Cardiorespiratory response to spontaneous cortical arousals during stage 2 and rapid eye movement sleep in healthy children

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SUMMARY Arousal from sleep is associated with transient and abrupt cardiorespiratory changes, and elevated arousals associated with sleep disorders may trigger adverse cardiovascular sequela. In this paper, we provide the first data in children on cardiorespiratory responses to cortical arousal. Heart rate and ventilatory responses to arousal from stage 2 and rapid eye movement (REM) sleep were investigated in 40 normal, healthy Caucasian children (age: 7.7 ± 2.6 years; body mass index z-score: 0.30 ± 0.8). All children underwent overnight polysomnography studies. Cortical arousals were scored according to standard criteria. Heart rate changes were assessed over 30 s, starting 15 s prior to cortical arousal onset. Breathing rates were quantified three breaths before and after arousal onset. Arousals from stage 2 as well as REM sleep resulted in an R–R interval shortening of about 15%, independent of age and gender. The R–R interval shortening initiated at least 3 s before the cortical arousal onset. The breathing interval immediately after cortical arousal onset was significantly shortened ($P < 0.001$). In conclusion, cortical arousals in children are associated with an increase in breathing rate and significant heart rate accelerations, which typically precede the cortical arousal onset.

KEYWORDS arousal, breathing rate, children, heart rate, sleep

INTRODUCTION Investigation of the physiological events associated with arousal from sleep has gained considerable interest among sleep researchers as increasing evidence indicates that arousals underlie many of the adverse sequela associated with sleep disorders, such as daytime sleepiness, neurocognitive deficits and cardiovascular dysfunction. While arousal from sleep is an important physiological and/or behavioural response to adverse stimuli or for homeostatic regulation, excessive arousals can disrupt normal sleep physiology, resulting in non-restorative sleep.

Arousal from sleep is associated with transient and abrupt cardiorespiratory changes, including an increase in heart rate and blood pressure, peripheral vasoconstriction and augmented ventilation (Horner, 2003). Sympathetic activation and vagal withdrawal appear to mediate these changes, which have been observed in association with a range of arousal types including evoked arousals, spontaneous and respiratory-related arousals and arousals associated with body and leg movements (Davies et al., 1993; Guggisberg et al., 2007; Khoo et al., 1996; Loredo et al., 1999; Morgan et al., 1996; Pennestri et al., 2007; Sforza et al., 1999; Smith et al., 2009; Somers et al., 1993; Trinder et al., 2001b).

Elevated arousals during sleep are observed in a range of sleep disorders, including sleep disordered breathing (SDB). In adults, the cardiovascular sequela of SDB including hypertension and cardiac arrhythmias are well recognized, with arousals implicated in the pathophysiology via the cumulative effect of repetitive sympathetic activation and/or destabilization of cardiorespiratory control (Arias and Sanchez, 2007; Blasi et al., 2003; Loredo et al., 1999; Morgan et al., 1996).
While the cardiorespiratory response to arousal has been investigated substantially in adults, comparatively little work has been done in children. It is now becoming evident that children with SDB may also be at increased risk of adverse cardiovascular outcomes, including abnormal heart rate and blood pressure regulation and cardiac remodelling, and that arousals may also contribute to this pathology (Aljadeff et al., 1997; Amin et al., 2002, 2004, 2005, 2008; Duman et al., 2008; Kwok et al., 2008; Marcus et al., 1998). For example, Tauman et al. (2004) found that cortical and autonomic arousals in children with SDB were associated with attenuated peripheral arterial tone, indicating increased sympathetic discharge. However, elucidating the pathways underlying the development of cardiovascular disorders in SDB requires an understanding of arousal responses in healthy individuals, and to date such data are lacking for children. The aim of this study therefore was to investigate cardiac and respiratory activity during spontaneous cortical arousals in stage 2 and rapid eye movement (REM) sleep in normal, healthy children, and to examine the effects of sleep stage, age and gender on these variables. Notably, this is the first study to describe heart rate and ventilatory changes during spontaneous arousal in normal children.

MATERIALS AND METHODS

Subjects

This study conformed to principles outlined in the Declaration of Helsinki, and was approved by the Women’s and Children’s Hospital Human Ethics Committee. Parental consent and child assent were obtained for all participants. The subject group comprised 41 normal, healthy Caucasian children with no underlying medical conditions, respiratory disorders or craniofacial abnormalities. Children were recruited from the local community as controls for a larger study. None of the children was reported to snore regularly, and children were excluded from further analysis if evidence of SDB [apnoea and hypopnoea index (AHI) ≥5] was demonstrated during polysomnography (PSG). No child was taking medication that would affect sleep architecture or cardiovascular physiology.

