nCPAP improves abnormal autonomic function in at-risk-for-SIDS infants with OSA

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Harrington, C., T. Kirjavainen, A. Teng, and C. E. Sullivan. nCPAP improves abnormal autonomic function in at-risk-for-SIDS infants with OSA. J Appl Physiol 95: 1591–1597, 2003. First published May 2, 2003; 10.1152/japplphysiol.00354.2002.—We evaluated cardiovascular autonomic control and arousability during sleep in infants with obstructive sleep apnea (OSA) before and after 10 days of treatment with nasal continuous positive airway pressure (nCPAP). Six OSA infants and 12 age-matched control infants were studied with polygraphic sleep studies at the age of 13 ± 4 wk. During the study, 45° head-up tilt tests were performed in slow-wave and rapid eye movement sleep. Blood pressure (BP) and heart rate (HR) were continuously monitored. All OSA infants had decreased initial BP and HR responses, followed by hypotension in two and hypertension in two. OSA infants displayed higher arousal thresholds in response to the tilt in rapid eye movement sleep (P < 0.005) and higher baseline HR (P < 0.05) than controls. nCPAP treatment normalized BP and HR responses as well as arousal thresholds to tilting and stabilized HR levels. OSA in infants may be linked with cardiovascular autonomic control disturbances and decreased arousability during sleep. These defects are improved by control of OSA with nCPAP.

infant; obstructive sleep apnea; blood pressure; heart rate; nasal continuous positive airway pressure; sudden infant death syndrome

OBSTRUCTIVE SLEEP APNEA (OSA) elicits significant cardiovascular consequences both in adults and children. In adults, OSA is associated with altered cardiovascular variability and increased sympathetic output (31). Adults suffering from moderate or severe OSA have increased heart rate (HR), attenuated heart rate variability (HRV), and increased blood pressure (BP) variability (BPV) during quiet wakefulness (31) and sleep (5). In children, OSA has been associated with altered HRV (2) and hypertension (15, 26). In adults, OSA is associated with altered cardiovascular autonomic control disturbances and decreased arousability during sleep. These defects are improved by control of OSA with nCPAP.

Six infants with OSA were enrolled into the study. Their mean age at the time of the study was 13 ± 4 wk. The OSA diagnosis was based on a previous full-night polygraphic sleep study (PSG). None of the six infants had obvious craniofacial or neurological abnormalities. Four of these infants had experienced an ALTE, and two were siblings of victims of the sudden infant death syndrome (SIDS). Two of the six infants snored, and both these infants had experienced an ALTE. Neither of the SIDS siblings was symptomatic. For the purposes of this study, an ALTE was defined as an apneic episode occurring during sleep that involved some color change or limpness and that severely alarmed the caregiver. Before the sleep study, an extensive clinical evaluation of these infants did not reveal any other abnormality.

METHODS

OSA Infants

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was 13 ± 3 wk. Parents of infants attending the local baby health center were asked to participate. All infants enrolled in the study had a normal clinical examination both on the third day of life and immediately before the study. Infants with a family history of ALTE or SIDS were excluded. All control data have been previously presented (19).

Written parental consent was obtained in all cases. The study protocol was approved by the Sydney Children’s Hospital Ethics Review Committee.

Study Protocol

The protocol has been described previously (19). All infants underwent full overnight PSG. After the initial sleep study, infants suffering from OSA were placed on a trial of nCPAP treatment. The decision to start nCPAP therapy was done on a clinical basis. The infants were hospitalized during this nCPAP trial time, and the nCPAP was used continuously during sleeping periods (observed compliance). The nCPAP treatment was carried out successfully in all of the OSA infants. OSA infants were restudied during a PSG on nCPAP treatment and/or medications were administered that would have affected the cardiovascular and respiratory system.

Polysomnography. The polygraphic recordings (Compumedics, Melbourne, Australia) consisted of continuous monitoring of two EEGs (C3A2, O2A1); two electrooculograms; chin, diaphragm, and abdominal muscle surface electromyograms; nasal airflow (pressure transducer); thoracic and abdominal respiratory belts (Respitrace, Ambulatory Monitorings, Melbourne, Australia) consisted of continuous monitoring of arterial oxyhemoglobin saturation (pulse oximeter); ECG; and BP measurement (Portapres, TNO Biomedical Instrumentation, Amsterdam, The Netherlands). HR was assessed by continuous ECG recording. Continuous, noninvasive arterial BP measurement was performed by using the Portapres device, with the inflatable cuff being placed around the infant’s wrist. BP data were recorded at the sampling rate of 125 Hz, and ECG was recorded with 500-Hz sampling rate.

