REM, rapid eye movement; NREM, non-REM; SWS, slow-wave sleep; I/II NREM, stage 1–2 NREM. *Significant difference of first diagnostic study (study 1) from follow-up diagnostic study (study 2), P < 0.05 (t-test).

RESPIRATORY AROUSAL AND SLEEP PATTERN

Respiratory arousal was defined as an arousal that occurred at the termination of, or immediately after, an apnea, whereas a spontaneous arousal was defined as an arousal that occurred without any preceding respiratory event. The number of each type of arousal for NREM and REM sleep was calculated and expressed as an arousal index (arousals/h). In addition, the percentage of central, obstructive, and total apneas that resulted in arousal was calculated for NREM and REM sleep for each study.

The apnea, sleep, and arousal data were combined and averaged according to the infant group and sleep state. The differences in the central and obstructive apnea index and in the respiratory and spontaneous arousal index between the first and follow-up diagnostic studies for each of the three groups of infants were examined according to sleep state with the paired t-test. The differences in the apnea and arousal patterns recorded in each of the diagnostic studies between the two groups of infants with OSA (groups I and II) and the control infants were examined by using ANOVA. The apnea, sleep, and arousal pattern of the CPAP study in group I infants was compared with their first diagnostic study by using the rank-sum test and paired t-test. The arousal pattern of CPAP was also compared with the first diagnostic study of the control infants by using the unpaired t-test. All data are expressed as means ± SE. A P value of <0.05 was considered significant.

RESULTS

Sleep Apnea and Sleeping Pattern

Obstructive apneas were recorded during NREM and REM sleep in the first and follow-up diagnostic studies of the group I and II infants, and the severity ranged from moderate to severe. Obstructive apnea was more frequent in group I than in group II infants (P < 0.05, t-test). The control infants had either occasional or no obstructive events recorded during their first diagnostic study (Table 2). Central apnea was recorded in all the infants and varied in severity among individual infants. The number of central apneas during NREM and REM sleep was significantly higher in group I and II infants, who had OSA, than in the control infants (P < 0.05, t-test). Apnea length and the arterial oxyhemoglobin saturation level associated with central and obstructive apnea were similar for all three groups of infants during both diagnostic studies (Table 3).

Table 3. Apnea length and SaO2 for central and obstructive apneas in OSA and control infants

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td>Study 1</td>
<td>Study 2</td>
<td>Study 1</td>
</tr>
<tr>
<td>NREM sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea length, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>6.4 ± 0.4</td>
<td>6.9 ± 0.3</td>
<td>5.6 ± 0.2</td>
</tr>
<tr>
<td>Obstructive</td>
<td>7.1 ± 0.7</td>
<td>6.2 ± 0.8</td>
<td>5.9 ± 4.0</td>
</tr>
<tr>
<td>SaO2, %</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Central</td>
<td>92.2 ± 0.6</td>
<td>92.7 ± 0.5</td>
<td>93.1 ± 0.6</td>
</tr>
<tr>
<td>Obstructive</td>
<td>92.3 ± 0.8</td>
<td>92.6 ± 0.7</td>
<td>92.8 ± 0.5</td>
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<tr>
<td>REM sleep</td>
<td></td>
<td></td>
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<tr>
<td>Apnea length, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>5.5 ± 0.5</td>
<td>5.1 ± 0.2</td>
<td>5.0 ± 0.3</td>
</tr>
<tr>
<td>Obstructive</td>
<td>7.0 ± 1.1</td>
<td>6.0 ± 0.8</td>
<td>5.5 ± 0.3</td>
</tr>
<tr>
<td>SaO2, %</td>
<td></td>
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</tr>
<tr>
<td>Central</td>
<td>92.6 ± 0.7</td>
<td>93.1 ± 0.4</td>
<td>92.8 ± 0.6</td>
</tr>
<tr>
<td>Obstructive</td>
<td>90.8 ± 1.7</td>
<td>92.5 ± 0.5</td>
<td>91.3 ± 0.9</td>
</tr>
</tbody>
</table>

