



Original Article

Altered cardio-respiratory response to spontaneous cortical arousals in children with upper airway obstruction

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ABSTRACT

Objective: Upper airway obstruction (UAO) during childhood is associated with cardiovascular morbidity. The aim of this study was to investigate the cardio-respiratory response to cortical arousal during sleep in children with UAO.

Methods: Standard paediatric overnight polysomnography (PSG) was conducted in 40 children with UAO (25 M, 7.5 ± 2.7 yrs) prior to and 6 months following adenotonsillectomy. For comparison a control group of 40 normal, sex and age matched children (21 M, 7.5 ± 2.6 yrs) underwent two PSGs without intervention at the same time points.

Results: Heart rate and respiratory rate were measured during spontaneous and respiratory arousals in stage 2 and REM sleep 15 s prior to and 15 s immediately following cortical arousal onset. Cortical arousal was associated with a significant increase in heart and respiratory rate in both groups of children. UAO children, however, showed a significantly higher heart rate response in stage 2 sleep (−17.5 ± 6.0 vs. −14.4 ± 4.8%; $p < 0.05$), a lower pre-arousal baseline respiratory rate (stage 2: 17.1 ± 1.4 vs. 18.2 ± 1.7 BPM; $p < 0.01$) and a prolonged increase in respiratory rate compared to control children. Cardiac and respiratory arousal responses were not significantly different from controls following adenotonsillectomy in the UAO children.

Conclusions: UAO in children is associated with an altered cardiorespiratory response to spontaneous arousal from sleep, which may indicate early signs of autonomic dysfunction. Surgical treatment of UAO appears to reverse these outcomes.

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1. Introduction

Arousals are an integral feature of normal sleep as well as a pathological consequence of sleep disruption. While arousal from sleep is an important physiological or behavioural response to adverse stimuli or homeostatic regulation, if frequent, sleep continuity is disrupted resulting in sleep fragmentation. Increasing evidence suggests that arousals underlie not only the pathophysiology of some sleep disorders but also lead to adverse *sequelae* including neurocognitive deficits and cardiovascular morbidity [1–3].

The pattern and intensity of a given arousal response is highly variable—influenced by factors which include age, sleep stage and type of stimulus. Experimental and clinical studies have shown

that the arousal process is a hierarchical continuum beginning at the brainstem level with progressive activation leading to cortical excitation [4–6]. Thus arousals range in appearance and intensity from low level autonomic activation through to awakening.

Initial efforts in understanding arousal behaviour and pathophysiology have focussed on cortical activation as this has been relatively easy to identify and measure during sleep studies via the electroencephalogram. However, evaluating the autonomic response to arousal has gained increasing interest due to the observation that sleep disorders, which have frequent arousal-related autonomic activation such as obstructive sleep apnoea (OSA) and limb movement disorders, are associated with increased cardiovascular morbidity [7,8].

OSA syndrome (OSAS) affects between 3–7% of adults [9] and 1–4% of children [10] with differing pathophysiology and presentation in the two groups [11]. In adults the association between OSA and increased cardiovascular morbidity is now well recognised [7]. While the mechanisms leading to cardiovascular morbidity are

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likely to be multifactorial, frequent arousals triggered by episodes of upper airway obstruction are believed to play a key role via repetitive sympathetic nervous system activation and destabilisation of cardiorespiratory control [12–16]. In addition, findings from empirical and modelling studies indicate that arousals can facilitate ventilatory instability during sleep thereby perpetuating episodes of apnoea or hypopnoea [17–19].

Evidence also suggests that children with UAO may also be at increased risk of developing cardiovascular disease [20–24]. Arousals may also play a role in the pathophysiology of these outcomes but relatively little is known about the autonomic response to arousal in children with UAO. The aims of this study were therefore to (1) characterise cardiac and respiratory responses to spontaneous cortical arousal in children with UAO during stage 2 and REM sleep and compare these findings to normal healthy controls and (2) investigate the effect of UAO treatment (via adenotonsillectomy) on the arousal-related cardiorespiratory response. Understanding of arousal responses may help elucidate some physiological pathways underlying the development of cardiovascular disorders in children with UAO.

2. Methods

Children in this study were participating in an investigation of sleep, breathing and psychological performance before and after treatment for suspected UAO by adenotonsillectomy. More details on the study protocol are published elsewhere [25]. Analysis was subsequently undertaken to describe the cardiac and respiratory changes associated with spontaneous and respiratory cortical arousal in children with UAO and matched healthy controls.

2.1. Subjects

Using a prospective repeated measures design this study conducted overnight polysomnography (PSG) in children with UAO awaiting adenotonsillectomy at baseline and at 6 months following surgery. Non-snoring control children matched for age and gender underwent PSG at the same time points. Fifty-four children with UAO and 53 control children were initially enrolled in this study. Children with UAO were those with a history of frequent snoring who were scheduled for adenotonsillectomy for suspected OSA as diagnosed by an experienced paediatric otorhinolaryngologist at the Adelaide Women's and Children's Hospital. All children were aged between 3 and 12.9 years of age at baseline. Children were excluded if they had undergone previous ear, nose, throat or craniofacial surgery; had a medical condition (other than UAO) associated with hypoxia or sleep fragmentation; or were taking medication known to affect sleep or cardiorespiratory physiology. Control children were recruited through the recommendation of parents of the participating UAO children and from advertisements in local newspapers and schools. The same exclusion criteria were applied to controls with the additional requirement that they did not snore on more than two nights per week as confirmed by parental report. Socioeconomic status (SES) was determined for each child using the Australian Bureau of Statistics' Index of Relative Socio-economic Advantage/Disadvantage 2006 national census data.

