Nasal CPAP treatment improves abnormal cardiovascular autonomic function and arousability in ALTE and SIDS-related infants with OSA

C Harrington, T Kirjavainen, A Teng, C E Sullivan

David Read Laboratory, University of Sydney, and Sydney Children’s Hospital, Sydney, Australia (C Harrington BSc, Prof C E Sullivan MD)

University of Helsinki, Finland (T Kirjavainen MD)

Sydney Children’s Hospital, Sydney, Australia (A Teng MD)

Running Title: n-CPAP improves autonomic function in OSA infants

Correspondence to: C Harrington, BSc

David Read Laboratory, University of Sydney

Missenden Road,

Camperdown, Sydney, 2006

Australia.

(email: cth@med.usyd.edu.au)

Fax: +61 2 95503851

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ABSTRACT

We evaluated cardiovascular autonomic control and arousability during sleep in infants with obstructive sleep apnea (OSA) before and after 10 (SD 4) days of treatment with nasal continuous positive airway pressure (n-CPAP). Six OSA infants and twelve age-matched control infants were studied with polygraphic sleep studies at the age of 13 (SD 4) weeks. During the study, 45° head-up tilt tests were performed in slow wave (SWS) and rapid eye movement (REM) 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 REM (p<0.005) and higher baseline HR (p<0.05) than controls. N-CPAP 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 n-CPAP.

KEY WORDS: Infant; obstructive sleep apnea, blood pressure, heart rate, n-CPAP
INTRODUCTION

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 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, many of these symptoms are abolished following treatment of the OSA with nasal-continuous positive airway pressure (n-CPAP) (5,32,33).

While it is not uncommon for young infants to have one or two obstructive breaths throughout their night time sleep, more frequent obstructions and oxygen 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 blood pressure and heart rate 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 heart rate and blood pressure responses in slow wave sleep (SWS) at the initiation of the 45° head-up tilt. This blunted response was followed by sustained hypotension, steady blood pressure 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 heart rate and blood pressure 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 n-CPAP treatment, and these infants were restudied on n-CPAP 10 (SD4) days after initiation of treatment.

METHODS

OSA infants

Six infants with obstructive sleep apnea were enrolled into the study. Their mean age at the time of the study was 13 (SD 4) weeks. 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 were symptomatic. For the purposes of this study, an ALTE was defined as an apneic episode occurring during sleep which involved some color change or limpness, and which severely alarmed the caregiver. Prior to 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 was 13 (SD 3) weeks. Parents of infants attending the local baby health centre were asked to participate. All infants enrolled in the study had a normal clinical examination both on the third day of life and immediately prior to 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 polygraphic sleep studies (PSG). Following the initial sleep study, infants suffering from OSA were placed on a trial of n-CPAP treatment. The decision to start n-CPAP therapy was done on a clinical basis. The infants were hospitalized during this n-CPAP trial time and the n-CPAP was used continuously during sleeping periods (observed compliance). The n-CPAP treatment was carried out successfully in all of the OSA infants. OSA infants were restudied during a PSG on n-CPAP after 10 (SD 4) days of treatment. During this period no other treatment and/or medications were administered that would have affected the cardiovascular/respiratory system.

**Polysomnography.** The polygraphic recordings (Compumedics, Melbourne, Australia) consisted of continuous monitoring of two electroencephalograms (EEGs; C3A2, O2A1), two electrooculograms, chin, diaphragm, and abdominal muscle surface electromyograms, nasal airflow (pressure transducer), thoracic and abdominal respiratory belts (Respitrace, Ambulatory Monitoring, USA), arterial oxyhaemoglobin saturation (SpO2, Pulse Oximeter, Ohmeda Biox 3700e, USA), electrocardiogram (ECG), and blood pressure measurement (Portapres, TNO Biomedical Instrumentation). Heart rate (HR) was assessed by continuous ECG recording. Continuous, non-invasive arterial blood pressure (BP) measurement was
performed using the Portapres device, (TNO Biomedical Instrumentation, Netherlands), with the inflatable cuff being placed around the infant's wrist. BP data was recorded at the sampling rate of 125 Hz, and ECG with 500 Hz sampling rate.

45° Head-up tilt test. During slow wave sleep (SWS) and rapid eye movement sleep (REM), eight consecutive 45° head-up tilts were performed with at least a one-minute control period between each tilt. The infant slept on a purpose-built mattress support which was tilted manually from the horizontal position to a 45° angle within 2-3 seconds. This position was intended to be maintained for a minimum of 60 seconds. However, in the circumstance where the infant's BP changed significantly and did not return to baseline within the first 15-20 seconds, the tilt was terminated earlier. This meant that, for a number of infants, tilts were only maintained for about 20 seconds. If the tilt resulted in a transient arousal, sigh or apnea, the tilt test data were excluded from the haemodynamic 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 more than 50% without a simultaneous reduction in respiratory effort and where the event was related to either an arousal or oxygen desaturation of more than 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 thirty second artifact and movement free reference period was calculated just prior to each tilt. Maximum values and standard deviations (SD) for DBP, SBP and HR were then calculated for every five-second-epoch throughout the pre-tilting reference period and tilting period, and expressed as the maximum percentage change from the reference period.