Values are means ± SE for infants with OSA treated with nasal CPAP (group I), infants with OSA who were not treated (group II), and control infants. SaO2, arterial oxyhemoglobin saturation. There was no significant difference between the first and second studies in each group of infants (P > 0.05, t-test), and there was no difference among the 3 groups of infants during each study (P > 0.05, ANOVA).
Treatment with nasal CPAP in group I infants resulted in a prevention of nearly all obstructive events during both NREM and REM sleep ($P < 0.05$, rank sum; Table 2). Nasal CPAP treatment was also associated with a significant reduction in central apnea during NREM sleep, whereas, during REM sleep, central apneas were decreased, but the difference was not significant ($P > 0.05$, t-test; Table 2). Each of the infants who was treated tolerated the CPAP mask and the CPAP well. Parents reported, at the time of the follow-up diagnostic study, that their infant had been sleeping well at home with the use of nasal CPAP therapy.

During the follow-up diagnostic study, central apnea and OSA were still recorded in both group I and II infants; however, the number was smaller than that recorded in the previous diagnostic studies (Table 2). The number of both central and obstructive events recorded from group I and II infants remained significantly higher than that of the control infants ($P < 0.05$, ANOVA). Control infants had a similar number of central apneas recorded during both diagnostic studies, and, although the number of obstructive events was low, the obstructive apnea index was significantly reduced during the second diagnostic study (Table 2).

The sleep disordered breathing of group I and II infants was associated with differences in the sleeping architecture. Infants of groups I and II had significantly less REM sleep than did the control infants during both diagnostic studies ($P < 0.05$, ANOVA). The treatment of OSA in group I infants with CPAP, however, was associated with a significant increase in the amount of REM sleep, similar to that recorded in the control infants ($P < 0.05$, t-test; Table 2).

**Arousal Pattern**

Respiratory arousals. The central and obstructive apneas recorded in group I and II infants were sometimes terminated or immediately followed by a brief cortical arousal from sleep (Fig. 1). The majority of apneas during the first diagnostic study for both groups of infants, however, were resolved without any change in EEG patterns during NREM and REM sleep (Fig. 2). Arousals terminating apneas during the diagnostic studies in the control infants occurred occasionally. The respiratory arousal index during NREM sleep in the first diagnostic study was $3.9 \pm 1.0$, $3.0 \pm 0.6$, and $0.3 \pm 0.1$ arousals/h for group I, group II, and control infants, respectively. During REM sleep, the respiratory arousal index was $5.7 \pm 1.1$, $5.5 \pm 1.0$, and $1.4 \pm 0.5$ arousals/h for group I, group II, and control infants, respectively. Respiratory arousals were significantly less frequent in control infants than in the two groups of OSA infants during both sleep states; however, controls had fewer apneas than did group I and II infants ($P < 0.05$, ANOVA).

During the follow-up diagnostic study, the respiratory arousal index was similarly low for all infants of groups I and II during NREM and REM sleep and was still significantly lower in control infants than in OSA infants ($P < 0.05$, ANOVA). During NREM sleep, the respiratory arousal index was $2.7 \pm 0.6$, $1.9 \pm 0.3$, and $0.3 \pm 0.1$ arousals/h for group I, group II, and control infants, respectively. During REM sleep, the respiratory arousal index was $6.3 \pm 1.1$, $3.6 \pm 0.8$, and $0.6 \pm 0.3$ arousals/h for group I, group II, and control infants, respectively. The respiratory arousal index during NREM and REM sleep for each group of infants was not significantly different from the first diagnostic study ($P > 0.05$ for each comparison, t-test). Although the arousal index for groups I and II was similar during both diagnostic studies, the apnea index...
recorded during the follow-up studies had decreased. During NREM sleep, the proportion of apneas that resulted in arousal was similar to the previous diagnostic study, and there was no difference between groups I and II (Fig. 3). During REM sleep, however, the proportion of apneas that was terminated by arousals in group I infants significantly increased during the follow-up study, i.e., during the first night of CPAP removal (P < 0.05, t-test). The percentage of apneas terminated with arousal during REM sleep was approximately double that of the previous diagnostic study (Fig. 4). In group II infants during REM sleep, however, there was no significant change in the proportion of apneas terminated by an arousal during REM sleep (Fig. 4). The increase in the proportion of apneas ending in arousal in group I infants was due to an increase in respiratory arousals after both central and obstructive apneas. The respiratory arousals after central apnea increased from 3.5 ± 0.3 to 11.7 ± 1.2% of apneas, and the respiratory arousals associated with obstructive apnea increased from 7.6 ± 0.7 to 16.2 ± 1.9% of apneas (P < 0.05 for both comparisons, t-test).