Overnight polysomnographies

Two non-consecutive PSGs were conducted for each child on average 27.5 ± 5.3 weeks apart (range 18.8-42.2 weeks) as part of the broader study protocol. PSG was only performed if children were well on the night and free of any recent respiratory infection. Overnight PSG was conducted without sedation or sleep deprivation, and began at each child’s usual bedtime. A parent accompanied each child throughout the procedure. PSG was performed using a computerized sleep data acquisition system (Compumedics S-Series Sleepwatch System; Melbourne, Vic., Australia). The following standard parameters were measured and recorded continuously utilizing the appropriate signal sampling and filtering protocols: electroencephalogram (EEG; C3–A2 or C4–A1); left and right electrooculogram (EOG); submental and diaphragmatic electromyogram with skin surface electrodes; leg movements by piezoelectric motion detection; heart rate by electrocardiogram (ECG) using a modified lead II sampled at 500 Hz; oro-nasal airflow by thermistor and nasal pressure; respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography; arterial oxygen saturation (SpO2) by finger pulse oximetry (Nellcor N595 with an averaging time of 3 s); and transcutaneous CO2 (TcCO2) using a heated (41°C) transcutaneous electrode (TINA, Radiometer Pacific, Melbourne, Vic., Australia). Each child was continuously monitored and observed via infrared camera by a paediatric sleep technician who also documented observations of sleep behaviour, including the presence or absence of snoring.

All PSGs were visually scored by the same sleep technician experienced in analysing paediatric sleep studies. Sleep stages were scored in 30 s epochs according to standardized criteria (Rechtschaffen and Kales, 1968). For reporting purposes, stage 3 and 4 non-REM sleep were combined as slow-wave sleep (SWS). Epochs were scored as movement if the EEG and EOG signals were obscured for ≥50% of the epoch by muscle tension or artefact associated with movement of the subject (Rechtschaffen and Kales, 1968). Movement time was scored as a separate category, and was not included in either sleep or wake time. Wake time refers to time spent awake during the recording period after initial sleep onset. Respiratory variables were scored according to standard guidelines recommended for paediatric sleep studies (American Thoracic Society, 1996). The AHI was calculated as the number of obstructive and non-obstructive events per hour of sleep. Cortical spontaneous arousals were scored according to the criteria of the American Sleep Disorders Task Force (1992), and are expressed as the total number of arousals per hour of sleep (arousal index). The point of arousal onset was determined visually from the EEG channel. Periodic limb movements (PLMS) were scored using standard criteria (ASDA, 1993). The PLM index (PLMI) was calculated as the number of PLMS per hour of sleep.

Heart rate analysis

Heart rate changes during spontaneous arousal were measured by extracting R–R intervals from the ECG that was recorded as part of the standard PSG (see above). Given the sampling frequency of 500 Hz, we were able to study R–R interval changes at a resolution of 2 ms, which is considered sufficient for heart rate variability analysis (Malik, 1996). ECG segments of 30 s duration were studied, beginning 15 s prior to the onset of each cortical arousal as seen visually on the EEG channel. In this way the prearousal baseline heart rate and the R–R change during arousal was determined. Arousals associated with a sleep state change (one epoch prior to or after an arousal) as well as arousals associated with limb movements were excluded. In addition, consecutive arousals less than 60 s apart were discarded from analysis.
Custom-written computer software developed under MATLAB® was used to extract the 30-s ECG segments associated with spontaneous arousals during stage 2 and REM sleep throughout the night. Evoked and respiratory-related arousals were excluded from the analysis. All extracted ECG segments were visually scanned for artefacts, and arousals were excluded from analysis if an artefact-free ECG could not be obtained.

All R–R intervals were extracted using template-matching algorithm-based computer software. Subsequently, all R–R intervals were visually checked for wrongly detected R-waves and manually edited if necessary. To obtain an equidistant time base, necessary for lining up the R–R interval traces to the EEG arousal onset, R–R intervals were interpolated at 500 ms.

For each arousal, the R–R interval response was quantified by means of: (i) the prearousal baseline R–R interval, i.e. the mean R–R interval averaged over −15 to −5 s prior to the EEG arousal onset, expressed in (ms); and (ii) the relative R–R interval decrease associated with cortical arousal (ΔRRI), i.e. the minimum R–R interval after cortical arousal onset, expressed as the percentage change from the prearousal baseline R–R interval. The prearousal baseline was calculated between −15 and −5 s period because heart rate changes were found to precede cortical arousal onset by up to 5 s.

Respiratory frequency analysis

Respiratory rate change in response to spontaneous arousal was determined by computing respiratory intervals from the thermistor signal. Respiratory intervals were calculated for the same 30 s period as ECG changes, i.e. 15 s prior to and 15 s postarousal. High-frequency distortions and low-frequency envelopes were removed from the signal using empirical mode decomposition. Subsequently, the signal offset was removed and local minima and maxima were 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: (i) there was a zero crossing between two consecutive minima; (ii) the time interval between consecutive minima was within the respiratory frequency range of 0.22–0.5 Hz; and (iii) 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 postarousal period and could not be clearly assigned to either phase.