Mean % maximum change was measured by calculating the maximum rate following the initiation of the tilt, which typically occurred within the first five seconds, and expressing that value as a percentage change from the 30 second reference baseline. Mean % drop was assessed by calculating the minimum rate, following the peak, (which typically occurred within 5–15 seconds from the initiation of the tilt), and expressing that value as a percentage change of the maximum rate. Mean drop (max–min) was calculated by a direct comparison of the raw maximum and minimum values following the tilt.

HR, HRV and BP analysis. Mean HR, SBP and DBP for each sleep state were calculated from a mean of three, 2-minute artifact-free epochs in both SWS and REM sleep. These epochs were taken from a period of sleep where no tests were performed. The mean and standard deviation were calculated for each group. The co-efficient of variation was calculated by dividing the standard deviation of the RR interval (ms) by the mean RR interval, obtained from the three, 2-minute epochs, and was used as a measure of HRV. The co-efficient of variation was used so as to minimize the effect of baseline HR. BPV was measured by taking
the same three, 2-minute 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 which was maintained for more than two seconds (10).

Statistical analysis

All the statistical analyzes were performed with SPSS® statistical software (SPSS for Windows, release 11.0.1, SPSS, Inc, Chicago, Ill). One-way analysis of variance (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 prior to n-CPAP and OSA infants on n-CPAP. Pre- and on- n-CPAP changes were compared using 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 (SD 6) breaths per hour of sleep. In all the OSA infants studied, obstructive breaths were frequently associated with an oxygen desaturation of greater than 10%, and occasionally oxygen saturation fell to below 75%. On average, oxygen desaturation was 2.3 (SD 1.3)% in control infants and 11.5 (SD 3)% in the
OSA infants (p< 0.005). During the subsequent PSG study, n-CPAP 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 (Fig 2A). In both SWS and REM sleep, HR and BP began to increase immediately upon tilt onset rising rapidly to a peak value within the first four to eight beats (Fig 1). This peak was typically reached within 4 seconds from the tilt onset, and the maximal value of HR, SBP and DBP were significantly increased compared to 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 which was maintained throughout the rest of the tilt.

Before n-CPAP treatment, none of the infants with OSA displayed this characteristic response to the head-up tilt in either SWS (Fig 2B) or in REM sleep. The change in HR and BP upon initiation of the tilt (Table 3), was significantly reduced compared to the control infants (p<0.05 and P<0.005 respectively), and there were no significant changes in either HR or BP compared to the reference epochs immediately following 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 to the control infants. The BP response to the tilt was variable: two infants displayed sustained hypotension, two no change, and two infants had a sustained increase in BP (Fig 3).

Following 10 (SD 4) days of n-CPAP 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:** Heart rates in the OSA infants were significantly increased in both SWS and REM prior to n-CPAP treatment (p<0.05) compared to the control group (Table 1), but following n-CPAP treatment there was no significant difference in the heart rates of the subject group in either sleep state.

Prior to n-CPAP treatment HRV was significantly lower in OSA infants in SWS compared to control infants (p<0.05). There was no difference in HRV in REM sleep. On n-CPAP 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 n-CPAP 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. Following n-CPAP 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 2).

Both systolic blood pressure variability (SBPV) and diastolic blood pressure variability (DBPV) were significantly increased in OSA group in SWS compared to controls before n-CPAP therapy (p<0.05). This difference was not observed in REM sleep. The abnormal increase of BPV was normalized after the onset of n-CPAP treatment, and on n-CPAP BPV in OSA infants did not differ significantly from the values in normal controls (Table 2).
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 to SWS, with the postural challenge test evoking arousal in two out of eight tests in SWS and six out of eight tests in REM. Before n-CPAP 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 n-CPAP therapy, and the percentage of arousal was similar to controls both in SWS and in REM sleep (Figure 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 following effective treatment of their OSA with n-CPAP - 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 to controls (4,27,28), and that infants with OSA have fewer spontaneous arousals during sleep compared to normal infants (30). In these studies, the treatment of the OSA normalised 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).
Prior to treatment with n-CPAP, 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 generalised increase in peripheral sympathetic activity (31). Our results indicate that infants with OSA also exhibit impaired baroreflex and other cardiovascular reflex functions.

When the infants with OSA were treated with n-CPAP, 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 which occur in cardiovascular control in adults with OSA after treatment with n-CPAP (32,33).