This study was approved by the Women's and Children's Hospital Human Ethics Committee. Parental consent and child assent were obtained from all participants.

2.2. Overnight polysomnography

Overnight polysomnography (PSG) was conducted twice for all children once at baseline and then again on average 29.4 ± 5.9 weeks later (range 19–55 weeks), following adenotonsillectomy for the UAO group or no intervention for the control group.

PSG was conducted without sedation or sleep deprivation and began close to each child's usual bedtime with a parent present throughout the procedure. PSG was only performed if children were well on the night and free of any recent illness including respiratory infection. The following standard parameters were recorded continuously using the S-Series® Sleepwatch System (Compumedics, Australia): electroencephalogram (EEG; C3-A2 and C4-A1), left and right electrooculogram (EOG), sub-mental and diaphragmatic electromyogram (EMG) with skin surface electrodes, leg movements by piezoelectric motion detection, HR by electrocardiogram (ECG), oro-nasal airflow by thermistor and nasal pressure, respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography, arterial oxygen saturation (SaO_2) by pulse oximetry (Nellcor N595 with a 3 s averaging time) and transcutaneous CO_2 , using a heated (43°C) transcutaneous electrode (TINA, Radiometer Pacific). Each child was monitored continuously overnight via infrared camera by a pediatric sleep technician who also documented observations of sleep behavior including the presence or absence of snoring.

Sleep stages were scored visually in 30 s epochs according to the standardized EEG, EOG and EMG criteria of Rechtschaffen and Kales [26]. For reporting purposes Stage 3 and 4 NREM sleep were combined as slow wave sleep. Movement time (>50% of an epoch obscured by movement artifact) was scored as a separate category and was not included in either sleep or awake time; awake time refers to time spent awake during the recording period after initial sleep onset.

Cortical arousals were scored according to the criteria of the American Sleep Disorders Task Force [27]. The spontaneous arousal index (SAI) represents the total number of spontaneous arousals per hour of sleep, while the respiratory arousal index (RAI) represents the total number of respiratory arousals per hour of sleep. The point of arousal onset was determined visually from the EEG channel. Periodic limb movements (PLM) were scored using standard criteria [28]. The PLM index (PLMI) was calculated as the number of periodic limb movements in sleep (PLMS) per hour of sleep.

Respiratory variables were scored according to standard guidelines recommended for pediatric sleep studies [29]. The obstructive apnea/hypopnea index (OAHl) was calculated as the total number of obstructive apneas, mixed apneas and obstructive hypopnoeas divided by the total sleep time and expressed as the number of events per hour of sleep. For the purpose of this study, obstructive sleep apnea was defined as an obstructive apnea and hypopnea index (OAHl) ≥ 1 . The SaO_2 desaturation index represents the number of $\geq 3\%$ oxygen desaturations per hour of sleep.

Height and weight were measured on the night of PSG and established growth charts corrected for age and gender were used to determine body mass index (BMI) z-scores [30].

2.3. Heart rate analysis

Heart rate analysis was conducted on data extracted from the ECG channel (bipolar lead II, sampling frequency of 500 Hz) of the standard PSG montage. All extracted ECG segments were visually scanned for artefact and arousals were excluded from analysis if an artifact free ECG could not be obtained. Time series of RR intervals were extracted using a template matching algorithm. All RR intervals were visually checked for falsely detected R waves and manually edited if necessary. For arousal analysis, ECG segments over a 30 s window were studied beginning 15 s prior to the onset of each cortical arousal as seen visually on the EEG channel. In order to correctly align the RR interval traces with the EEG arousal onset, RR intervals were interpolated at 500 ms thereby providing a uniform time base.

For each arousal, the RR interval response was quantified by (1) the pre-arousal baseline RR interval, i.e., the mean RR interval

averaged over -15 to -5 s prior to the EEG arousal onset, expressed in [ms] and (2) the relative RR interval decrease associated with cortical arousal (Δ RR), i.e., the minimum RR interval after cortical arousal onset, expressed as the percentage change from the pre-arousal baseline RR interval. The pre-arousal baseline was calculated for the period -15 to -5 s prior to arousal onset because HR changes were found to precede cortical arousal onset by up to 5 s.

Due to the relative infrequent occurrence of arousals in slow wave sleep, arousal analysis was restricted to Stage 2 and REM sleep. In addition, arousals associated with limb movements or a sleep state change (one epoch prior to or after an arousal), as well as consecutive arousals less than 60 s apart were excluded from analysis.