45° Head-up tilt test. During SWS and rapid eye movement sleep (REM), eight consecutive 45° head-up tilts were performed with at least a 1-min control period between each tilt. The infant slept on a purpose-built mattress support that was tilted manually from the horizontal position to a 45° angle within 2–3 s. This position was intended to be maintained for a minimum of 60 s. However, in the circumstance in which the infant’s BP changed significantly and did not return to baseline within the first 15–20 s, the tilt was terminated earlier. This meant that, for a number of infants, tilts were only maintained for ~20 s. If the tilt resulted in a transient arousal, sigh, or apnea, the tilt test data were excluded from the hemodynamic analysis but were included in the assessment of arousal response.

Data Analysis

PSG scoring. Sleep staging was done according to the criteria of Guilleminault and Souquet (14). Apneas were recorded if there was a pause in breathing of greater than or equal to two respiratory cycles with or without oxygen desaturation. Apneas were divided into central, obstructive, and mixed apneas. An obstructive hypopnea was scored if there was a periodic reduction of airflow signal amplitude of >50% without a simultaneous reduction in respiratory effort and if the event was related to either an arousal or oxygen desaturation of >4%. An obstructive respiratory disturbance index (ORDI) was defined as the sum of mixed, obstructive apneas, and obstructive hypopneas per hour of sleep. An ORDI of greater than two was considered to be abnormal (22).

Tilt test analysis. The test periods were extracted and imported into Microsoft Excel, where the data were analyzed by using Visual Basic software made for the purpose. Systolic BP (SBP), diastolic BP (DBP), and ECG R waves were detected under visual control with the accuracy of the original sampling frequency. A 30-s artifact- and movement-free reference period was calculated just before each tilt. Maximum values and standard deviations for DBP, SBP, and HR were then calculated for every 5-s epoch throughout the pretilting reference period and tilting period and were expressed as the maximum percentage change from the reference period.

Mean percent maximum change was measured by calculating the maximum rate after the initiation of the tilt, which typically occurred within the first 5 s, and expressing that value as a percentage change from the 30-s reference baseline. Mean percent drop was assessed by calculating the minimum rate after the peak (which typically occurred within 5–15 s from the initiation of the tilt) and expressing that value as a percentage change of the maximum rate. Mean percent drop (maximum − minimum) was calculated by a direct comparison of the raw maximum and minimum values after the tilt.

HR, HRV, and BP analysis. Mean HR, SBP, and DBP for each sleep state were calculated from a mean of three 2-min artifact-free epochs in both SWS and REM sleep. These epochs were taken from a period of sleep in which no tests were performed. The mean and standard deviation were calculated for each group. The coefficient of variation was calculated by dividing the standard deviation of the R-R interval (ms) by the mean R-R interval, obtained from the three 2-min epochs, and was used as a measure of HRV. The coefficient of variation was used so as to minimize the effect of baseline HR. BPV was measured by taking the same three 2-min artifact-free epochs and calculating the standard deviation for that period. The mean and standard deviation were then calculated for each group.

Arousal responses. Arousal responses were calculated as a percentage of the number of 45° head-up tilt tests to cause a sleep state change or short arousal as evidenced by the PSG. For the purposes of this study, an arousal was scored if there was a body movement (evident from the chin, diaphragm, and abdominal muscle surface electromyograms) or a sudden change in respiration accompanied by a shift in EEG frequency or increase in chin EMG activity that was maintained for ~2 s (10).

Statistical Analysis

All the statistical analyses were performed with SPSS statistical software (SPSS for Windows, release 11.0.1, SPSS, Chicago, IL). One-way ANOVA followed by Tukey’s multiple-comparison tests were used to determine the significance of the difference between the three study groups: controls, OSA infants before nCPAP, and OSA infants on nCPAP. Pre- and on-nCPAP changes were compared by use of paired t-test. A P value of <0.05 was considered statistically significant.