Respiratory arousals in the control infants were less frequent than in infants of groups I and II; however, the controls aroused frequently to their occasional obstructive events. During the first diagnostic study, 2 of 6 and 9 of 22 obstructive apneas were terminated by an arousal during NREM and REM sleep, respectively. During the follow-up diagnostic study of the control infants, there were no obstructive events during NREM sleep; however, during REM sleep one of five obstructive apneas was terminated by an arousal. The proportion of obstructive apneas that were terminated by an arousal in both studies was greater than that recorded in the infants with OSA; however, because of the low number of obstructive events recorded during the control infant studies, compared with group I and II infants, no statistical analysis was performed.

Spontaneous arousals. Spontaneous arousals occurred in all infants studied during NREM and REM sleep and varied from brief arousals to full sustained awakenings. During the first diagnostic study, the spontaneous arousal index during NREM sleep was similar for all three groups of infants. During REM sleep, however, the infants of groups I and II had significantly fewer spontaneous arousals than did the control infants (P < 0.05, ANOVA; Table 4).

The treatment of OSA with nasal CPAP in group I infants resulted in a significant increase in the spontaneous arousals during REM sleep (P < 0.05, t-test). The frequency of REM spontaneous arousals during CPAP treatment was similar to the number recorded during REM sleep in the first diagnostic study in the control infants. During NREM sleep, the frequency of spontaneous arousals was not different during treatment with nasal CPAP (Table 4).

The spontaneous arousal index during NREM and REM sleep in the follow-up diagnostic studies ~7 wk later was not significantly different among the three groups of infants (P > 0.05, ANOVA). The infants in groups I and II had a similar number of spontaneous arousals during NREM and REM sleep compared with their first diagnostic study. The control infants, on the
other hand, had significantly fewer spontaneous arousals during both sleep states in their follow-up diagnostic study than in their previous diagnostic study (P < 0.05, for both comparisons, t-test; Table 4).

DISCUSSION

Our study has revealed new findings on the interaction between OSA and arousal in infants and the effects of nasal CPAP treatment on the infant arousal response. Nasal mask CPAP is the treatment of choice for the adult OSA syndrome (28) and is now commonly used in the treatment of OSA in children (15, 30). Nasal CPAP has been used less often in infants but has been documented to effectively prevent obstructive events and reverse sleep disturbances in infants with OSA (8, 17). The present study has reaffirmed the effectiveness of nasal CPAP as a therapy to treat OSA in infants.

More importantly, it is now clear that the spontaneous and respiratory arousal patterns during REM sleep are possibly depressed in infants who have OSA, and arousal responses are increased by the treatment of OSA with nasal CPAP.

The infants in the present study who had OSA had reduced respiratory and spontaneous arousals during REM sleep. Arousal from sleep is considered to be an important response to a respiratory stimulus, allowing an individual to initiate protective reflexes that are depressed or absent during sleep (22). The OSA syndrome in adults is characterized by repeated episodes of obstructive apnea resulting in repeated arousal from sleep (27). Arousal was previously thought to be necessary to terminate obstructive apneas and to reestablish upper airway patency (25). It has been demonstrated recently, however, that arousal defined by EEG criteria does not always terminate obstructive apnea in adults (24) and in pediatric patients (18). It is possible that the termination of obstructive and central apneas without any clear EEG arousal may indicate that cortical arousal is not an important phenomenon to resolve apnea, and subcortical mechanisms may be necessary (3, 18).