2.4. Respiratory frequency analysis

Respiratory rate changes in response to spontaneous arousals were determined by calculating respiratory intervals from the thermistor signal as there was less signal loss and artefact observed in this channel. Respiratory intervals were computed for the same 30 s window as the ECG changes (i.e., 15 s prior to and 15 s post-arousal as seen visually on the EEG channel). High frequency distortions and low frequency envelopes were removed from the thermistor signal using empirical mode decomposition. The signal offset was subsequently removed and local minima and maxima calculated based on the differentiated signal. Very short intervals (<1 s) between consecutive minima/maxima were omitted. The distance between two local minima was considered a respiratory cycle if: (1) there was a zero crossing between two consecutive minima, (2) the time interval between consecutive minima was within the respiratory frequency range of 0.22–0.5 Hz, and (3) the amplitude of the signal was greater than 5 mV. For each arousal the breath occurring at arousal onset was discarded from analysis because it overlapped the pre- and post-arousal period and could not be clearly assigned to either phase. Arousals were only included if they had a minimum of 2 breaths both before and after arousal onset within the -15 to 15 s time window.

2.5. Statistical analysis

Due to the large variation in the number of arousals generated between subjects, arousal-related HR and respiratory responses were averaged for each individual within respective sleep stages so that each child contributed equally to the group mean. Student's *t*-test and one-way ANOVA were used to compare demographic data and PSG results between groups. ANOVA was used to test for group differences in RR arousal response and to test for differences in RR arousal response across groups and between sleep stages. Repeated measures ANOVA were used to assess differences in HR and respiratory response to arousal across studies. Post-hoc analysis was performed using Student *t*-tests. Significant associations were determined using linear regression and ANOVA. Skewed data were corrected using an inverse transformation $[1/(x+1)]$. Data are presented as means $\pm$ SD unless stated otherwise and *p* values are 2-tailed with statistical significance determined at $\alpha = 0.05$. All statistical analyses were performed using SPSS version 15.0 for Windows (Chicago, IL).

3. Results

3.1. Subject characteristics and PSG results

The PSG data for 13 of the 53 control children and 4 of the 54 children with UAO were excluded due to poor signal quality. Of

the remaining 50 children with UAO, a further 10 were excluded due to significantly greater age and lower SES compared to the control children (Table 1).

As anticipated baseline PSG confirmed the presence of respiratory abnormalities in the UAO children who had a significantly higher OAH1, elevated respiratory arousals, increased frequency of SaO_2 desaturations and a significantly lower mean SaO_2 nadir compared to controls. There were no significant differences between groups with respect to sleep architecture, spontaneous arousals or PLMS (Table 1). Sleeping HR did not differ between controls and the UAO children in Stage 2 or REM sleep, but HR was significantly higher in REM sleep (84.4 ± 10.0 BPM) compared to Stage 2 sleep (78.2 ± 10.4 BPM) across both groups ($F = 16.6$, $p < 0.001$).

Follow-up PSG data suitable for HR analysis was available for 37 of the 40 initial controls and 33 of the 40 children with UAO. The time between adenotonsillectomy and follow-up PSG ranged between 14 and 44 weeks and ensured full recovery from surgery. In the UAO group following adenotonsillectomy there was a marked reduction in OAH1, SaO_2 desaturation frequency and respiratory arousal rate, but the UAO group still had significantly greater OAH1, SaO_2 desaturation frequency and SaO_2 nadir than the controls. Small statistically significant differences were also observed between groups at the follow-up PSG for wake time after sleep onset (WASO), stage 2 and slow wave sleep percentages (Table 1).

3.2. Arousal characteristics

In the first study, a total of 2888 spontaneous arousals were scored across all sleep stages in the control children, and 2446 spontaneous arousals in the UAO group. In the follow-up PSG, 2467 spontaneous arousals were scored in all sleep stages in the control children and 2198 spontaneous arousals in children with UAO. The number of spontaneous arousals that met the inclusion criteria for heart rate and breathing rate analyses are summarized in Table 2.

The number of spontaneous cortical arousals was not significantly different between controls and UAO children in both PSGs (Table 1). During the baseline PSG spontaneous arousal duration was shorter during stage 2 sleep compared to REM sleep in both groups. In addition, arousal duration was significantly shorter in UAO children during both stage 2 and REM sleep compared to controls (Table 3). At the follow-up PSG, however, arousal duration was no longer significantly different between controls and UAO children (6.2 ± 1.0 vs. 5.7 ± 1.1 s, $t = 1.8$, $p > 0.05$).

Heart rate changes associated with respiratory arousals were analysed only in the UAO children during their first PSG (i.e., prior to adenotonsillectomy) due to the small number of respiratory arousals observed in control children and the UAO group after surgery. Of the 896 respiratory arousals scored across the whole night, 216 from stage 2 and 162 from REM sleep met the inclusion criteria for analysis. While there was no significant difference in respiratory arousal duration between stage 2 and REM sleep, respiratory arousals were significantly longer than spontaneous arousals (9.7 ± 2.8 s vs. 5.4 ± 1.3 s, $F = 87.8$, $p < 0.001$).