RESULTS

From the PSG studies, all control infants had normal breathing during sleep. The six infants with OSA were found to have a mean ORDI of 17 ± 6 breaths per hour of sleep. In all the OSA infants studied, obstructive breaths were frequently associated with an oxygen desaturation of >10%, and occasionally oxygen satura-
tion fell to below 75%. On average, oxygen desaturation was 2.3/1006 1.3% in control infants and 11.5/1006 3% in the OSA infants (P < 0.005). During the subsequent PSG study, nCPAP treatment effectively controlled the OSA (Table 1): the ORDI did not differ between the control infants and those infants who were being treated for OSA, and the OSA infants no longer displayed any oxygen desaturation.

45° Head-Up Tilt Tests

All control infants displayed a similar characteristic response to the 45° head-up tilt (see Fig. 2A). In both SWS and REM sleep, HR and BP began to increase immediately on tilt onset rising rapidly to a peak value within the first four to eight beats (Fig. 1). This peak was typically reached within 4 s from the tilt onset, and the maximal values of HR, SBP, and DBP were significantly increased compared with the reference epochs (P < 0.005). The rapid increase in values was followed a rapid fall in both HR and BP to a more stable level that was maintained throughout the rest of the tilt.

Before nCPAP treatment, none of the infants with OSA displayed this characteristic response to the head-up tilt in either SWS (Fig. 2B) or in REM. The change in HR and BP on initiation of the tilt (Table 2) was significantly reduced compared with the control infants (P < 0.05 and P < 0.005, respectively), and there were no significant changes in either HR or BP compared with the reference epochs immediately after the tilt. Five of the six infants with OSA displayed little or no HR response to the tilt, either in SWS or in REM sleep (Fig. 3). The only subject to show a HR response had a very slow response compared with the control infants. The BP response to the tilt was variable: two

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>M/F</th>
<th>Age, wk</th>
<th>ORDI</th>
<th>ODS</th>
<th>%Arousal</th>
<th>HR, beats/min</th>
<th>HRV (CV), %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SWS</td>
<td>REM</td>
</tr>
<tr>
<td>Controls</td>
<td>12</td>
<td>6/6</td>
<td>13 ± 2</td>
<td>1 ± 1</td>
<td>2 ± 1</td>
<td>23 ± 11</td>
<td>71 ± 18</td>
<td>116 ± 10</td>
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<td>124 ± 11</td>
<td>3.7 ± 0.7</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>5.0 ± 1.5</td>
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<tr>
<td>OSA Pre-nCPAP</td>
<td>6</td>
<td>5/1</td>
<td>12 ± 4</td>
<td>17 ± 6*</td>
<td>12 ± 3†</td>
<td>20 ± 23</td>
<td>19 ± 19†</td>
<td>131 ± 9*</td>
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<td></td>
<td>137 ± 9†</td>
<td>2.4 ± 0.8*</td>
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<td></td>
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<td></td>
<td></td>
<td>4.5 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>OSA During nCPAP</td>
<td>6</td>
<td>5/1</td>
<td>13 ± 1</td>
<td>1 ± 1</td>
<td>2 ± 1</td>
<td>19 ± 19</td>
<td>68 ± 11</td>
<td>118 ± 5</td>
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<td></td>
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<td></td>
<td>124 ± 5</td>
<td>3.0 ± 1.2</td>
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<td></td>
<td></td>
<td></td>
<td>4.1 ± 1.6</td>
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</tbody>
</table>

Values are means ± SD; n, no. of infants. M/F, male/female; CV, coefficient of variation; ORDI, obstructive respiratory disturbance index; ODS, mean oxygen desaturation; %Arousal, percent of arousal responses to 45° head-up tilt; HR, heart rate; HRV, heart rate variability in slow-wave sleep (SWS) and rapid eye movement sleep (REM), in control infants and obstructive sleep apnea (OSA) infants before and on nasal continuous positive airway pressure (nCPAP) treatment. Comparison between control infants and OSA infants: *P < 0.05, †P < 0.005.
infants displayed sustained hypotension, two no change, and two infants had a sustained increase in BP (Fig. 3).

After 10 ± 4 days of nCPAP treatment, five of the six infants continued to show a blunted HR response to the tilt (Fig. 2C). However, four of these five infants had improved, although not normal, BP responses. Only one infant had a HR and BP response similar to the control infants (Fig. 3D).

HR, HRV, BP, and BPV

HRs in the OSA infants were significantly increased in both SWS and REM before nCPAP treatment ($P < 0.05$) compared with the control group (Table 1), but after nCPAP treatment there was no significant difference in the HRs of the subject group in either sleep state.