Arousal in our infants could be depressed, or the arousal threshold may be increased as a consequence of the OSA. Adult OSA patients have been shown to have higher arousal thresholds compared with control subjects (13). Potential explanations suggested for the difference in arousability between OSA patients and control subjects have included an inherently higher arousal threshold in patients with OSA or the consequence of repeated obstructive apnea, resulting in the habituation of the arousal response (3). In the present study, although no statistical analysis was performed, the arousability to obstructive apnea in the control infants appeared to be higher than in the infants with OSA. The control infants aroused more often to occasional obstructive events during NREM and REM sleep than did infants who had significant OSA. Although we cannot be certain of the mechanism, the respiratory arousal responses of infants with OSA are likely depressed.

After several weeks of nasal CPAP treatment, withdrawal of CPAP treatment for one night resulted in a return of significant obstructive and central apnea during NREM and REM sleep and an increase in the arousability to central and obstructive apnea during REM sleep in infants with OSA. Similar to our findings, the removal of CPAP treatment in adults is followed by a return of apnea, the associated hypoxic episodes, and sleep fragmentation (14). The number of apneas was smaller than the level initially recorded; however, there was a similar reduction in apnea in group II infants who were not treated with nasal CPAP. The improvement in apnea severity was possibly a consequence of increasing age and development, because OSA in infants has been shown to diminish with age (19). Recently, some investigators have demonstrated changes in the arousability to respiratory stimuli in adult OSA patients after treatment with nasal CPAP. Berry et al. (4) found that, after withdrawal of CPAP, the arousal response to nasal occlusion occurred more rapidly than that measured before treatment. In a separate study, Boudewyns et al. (5) found that, on the first night of CPAP withdrawal, apnea duration was shorter and arousal occurred more quickly compared with the pretreatment values. Both of these studies imply that OSA impairs the arousal response, which can at least be partially reversed by CPAP treatment. Recently, Marcus et al. (16) found that the arousal threshold to inspiratory stimuli was higher in children with OSA than in controls and that treatment of OSA with adenotonsillectomy resulted in a decreased arousal threshold. These investigators suggested that the blunted arousal response in these children was secondary to OSA. The increase in the proportion of apneas that were terminated by an arousal on the first night of CPAP withdrawal suggests that the decreased arousability is possibly secondary to OSA in infants and can be partly reversed by prevention of the sleep-disordered breathing with CPAP treatment.

The spontaneous arousability was also depressed during REM sleep in infants with OSA. Although the arousals occurred at a similar frequency between infants with OSA and control infants during NREM sleep, the number of spontaneous arousals during REM sleep was smaller in both groups of infants with OSA than in controls. This is consistent with our previous findings in which we found a selective depression of spontaneous arousals during REM sleep associated with OSA in infants (18). Also similar to our previous findings, OSA in infants was associated with a reduced amount of REM sleep (19). When nasal CPAP was used to treat the OSA in some infants, the number of spontaneous arousals during REM sleep increased to a similar level as that measured in the control infants. Nasal CPAP therapy prevented obstructive events and increased the amount of REM sleep in these infants. The improvement in the frequency of spontaneous arousals during REM sleep to a level similar to the controls during CPAP treatment suggests that the decrease in spontaneous arousability is secondary to sleep-disordered breathing. The increase in sponta-
neous arousals during CPAP therapy could be related to the elimination of obstructive apnea or the normalization of REM sleep architecture.