3.3. Time course of arousal response

Fig. 1A shows the averaged time course of RR intervals immediately prior to and during spontaneous arousal in stage 2 and REM sleep for control and UAO children. The HR response to arousal in both groups was biphasic with a significant acceleration in HR that peaked approximately 3 s after cortical arousal onset, followed by a decrease and return to pre-arousal baseline levels within 15 s of arousal onset irrespective of sleep stage. Cardiac acceleration preceded cortical arousal onset by 3 s on average in both subject groups and sleep stages and across both studies.

Table 1

Subject demographics and overnight PSG results for the baseline and follow up PSG.

	Baseline		Follow-up	
	Control (n = 40)	UAO (n = 40)	Control (n = 37)	UAO (n = 33)
Age, years	7.5 ± 2.6	7.5 ± 2.7	8.2 ± 2.6	7.9 ± 2.6
Gender, n males (%)	21 (52.5)	25 (62.5)	19 (51.4)	21 (63.6)
BMI percentile (%)	60.7 ± 26.4	65.8 ± 31.9	61.5 ± 25.9	71.2 ± 28.9
SES	994.9 ± 93.0	976.9 ± 93.9	997.7 ± 91.3	975.5 ± 94.0
TST (min)	446.9 ± 37.3	425.6 ± 59.5	451.5 ± 50.5	439.0 ± 53.9
Stage 1 sleep (% TST)	2.9 ± 1.5	3.3 ± 2.3	2.8 ± 1.8	3.3 ± 2.6
Stage 2 sleep (% TST)	44.2 ± 6.9	42.4 ± 6.2	47.6 ± 4.8	42.6 ± 7.5***
Slow wave sleep (% TST)	32.2 ± 6.3	34.6 ± 6.5	30.1 ± 5.0	33.5 ± 6.7*
REM sleep (% TST)	20.6 ± 3.9	19.7 ± 5.7	19.5 ± 3.5	20.6 ± 3.3
REM latency (min)	92.8 ± 22.0	85.8 ± 31.2	89.1 ± 21.5	91.2 ± 21.2
Movement time (min)	9.1 ± 4.9	8.7 ± 4.5	9.3 ± 4.7	8.6 ± 3.7
WASO (min)	39.7 ± 30.9	53.4 ± 44.9	38.9 ± 32.1	60.1 ± 47.5*
PLMI ¹ (median, range)	3.3 ± 4.9 (1.2, 0–19.6)	4.9 ± 7.3 (1.3, 0–27.2)	2.1 ± 3.1 (0.8, 0–11.7)	3.6 ± 5.3 (2.1, 0–26.4)
SAI	9.4 ± 2.7	8.4 ± 2.4	9.2 ± 2.7	9.2 ± 3.0
RAI ¹ (median, range)	0.4 ± 0.4 (0.3, 0–1.7)	3.2 ± 4.2**** (1.1, 0–17.0)	0.5 ± 0.5 (0.4, 0–2.4)	0.8 ± 0.7 (0.7, 0–2.6)
SaO ₂ nadir	92.9 ± 1.9	90.6 ± 5.7*	93.1 ± 1.6	90.9 ± 3.0****
SaO ₂ desaturation index ¹ (median, range)	0.8 ± 0.8 (0.8, 0–4.9)	5.1 ± 9.4**** (1.3, 0–53.1)	0.8 ± 0.7 (0.6, 0–3.0)	1.5 ± 0.9*** (1.5, 0–3.1)
OAH1 ¹ (median, range)	0.1 ± 0.2 (0.1, 0–0.9)	5.0 ± 9.0**** (0.9, 0–49.8)	0.3 ± 0.3 (<0.1, 0–0.5)	0.8 ± 1.0** (0.2, 0–2.4)

SES, socioeconomic status; TST total sleep time; WASO wake after sleep onset time; PLMI periodic limb movement index; SAI spontaneous arousal index; RAI respiratory arousal index; OAH1 obstructive apnoea hypopnoea index.

* $p < 0.05$.** $p < 0.01$.*** $p < 0.005$.**** $p < 0.001$ UAO vs. control.¹ Analysis using transformed values.**Table 2**

Number of spontaneous arousals included in the heart rate/breathing rate analysis.

	Sleep stage	Control	UAO
Baseline PSG	Stage 2	1000/912	816/698
	REM	521/462	268/223
Follow-up PSG	Stage 2	882/588	811/444
	REM	403/261	287/145

3.4. Arousal-related heart rate response during baseline PSG

During the first PSG the pre-arousal baseline HR (–15 to –5 s preceding arousal onset) was not significantly different between UAO children and controls but was significantly higher in REM sleep compared to stage 2 sleep across both groups (Table 3). However, the magnitude of HR change during spontaneous arousal (Δ RR) was significantly higher in the UAO group compared to controls in stage 2 sleep and approached significance in REM sleep (Fig. 1A and B, and Table 3). There was no significant sleep stage by group interaction for arousal duration, pre-arousal baseline HR or Δ RR (Table 3). Furthermore, there was no significant correlation between spontaneous arousal duration and Δ RR ($r = 0.005$, $p > 0.05$).

Lastly, for the UAO children, pre-arousal RR and Δ RR were not significantly different between respiratory and spontaneous cortical arousals. Due to small numbers no further analysis was undertaken for respiratory arousals.