Before nCPAP treatment HRV was significantly lower in OSA infants in SWS compared with control infants ($P < 0.05$). There was no difference in HRV in REM sleep. On nCPAP treatment, HRV in SWS was normalized in the OSA infants (Table 1).

All control infants showed an increase in both SBP and DBP from SWS to REM (Table 2). This was not found in OSA infants before the nCPAP therapy. Only two OSA infants displayed a very slight increase in BP from SWS to REM sleep, and, notably, two OSA infants had clearly decreased BP level in REM. After nCPAP treatment, the BP changes in the different sleep stages were normalized and OSA infants showed a similar increase in BP from SWS to REM sleep as that of the control infants (Table 3).

Both systolic and diastolic BPV were significantly increased in OSA group in SWS compared with controls before nCPAP therapy ($P < 0.05$). This difference was not observed in REM. The abnormal increase of BPV was normalized after the onset of nCPAP treatment, and on nCPAP BPV in OSA infants did not differ significantly from the values in normal controls (Table 3).

Arousal Responses to Head-Up Tilts

Infants’ arousability was quantified as a percentage of arousal responses to 45° head-up tilt tests. There was a marked difference in the arousal response to the head-up tilt in the control group between the two sleep states. Control infants had significantly increased percentage of arousals in REM ($P < 0.005$) compared with SWS, with the postural challenge test evoking arousal in two of eight tests in SWS and six of eight tests in REM. Before nCPAP treatment, OSA infants had an increased arousal threshold in REM sleep, and the threshold was similar in SWS and REM sleep (Table 1). Arousal threshold was normalized on nCPAP therapy, and the percentage of arousal was similar to controls both in SWS and in REM sleep (Fig. 4).

DISCUSSION

The major finding of this study is that infants with OSA who had altered cardiovascular autonomic function and depressed arousal responses showed significant improvement after effective treatment of their OSA with nCPAP: their autonomic cardiovascular control of BP improved, and their arousability normalized.

Previous studies have provided evidence that adults and children with OSA have altered arousal responses to ventilatory challenges during sleep compared with controls (4, 27, 28) and that infants with OSA have fewer spontaneous arousals during sleep compared with normal infants (30). In these studies, the treatment of the OSA normalized the responses. Additionally, previous studies show that ALTE infants have defective arousal responses to hypoxia (7, 21, 29) and have fewer arousals from sleep and fewer body movements (6, 18, 23).

Before treatment with nCPAP, the infants with OSA showed very few arousals in REM in response to the postural challenge. In contrast, after treatment for OSA, the number of arousals induced by this test increased to a level similar to that of the control infants (Fig. 4). This finding suggests that OSA caused a selective depression of arousability in REM, as we have reported in other studies (20, 30).

As described previously (17, 19, 34), HR, HRV, and BPV were higher in REM than in SWS in all control infants, but over and above these differential levels a significant increase in HR occurred across both sleep states in the infants with OSA, accompanied by a significantly decreased HRV and significantly increased BPV in SWS.

Adults suffering from moderate-severe OSA have an increased HR, an attenuated HRV, increased BPV, and a generalized increase in peripheral sympathetic activity (31). Our results indicate that infants with OSA also exhibit impaired baroreflex and other cardiovascular reflex functions.
Fig. 3. HR and BP responses to a 45° head-up tilt in 6 infants with OSA, before (i) and on (ii) CPAP treatment. The start and the end of the tilt is indicated by the vertical dashed lines. Note: Before CPAP treatment, 5 of the 6 infants with OSA displayed little or no HR response to the tilt, either in SWS or REM. Infant D was the only infant to show a HR response, although this was much slower than that exhibited by the control group. The BP response to the tilt before nCPAP treatment was varied, with 2 infants displaying sustained hypotension (A and B), 2 infants showing no change (E and F), and 2 infants having a sustained increase in BP (C and D). After nCPAP treatment, all but infant D continued to show a blunted HR response to the tilt. However, 4 of the infants had an improved, although not normal, BP response.
When the infants with OSA were treated with nCPAP, the altered cardiovascular variability observed initially was abolished, and HR, HRV, and BPV all were within the same range as the control infants. Again, this change mirrors the changes that occur in cardiovascular control in adults with OSA after treatment with nCPAP.