The depression of spontaneous as well as respiratory arousal responsiveness in infants with OSA was only apparent during REM sleep. In contrast, arousal responses during NREM sleep were similar between both groups of infants with OSA and infants with normal breathing during sleep. Previous studies investigating the arousal responsiveness in neonatal animal models have found that depression of arousal often occurs more readily during REM sleep than NREM sleep. Fewell et al. (7) demonstrated in a lamb model that repeated upper airway obstruction resulted in a depression of the arousal response only during REM sleep. In addition, Johnston et al. (11) showed that repetitive hypoxia in lambs resulted in a depression of arousal and that the arousal decrement was first apparent in REM sleep. Furthermore, other investigators demonstrated that the arousal threshold to airway obstruction in lambs was shown to be greater during REM sleep than during NREM sleep, leading to a possible increased vulnerability during this sleep state (2, 9). These studies suggest that the primary mechanisms initiating arousal from NREM and REM sleep are different. The sleep-state-specific arousal depression in the present study, as well as others, suggests that the possibility of arousal failure is greater in REM sleep than in NREM sleep. Infants spend a greater proportion of sleep in REM sleep than do children or adults, and REM sleep in infants is believed to be important for brain growth and development (20). Although there may be a combination of factors, the depression of arousal responsiveness during REM sleep may, therefore, have been caused by an increasing drive to preserve REM sleep.

The difference in the spontaneous and respiratory arousal frequency between infants with OSA and normal infants in the present study is interesting considering the previous polysomnographic and pneumogram findings of infants who subsequently became SIDS victims (12, 26). It was demonstrated that SIDS infants have more frequent obstructive events during sleep than do age-matched controls, suggesting that OSA may predispose an infant to SIDS (12). In addition, a further finding from both of the previous studies was a reduced amount of movement activity during sleep in infants who subsequently became SIDS victims than in matched controls (12, 26). It is possible that the movements recorded were associated with arousal behavior in these infants, and a reduced number of movements could, therefore, imply a reduced number of arousals. Furthermore, some investigators have suggested that recovery from an asphyxiating stimulus by arousal or resumption of breathing is the crucial vulnerability of SIDS victims (10, 22). The depression of arousal responses from REM sleep associated with OSA in infants allows us to speculate that these findings could have implications for an increased risk of SIDS in such infants.

The present study has provided information on the arousal responses and their changes with development in infants with normal sleep and breathing patterns and infants with OSA who are left untreated. Although arousal responses in infants to various chemical and mechanical stimuli have been studied (7, 9, 11), the natural arousal pattern and its changes with development have not previously been reported. The main finding was that the number of spontaneous arousals during REM sleep decreased with age in the control infants and remained the same for the OSA infants. During the follow-up diagnostic study, the spontaneous arousal frequency was not different, however, among the three groups of infants. Spontaneous arousals are very frequent during REM sleep in normal young infants (18); however, it appears that their importance possibly diminishes with time. Although OSA appears to depress spontaneous arousals during REM sleep in young infants, this effect is likely diminished with development. In contrast, the frequency of respiratory arousals in infants with OSA did not change with age. In infants whose OSA was left untreated, the arousability to respiratory events was unchanged with development, despite an improvement in their apnea index. It is possible that these infants will continue to have reduced arousal responses until their OSA is resolved with development.

This study has shown that the spontaneous and respiratory arousals during REM sleep are possibly depressed in infants who have OSA compared with infants with normal breathing patterns during sleep. Treatment of OSA with nasal CPAP improves the REM sleep spontaneous arousal pattern, and the immediate withdrawal of CPAP leads to increased respiratory arousals in response to central and obstructive apneas during REM sleep. We believe that the OSA and its associated sleep disturbances in infants alter and possibly impair the spontaneous and respiratory arousal responses during REM sleep. The depression in arousability is partially reversed by the treatment of OSA by using nasal CPAP treatment. The state-specific changes in arousal responses in infants with OSA imply that infants may be more vulnerable to a life-threatening stimulus during REM sleep and that treatment of the OSA may protect an infant from such a stimulus.

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