To assess the association between UAO severity and Δ RR for spontaneous arousals, subjects were divided into 3 subgroups based on snoring and OAH1 criteria (controls – no snoring and OAH1 < 1, $n = 40$; primary snoring – frequent snoring [snoring ≥ 3 days/week] and OAH1 < 1, $n = 21$; OSA – frequent snoring and OAH1 ≥ 1 , $n = 19$). All subgroups had comparable age, BMI and SES values. During stage 2 sleep the relative heart rate increase (Δ RR) was significantly higher in both primary snoring and OSA children compared to controls, with no differences found between primary snoring and OSA groups (Fig. 2). A similar pattern was observed in REM sleep. Differences between groups, however, were not statistically significant.

3.5. Arousal-related heart rate response during follow-up PSG

Pre-arousal baseline HR was lower at follow-up PSG in stage 2 sleep across both groups (PSG 1: 786.6 ± 104.6 vs. PSG 2: 814.2 ± 103.7 ms, $t = -2.3$, $p < 0.05$) but no change was observed in REM sleep (PSG 1: 746.7 ± 95.4 vs. PSG 2: 759.0 ± 82.7 ms, $t = -1.1$, $p > 0.05$). The differences in Δ RR between controls and children with UAO observed at baseline were not found at follow-up (Fig. 1B).

Despite the fact that Δ RR normalised post-surgery, there was no significant association between the reduction in OAH1 severity across studies and change in Δ RR for the children with UAO

Table 3

Arousal and arousal-related R–R interval characteristics during stage 2 and REM sleep for control and UAO children during the first PSG.

	Control		UAO		F-value		
	Stage 2	REM	Stage 2	REM	Group	Stage	Group × stage
Arousal Duration, s	6.5 ± 1.2	7.4 ± 1.4	5.4 ± 1.2	6.4 ± 1.8	21.5****	19.4****	0.03
Pre-arousal RR, ms	798 ± 101	753 ± 87	777 ± 100	714 ± 99	3.5	11.4***	0.3
(Pre-arousal HR, BPM)	76.4 ± 9.7	80.7 ± 9.4	78.5 ± 10.6	85.5 ± 11.6			
Δ RR, %	–14.4 ± 4.8	–15.1 ± 5.6	–17.5 ± 6.0	–16.9 ± 6.3	7.1**	0.01	0.5

** $p < 0.01$.*** $p < 0.005$.**** $p < 0.001$.

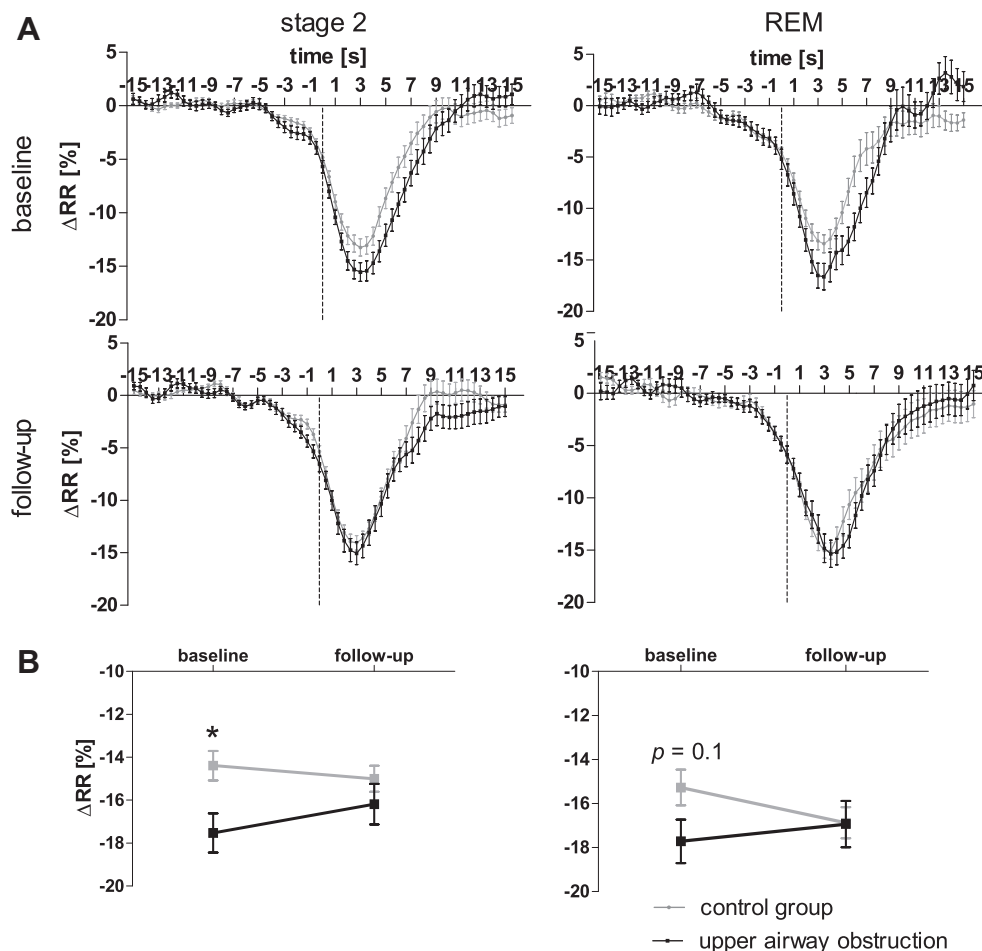


Fig. 1. (A) Averaged time course of RR intervals immediately prior to and following spontaneous cortical arousal during stage 2 and rapid eye movement (REM) sleep in controls and children with upper airway obstruction at baseline polysomnography and 6-month follow-up. The dashed vertical line (zero time point) indicates the onset of the arousal as seen visually on the electroencephalogram. (B) Mean maximal heart rate change (ΔRR as % change from baseline) during spontaneous arousal during stage 2 and REM sleep at baseline and follow-up polysomnography. Error bars indicate standard error of the mean. * $p < 0.05$.