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 n-CPAP, the difference in BP between SWS and REM re-emerged. 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 normalisation on n-CPAP 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 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 non-cardiovascular 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 n-CPAP. 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), where a clear BP drop in response to a postural challenge performed with the tilt-table test was seen in some of the adults tested. Further, 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° heap-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 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 which may occur in association with a partially reversible autonomic cardiovascular control. Our results could account for the reduction of movement arousals (22) which appear to be sleep state linked (35), and the subtle cardiovascular autonomic defects which have been identified in a number of infants who become subsequent SIDS victims.
Bibliography


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**TABLE 1:**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>M/F</th>
<th>Age (weeks)</th>
<th>ORDI</th>
<th>ODS</th>
<th>% Arousal</th>
<th>HR (bpm)</th>
<th>HRV (co-var)</th>
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<td></td>
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<td>SWS</td>
<td>REM</td>
<td>SWS</td>
<td>REM</td>
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<td>REM</td>
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<tr>
<td>Controls</td>
<td>12</td>
<td>6/6</td>
<td>13 (2)</td>
<td>2 (1)</td>
<td>23 (11)</td>
<td>71 (18)</td>
<td>116 (10)</td>
<td>124 (11)</td>
</tr>
<tr>
<td>OSA – Pre CPAP</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>OSA – During CPAP</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>

* p<0.05; ** p< 0.005

Table 1: Age (weeks), obstructive respiratory disturbance index (ORDI), mean oxygen desaturation (ODS, percent of arousal responses to 45° head-up tilt, heart rate (HR), and heart rate variability (HRV) in slow wave sleep (SWS) and REM sleep, in control infants and OSA infants pre and on n-CPAP treatment. (p values refer to comparison between control infants and OSA infants).
**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>SBP</th>
<th>SBPV</th>
<th>DBP</th>
<th>DBPV</th>
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<td>REM</td>
<td>SWS</td>
<td>REM</td>
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<tr>
<td>Controls</td>
<td>12</td>
<td>80(7)</td>
<td>87(9)</td>
<td>58(5)</td>
<td>65(6)</td>
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<td>84(6)</td>
<td>60(10)</td>
<td>60(6)</td>
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<td>Subjects – On CPAP</td>
<td>6</td>
<td>82(9)</td>
<td>89(9)</td>
<td>58(11)</td>
<td>64(7)</td>
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</table>

*p < 0.05;

Table 2: Systolic blood pressure (SBP), diastolic blood pressure (DBP), systolic blood pressure variability (SBPV), and diastolic blood pressure variability (DBPV) in control and OSA infants before and on n-CPAP treatment. (p values refer to comparison between control infants and OSA infants).
### Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
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<tr>
<td></td>
<td>% max change</td>
<td>% drop (max-min)</td>
<td>Drop (max-min)</td>
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<tr>
<td></td>
<td>SWS</td>
<td>REM</td>
<td>SWS</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>HR 16 (7)</td>
<td>15 (6)</td>
<td>21 (7)</td>
</tr>
<tr>
<td></td>
<td>SBP 16 (6)</td>
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<td>16 (4)</td>
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<td></td>
<td>DBP 22 (10)</td>
<td>21 (12)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Pre n-CPAP (n=6)</td>
<td>HR 9 (6)*</td>
<td>8 (6)</td>
<td>9 (6)**</td>
</tr>
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<td>SBP 4 (8)**</td>
<td>15 (8)</td>
<td>11 (9)</td>
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<tr>
<td></td>
<td>DBP 9</td>
<td>19 (10)</td>
<td>12 (6)*</td>
</tr>
<tr>
<td>On n-CPAP (n=6)</td>
<td>HR 9 (4)*</td>
<td>9 (7)</td>
<td>15 (7)*</td>
</tr>
<tr>
<td></td>
<td>SBP 5 (8)**</td>
<td>10 (9)</td>
<td>9 (7)*</td>
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<tr>
<td></td>
<td>DBP 11 (8)*</td>
<td>12 (9)</td>
<td>11 (6)*</td>
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</table>

*p<0.05; **p<0.005

**Table 3:** Heart Rate (HR) bpm, systolic blood pressure (SBP), and diastolic blood pressure (DBP), changes following 45° head-up tilt in SWS and REM sleep. (*p* values refer to comparison between control infants and OSA infants).
Fig 1: Typical heart rate and blood pressure changes in a representative control infant during a 45° head-up tilt in SWS and in REM sleep.
FIGURE 2

Fig 2: Heart rate (HR) and blood pressure (BP) changes before, during and after a $45^\circ$ head-up tilt in SWS in (A) controls (n=12); (B) OSA infants, pre-CPAP treatment (n=6); and (C) OSA infants on n-CPAP treatment (n=6). Values are means +/- SD.
FIGURE 3:

A (i) 

B (i) 

C (i) 

D (i) 

A (ii) 

B (ii) 

C (ii) 

D (ii)
FIGURE 3 (cont'd):

Fig 3: Heart rate (HR) and blood pressure (BP) responses to a 45° head-up tilt in 6 infants with OSA, (i) pre- and (ii) on- CPAP treatment. The start and the end of the tilt is indicated by the vertical dashed lines. Note that:

- Prior to CPAP treatment five of the six 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 prior to n-CPAP treatment was varied, with two infants displaying sustained hypotension (A & B), two infants showing no change (E & F) and two infants having a sustained increase in BP (C & D).

- Following n-CPAP treatment, all but infant D continued to show a blunted HR response to the tilt. However, four of the infants had an improved, although not normal, BP response.
**FIGURE 4**

Fig 4: Mean percent arousal in response to the head-up tilt in SWS and REM in control infants (n=12) and in OSA infants, before and on n-CPAP treatment (n=6).