Of considerable interest was the finding that some infants with OSA did not show the differential elevation of BP in REM found in the control infants. However, after treatment with nCPAP, the difference in BP between SWS and REM reemerged. These findings are similar to what has been found in adults (1). The increase in phasic activity in REM, normally observed in infants, likely drives the increase in BP in this sleep state. A likely explanation for the lack of the sleep state contribution a few seconds into the response. This is consistent with other noncardiovascular reflex systems operating, with the vestibular system being the likely candidate (16). Of major significance was our finding that all six infants with OSA had abnormal cardiovascular responses to the postural challenge, with two having frank postural hypotension, two having sustained hypertension, and two having no change in BP. All OSA infants studied had severe OSA, and their varying responses to the postural challenge did not appear to be directly associated with either the frequency of apnea or the severity of oxygen desaturation associated with obstructive breaths.

Notably, in all six infants, cardiovascular patterns returned toward normal patterns after treatment with nCPAP. This finding is consistent with the changes in cardiovascular control seen in adult patients with OSA after treatment. However, the persistence of some degree of abnormality suggests that these infants had some form of underlying defect of autonomic cardiovascular control in addition to the OSA, or that CPAP had not resolved all the issues of OSA. The present study suggests that OSA itself would cause at least an aggravation of autonomic dysfunction. Some support to this is found in adults presenting with high upper airway resistance during sleep (12), in whom a clear BP drop in response to a postural challenge performed with the tilt-table test was seen. Furthermore, inocument study of ALTE infants, it has been shown that those ALTE infants who do not have OSA have normal HR and BP responses to 45° head-up tilting (20).

It remains unknown what characteristic of OSA causes this observed, at least partly reversible, autonomic dysfunction. One potential explanation is the hypoxia episodes observed in severe OSA in infants. In this study, all of the studied OSA infants presented with significant number of these oxygen desaturation events. Chronic hypoxia without hypercapnia is known to dampen ventilatory responses derived from the carotid body in infants (8), normal adults (25), cats (36), and piglets (37). The combination of upper airway obstruction, depressed arousal, and defective cardiovascular control is clearly a potentially lethal one, which could result in SIDS. Although such defects could be independent, it is also possible, given that the infants studied had either

Table 3. Heart rate and blood pressure changes after 45° head-up tilt

<table>
<thead>
<tr>
<th>Group</th>
<th>%Maximum change</th>
<th>%Drop (max – min)</th>
<th>Drop (max – min)</th>
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<tbody>
<tr>
<td></td>
<td>SWS</td>
<td>REM</td>
<td>SWS</td>
</tr>
<tr>
<td>Controls (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>16 ± 7</td>
<td>21 ± 7</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>16 ± 6</td>
<td>16 ± 5</td>
<td>71 ± 6</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>22 ± 10</td>
<td>19 ± 7</td>
<td>99 ± 10</td>
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<tr>
<td>Pre-nCPAP (n = 6)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>9 ± 6*</td>
<td>15 ± 7</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>4 ± 8*</td>
<td>13 ± 7</td>
<td>91 ± 10</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>9</td>
<td>15 ± 6</td>
<td>9</td>
</tr>
<tr>
<td>On nCPAP (n = 6)</td>
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<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>9 ± 4*</td>
<td>13 ± 7</td>
<td>72 ± 7</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>5 ± 8†</td>
<td>14 ± 5</td>
<td>9 ± 7</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>11 ± 8*</td>
<td>14 ± 5</td>
<td>11 ± 6*</td>
</tr>
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</table>

Values are means ± SD; n, no. of infants. Shown are heart rate (HR), SBP, and DBP changes after 45° head-up tilt in SWS and REM sleep. Comparison between control infants and OSA infants: *P < 0.05; †P < 0.005.
experienced an ALTE or had a family history of SIDS, that some underlying common defect led to both the autonomic disturbance and the OSA. A recent report of autonomic abnormalities with hypotension in adults with high upper airway resistance syndrome by Guilleminault et al. (13) may have relevance to our present findings in infants.

In conclusion, our results demonstrate that some infants with OSA have a reversible defect in arousability in REM that may occur in association with a partially reversible autonomic cardiovascular control. Our results could account for the reduction of movement temporarily reversible autonomic cardiovascular control. Our results could account for the reduction of movement in sleep and with simple, provocative tests of autonomic activity in sleeping infants. J Appl Physiol 91: 561–568, 2001.

DISCLOSURES

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REFERENCES