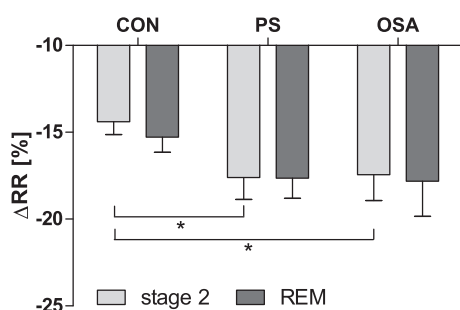


Fig. 2. Relative change in RR interval from mean baseline heart rate during spontaneous arousal as a function of obstructive sleep apnea severity (controls [CON], primary snoring [PS] and obstructive sleep apnea [OSA]) during stage 2 and rapid eye movement (REM) sleep for the first polysomnogram. Error bars indicate standard error of the mean. * $p < 0.05$.

($r = 0.07$, $p > 0.05$, and, $r = 0.03$, $p > 0.05$ for Stage 2 and REM respectively).

3.6. Respiratory rate changes associated with spontaneous arousal

Arousal-related ventilatory changes were analysed for spontaneous arousals only as respiratory arousals were frequently associated with distortion and artefact in the respiratory signals. The

rates of the three respiratory cycles before and after the onset of spontaneous arousal are shown for both controls and UAO children in Fig. 3. The respiratory rates within the three breaths immediately prior to arousal were not significantly different from each other and were subsequently averaged to obtain pre-arousal baseline respiratory rates.

When comparing the pre-arousal and post-arousal respiratory rates in the control group there was a significant increase in respiratory rate immediately following arousal onset with a return to baseline levels within three breaths. This pattern was observed in both stage 2 and REM sleep for both PSGs. Post-hoc analysis showed that the respiratory rate was typically highest for the first breath immediately following arousal onset (Fig. 3).

Children with UAO demonstrated a significantly lower pre-arousal respiratory rate compared to controls during stage 2 sleep at baseline PSG (Controls: 18.2 ± 1.7 BPM; UAO: 17.1 ± 1.4 BPM, $t = 2.9$, $p < 0.01$, Fig. 3). This difference was not evident following adenotonsillectomy. Similar to the control group, there was also a significant increase in respiratory rate immediately following arousal onset in stage 2 sleep in the UAO group during both studies. However, respiratory rate did not return to pre-arousal levels within three breaths as was observed in controls. During REM sleep the post-arousal respiratory rate did not increase significantly in the UAO children in the baseline PSG. Following adenotonsillectomy, however, the increase in respiratory rate post-arousal approached statistical significance for the first breath ($p = 0.06$, Fig. 3).

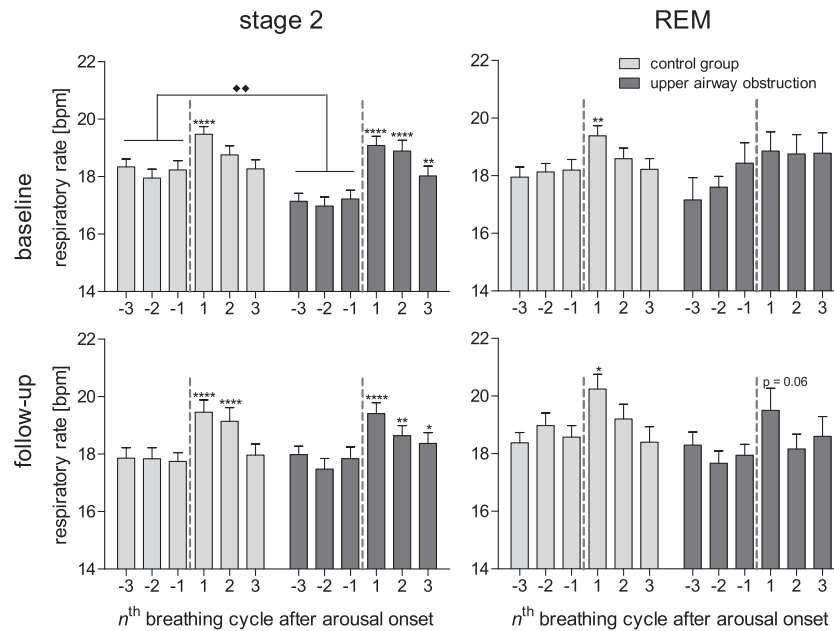


Fig. 3. Mean breath-to-breath respiratory rate for the three breaths pre- and post-arousal for control and upper airway obstruction children in stage 2 sleep (left) and rapid eye movement (REM) sleep (right) at baseline and follow-up polysomnography. The vertical dashed line indicates the point of spontaneous arousal onset as seen on the electroencephalogram. Error bars indicate standard error of the mean. Asterisks indicate significant within group differences in post-arousal respiratory rates compared to pre-arousal baseline respiratory rate. Diamonds indicate significant group differences in pre-arousal baseline respiratory rate between control children and children with upper airway obstruction. * $p < 0.05$, ** $p < 0.01$, **** $p < 0.005$, ♦♦ – $p < 0.01$.

