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.

OSA Infants

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 desaturations are rarely counted (24), and OSA is considered to be rare in infancy. However, OSA is common in a selected group of infants who have suffered an apparent life-threatening event (ALTE) (3, 11).

ALTE infants show abnormal BP and HR responses to postural challenge in head-up tilting during sleep (9). This aberrant response to tilt is especially enhanced in the ALTE infants with OSA. In a previous study (20), infants with OSA who suffered an ALTE showed significantly reduced HR and BP responses in slow-wave sleep (SWS) at the initiation of the 45° head-up tilt. This blunted response was followed by sustained hypotension, steady BP level, or hypertension as the 45° head-up tilt continued. Infants who experienced an ALTE but did not have OSA had normal BP and HR responses to comparable tilt tests.

In this study, we examined whether obstructed breathing during sleep, in itself, caused the abnormal HR and BP responses observed in infants with OSA. We performed 45° head-up tilt tests during polygraphic sleep studies in both control infants and infants with OSA. Infants with OSA were started on nCPAP treatment, and these infants were restudied on nCPAP 10 ± 4 days (mean ± SD) after initiation of treatment.

METHODS

OSA Infants

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.

Control Subjects

Twelve full-term, healthy, aged-matched control infants were studied. Their mean age at the time of the PSG study

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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 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).

Polysomnography. The polygraphic recordings (Compu-medics, 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 Monitor- ing); arterial oxyhemoglobin saturation (pulse oximeter); abdominal respiratory belts (Respitrace, Ambulatory Monitor- ing); 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 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 breathing 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 ± 1.3% in control infants and 11.5 ± 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 1. Age, sex, respiratory, and heart rate data for control and OSA infants

<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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SWS</td>
<td>REM</td>
<td>SWS</td>
<td>SWS</td>
<td>SWS</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>
</tr>
<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>
</tr>
<tr>
<td>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>
</tr>
</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.

Fig. 1. Typical heart rate (HR) and blood pressure (BP) changes in a representative control infant before (Pre), during, and after (Post) a 45° head-up tilt in slow-wave sleep (SWS) and in rapid eye movement sleep (REM). bpm, Beats/min.

Fig. 2. HR and BP changes before, during, and after a 45° head-up tilt in SWS in controls (A; n = 12); obstructive sleep apnea (OSA) infants, pre-CPPAP treatment (B; n = 6); and OSA infants on nasal continuous positive airway pressure (nCPAP) treatment (C; n = 6). Values are means ± SD.
infants displayed sustained hypotension, two no
change, and two infants had a sustained increase in BP

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 differ-
ence 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 con-
trols 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 treat-
ment, 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 arousals 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 per-
centage 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 ther-
apy, 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 func-
tion and depressed arousal responses showed signifi-
cant improvement after effective treatment of their
OSA with nCPAP; their autonomic cardiovascular con-
trol 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. Addition-
ally, previous studies show that ALTE infants have
defective arousal responses to hypoxia (7, 21, 29) and
have fewer arousals from sleep and fewer body move-
ments (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 se-
lective 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 in-
creased 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 activ-
ity (31). Our results indicate that infants with OSA
also exhibit impaired baroreflex and other cardiovas-
cular 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 (32, 33).

Of considerable interest was the finding that some infants with OSA did not show the differential elevation of BP in REM in control infants, but 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 BP differential in the infants with OSA is that the absence of a BP increase during REM may reflect a suppression of the normal phasic activity in REM, and its normalization on nCPAP treatment reflects a return to normal phasic density in that sleep state.

The HR and BP responses to postural challenge in infants are similar in character to that found in adults (19), but the short latency of the response suggests that the early operation of a “feed forward” control, increasing BP before venous pooling is able to compromise cerebral blood flow, with baroreceptor systems coming into operation 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, in our previous 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>
</tr>
</thead>
<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>15 ± 6</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>16 ± 6</td>
<td>20 ± 10</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>22 ± 10</td>
<td>21 ± 12</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>Pre-nCPAP (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>9 ± 6*</td>
<td>8 ± 6</td>
<td>9 ± 6†</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>4 ± 8†</td>
<td>15 ± 8</td>
<td>12 ± 6*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>9</td>
<td>19 ± 10</td>
<td>8 ± 4*</td>
</tr>
<tr>
<td>On nCPAP (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>9 ± 4*</td>
<td>9 ± 7</td>
<td>15 ± 7*</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>5 ± 8†</td>
<td>10 ± 9</td>
<td>9 ± 7†</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>11 ± 8*</td>
<td>12 ± 9</td>
<td>11 ± 6*</td>
</tr>
</tbody>
</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 arousals (22) that appear to be sleep state linked (35) and the subtle cardiovascular autonomic defects that have been identified in a number of infants who become subsequent SIDS victims.

DISCLOSURES

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