4. Discussion

This is the first study to report heart- and respiratory-related changes associated with spontaneous and respiratory cortical arousals in children with UAO before and after adenotonsillectomy. The major findings of this study are as follows: (1) the baseline pre-arousal HR did not differ between children with UAO and healthy controls; (2) HR acceleration associated with spontaneous cortical arousal was more pronounced during stage 2 sleep in children with UAO compared to controls; (3) this difference was no longer evident after UAO children underwent adenotonsillectomy; (4) in children with UAO there were no differences in arousal-related HR changes between spontaneous and respiratory arousals; (5) the pre-arousal respiratory rate was significantly lower in UAO children compared to controls in stage 2 sleep in the first PSG; (6) control children showed a significant increase in respiratory rate immediately post-arousal in both stage 2 and REM sleep; (7) UAO children showed an increase in respiratory rate only during stage 2 sleep.

4.1. Heart rate pattern during arousal

Cortical arousals in both the normal healthy children and those with UAO were typically characterised by a biphasic increase–decrease in HR of approximately 10 s duration with HR changes preceding cortical arousal onset by 3–5 s. This HR pattern is comparable to that found in adults [6] and supports the hypothesis of a hierarchical arousal response, where subcortical areas involving autonomic control are activated before cortical regions [31]. The sympatho-vagal mechanisms mediating arousal-related cardiac changes are not fully understood. Abrupt HR accelerations, such as those seen during arousal from sleep, are predominantly the result of vagal withdrawal, although sympathetic cardiac nerve activity is also likely to be increased [32]. Sympathetic activation during arousal has been observed in peroneal nerve spikes 2 s after auditory-induced arousal [33], while patients with reduced sympathetic nervous system activity show an attenuated HR response to arousal [34].

4.2. Obstructive sleep apnea and cardiac arousal response

The average RR interval immediately prior to spontaneous cortical arousal was not significantly different between children with UAO and controls. In contrast, the magnitude of the arousal-related RR interval shortening (i.e., HR acceleration) during spontaneous arousal was significantly higher in stage 2 sleep in the UAO children compared to controls. There was no association between individual arousal frequency and mean HR acceleration (data not shown) and no correlation between arousal length and the degree of cardiac activation. These findings suggest that the arousal process in the UAO children is altered at the subcortical level, resulting in augmented autonomic activation. The increased autonomic response could be due to increased sympathetic activation and/or stronger vagal withdrawal.

We found no significant correlation between UAO severity and the magnitude of arousal-related HR changes. This could be due to the relatively mild level of UAO observed in the study group. However, the children with primary snoring (i.e., not experiencing apnoea or blood gas abnormalities) still had a significantly higher HR response to spontaneous arousal compared to controls (in stage 2 sleep) and similar HR changes as the UAO group, suggesting that even mild UAO was having an effect on autonomic arousal activation. The clinical significance of primary snoring in children is currently subject to significant debate with increasing evidence indicating that it is not as benign as once thought. Neurocognitive and behavioural deficits [35,36] and elevated BP [37,38] have been demonstrated in children with habitual snoring but not exhibiting apnoea or abnormal blood gas exchange.

Two unexpected findings in this study were that (i) there was no relationship between arousal duration and the degree of cardiac activation and (ii) that there was no difference in the degree of cardiac acceleration between spontaneous and respiratory arousals in the UAO children. These results differ from published reports in adults where cardiovascular activation is enhanced with arousal duration and intensity [6,39,40]. Several studies in adults have demonstrated marked differences in cardiorespiratory response

between different types of arousal [6,41]. Even when respiratory and spontaneous arousals were of similar duration respiratory arousals had a more pronounced degree of cardiac acceleration compared to spontaneous arousals, which did not appear to be influenced by the characteristics of the preceding respiratory event [41].

Given that the respiratory arousals in the UAO children were almost twice as long as spontaneous arousals, it is even more surprising that the respiratory arousals did not provoke greater cardiac activation. The reason for this lack of association between arousal duration/type and cardiac response in our study may reflect differences in the sympatho-vagal regulation of HR between children and adults due to maturational changes in autonomic nervous system development during childhood. Heart rate variability analysis suggests that younger children have lower vagal tone [42].

4.3. Respiratory rate response to arousal

Arousal from sleep is associated with increased respiratory activity [43] and this may facilitate ventilatory instability during sleep thereby perpetuating abnormal breathing. While the ventilatory response to arousal has been investigated in adults [44–46] data describing the ventilatory response to non-evoked arousals are lacking for children. We were unable to analyse the ventilatory response to respiratory arousals due to the associated obstructed apnoeas and hypopnoeas. Control children showed a consistent respiratory response to arousal across sleep stages (stage 2 vs. REM sleep) and time points (baseline vs. 6 month follow-up PSG). In all instances the post-arousal respiratory rate was significantly higher than pre-arousal values with a return to baseline levels within two breaths of arousal initiation.

Children with UAO demonstrated a markedly different pattern of respiratory response with a lower pre-arousal respiratory rate and a more sustained post-arousal ventilatory response during stage 2 sleep compared to controls. The sustained ventilatory response is in keeping with the larger HR response to arousal also seen in the UAO children.

The lower pre-arousal respiratory rate in the UAO children may be due to increased inspiratory loading of the upper airway prolonging the respiratory cycle. Prolonged partial upper airway obstruction rather than frank apnoea is commonly present in children with obstructed breathing. Marcus et al. found that normal children increased their inspiratory time when subjected to resistive loading during sleep, although this appeared to be at the expense of expiratory time rather than prolonging the respiratory cycle [47]. Alternatively, the lower pre-arousal respiratory rate could be due to reduced ventilatory drive. Adults with UAO demonstrate abnormalities in ventilatory control including reduced ventilatory drive [48]. In children with UAO only subtle abnormalities in ventilatory control have been reported [49,50] although there have only been few studies with small sample sizes investigating this. A study in normal children showed a reduction in respiratory rate (due to a prolongation of expiratory time) when subjected to awake hypercapnic challenge, but respiratory rate remained unchanged in UAO children possibly due to a blunted ventilatory response [51].

4.4. Effect of adenotonsillectomy

The treatment of UAO by adenotonsillectomy improved respiratory parameters in our cohort of UAO children, although some children still exhibited a small degree of residual obstruction.

The pre-arousal baseline HR was lower in stage 2 sleep at the follow up PSG of both healthy and UAO children and is likely an age effect. We have previously reported age-related effects on the pre-arousal baseline heart rate [52]. Importantly, we did not observe a significant age or gender effect on the heart rate response to arousal in normal children. Age effects are more likely to be seen

when the heart is predominantly under vagal control as occurs during NREM sleep.

The significantly larger HR response associated with spontaneous arousal seen in UAO children prior to adenotonsillectomy was no longer evident after surgery, pointing towards the normalization of autonomic cardiac control. In support of this interpretation, HR variability has shown to normalize after adenotonsillectomy [53], and cardiac remodelling appears also to reverse after treatment [54,55]. The pre-arousal respiratory rate in the UAO children was similar to controls after surgery. Although the underlying cause of this cannot be determined from this study, these findings support those of others indicating subtle abnormalities in ventilatory control in pre-pubertal children with UAO [50,51,56].

4.5. Clinical significance

As arousals are associated with sympathetic activation, the increased arousal frequency commonly observed in individuals with breathing disorders may be part of the pathophysiological mechanism leading to cardiovascular dysfunction. This study indicates that elevated sympathetic nerve activity or stronger vagal withdrawal could be responsible for the augmented cardiac response to spontaneous arousal in children with UAO. Evidence for increased sympathetic nervous system activity has been found in children with UAO [21,57,58]. While children have fewer cortical arousals than adults in response to abnormal breathing events, subcortical autonomic activation is frequent [57]. Although we did not evaluate subcortical arousals in our study an increase in autonomic activation may account for an overall increase in sympathetic nervous system responsiveness. This may also explain why children with relatively mild UAO (i.e., in the absence of hypoxia or frank obstruction) show adverse cardiovascular outcomes including elevated BP.

Previous studies to date have investigated the ventilatory response to respiratory stimuli. Alterations in ventilatory behaviour in response to repeated respiratory stimuli are understandable in the context of UAO. If spontaneous arousals are also altered, however, this suggests that the *sequelae* of UAO on arousal processes may be more generalised than previously thought.

4.6. Limitations

As we used strict inclusion criteria for arousal selection to ensure signals were free of movement or respiratory artefact (known to confound cardiac and respiratory dynamics), some arousals were discarded, which may have resulted in a degree of selection artefact. In this study we did not consider potential circadian influences on cardiac and respiratory behaviour. We were unable to undertake a more detailed analysis of respiratory dynamics as the airflow pressure and respiratory inductive plethysmograph signals were subject to movement artefact and signal dropout during arousals. It is also unclear whether the differences in ventilatory behaviour between controls and UAO children are restricted to arousal responses or if there are broader differences in respiratory function during sleep, as we only examined the period immediately before and after arousal. Further, we cannot exclude age-related effects on the difference in cardiac arousal response observed during the follow-up study. However, our previous study in normal children suggested that Δ RR is age-independent [52].

5. Conclusion

This is the first study to show that children with relatively mild UAO have an augmented and sustained cardiovascular and respiratory response to spontaneous arousal which is ameliorated after

adenotonsillectomy. These findings raise important questions regarding the indications for treatment of children even with mild UAO.

Conflict of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: [doi:10.1016/j.sleep.2010.07.018](https://doi.org/10.1016/j.sleep.2010.07.018).

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