Statistical analysis

Student’s t-test and one-way ANOVA was used to compare demographic, PSG and heart rate variables between the first and second PSG, between genders and between age groups. Two-way ANOVA for repeated measures was used to test for differences in R–R arousal response between stage 2 and REM sleep, and between the first and second PSG. Two-way ANOVA for repeated measures was also used to test for differences in respiratory rate between respiratory intervals during the 15 s prior and postarousal. Significant associations between variables were determined using Pearson correlation and multiple regressions. To assess the effect of arousal duration on the R–R response, we compared each child’s heart rate change during their shortest arousal to that of their longest arousal using twosided paired t-tests, during both stage 2 and REM sleep. To test whether the heart rate changes precede the cortical arousal, we applied CUSUM analysis (Davey et al., 1986) on the averaged R–R interval time series, where the prearousal baseline R–R intervals within the interval −15 to −5 s prior to the EEG arousal onset was used to compute baseline variability. The time point where the cumulated R–R interval time series passed the significance limits obtained from the baseline data was used to identify the onset of heart rate change. Due to the variation in the number of spontaneous arousals generated between subjects, arousal-related cardiovascular and respiratory variables were averaged for each individual within each sleep stage so that each child contributed equally to the group mean. Where appropriate heart rate and arousal analyses were co-varied for age and Games–Howell post hoc analyses were conducted. All P-values are two-tailed with statistical significance determined at α = 0.05. Data are presented as mean ± SD unless stated otherwise. All statistical analyses were performed using sss version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Anthropomorphic and arousal characteristics

A total of 41 children completed both the first and second overnight PSG. The data for one child were excluded due to elevated AHI (AHI = 12.9). At the first study children had a mean age of 7.7 ± 2.6 years (range = 3.1–12.2 years) and a body mass index (BMI) z-score of 0.30 ± 0.8 (range = −1.7–2.3). At the second PSG children had a mean age of 8.2 ± 2.6 years (range = 3.6–12.9 years) and a BMI z-score of 0.22 ± 0.9 (range = −1.7–2.15). Sixteen children were male (40%) and 24 female (60%). Demographic and PSG data for both studies are presented in Table 1.

A total of 2987 spontaneous arousals were scored across all sleep stages in the first PSG. Of these, 994 from stage 2 and 515 from REM sleep met the inclusion criteria for analysis. In the second PSG a total of 2944 spontaneous arousals were scored across all sleep stages, with 992 from stage 2 and 467 from REM sleep meeting the inclusion criteria for analysis.

Time course of arousal-related R–R changes

Individual arousal heart rate patterns varied substantially with each single arousal event. Fig. 1 shows the averaged time course of R–R intervals immediately prior to and during spontaneous arousal in stage 2 and REM sleep. The heart rate response to arousal was biphasic with a significant acceleration in heart rate that peaked approximately 3 s after cortical arousal onset followed by a decrease and return to prearousal
baseline levels within 15 s of arousal onset. In the first PSG the mean prearousal heart rate was 75 bpm for stage 2 and 80 bpm for REM sleep, with a mean ΔRR of 15 bpm for both sleep stages. In the second study, the mean prearousal heart rate was 73 bpm for stage 2 and 78 bpm for REM sleep, with a mean ΔRR of 11 and 13 bpm, respectively.

In both studies, cardiac acceleration preceded cortical arousal onset by several seconds. In the first PSG a significant shortening of the R–R interval preceded cortical arousal by 3.5 s in stage 2 sleep and 5.0 s in REM sleep. In the second PSG, the R–R interval preceded cortical arousal by 4 s in stage 2 sleep and 5.0 s in REM sleep (see Fig. 1).

Sleep stage and study order effects on arousal duration and R–R interval characteristics

Arousal duration, prearousal baseline R–R and ΔRR according to sleep stage (stage 2 versus REM) and study order (first versus second PSG) are presented in Table 2. Arousal duration was significantly longer during REM sleep compared with stage 2 sleep (Table 2), and was not significantly different between the first and second PSG. In addition, there was no significant interaction between sleep stage and study (first versus second PSG) for arousal length.

The prearousal baseline heart rate (–15 to −5 s preceding EEG arousal onset) was significantly higher (i.e. shorter R–R interval) during REM sleep compared with stage 2 sleep (Table 2), and was not significantly different between the first and second PSG. In addition, there was no significant interaction between sleep stage and study (first versus second PSG) for arousal length.

The ΔRR during arousal (Δ change from baseline) was similar in stage 2 and REM sleep, with no significant differences between the first and second PSG for either sleep stage. There was also no interaction between sleep stage and study (first versus second PSG) for ΔRR (Table 2). Further arousal-related heart rate characteristics including gender and age effects are presented for the first PSG only.

Effect of arousal duration on heart rate characteristics

Values for time of arousal onset after initial sleep onset, arousal duration, prearousal baseline R–R and ΔRR for both the shortest and longest arousal during stage 2 and REM sleep are presented in Table 3. Arousal duration gradually increased across the night, with the longest arousals occurring significantly later after initial sleep onset during both stage 2 and REM sleep (Fig. 2).

There was a significant interaction between sleep stage and arousal length with respect to the occurrence of the shortest and longest arousal from initial sleep onset. Given the later appearance of the first REM period during the sleep cycle, the shortest arousal in stage 2 occurred significantly earlier than the shortest arousal in REM sleep; however, there was no

Table 1 Subject demographics and PSG values for the first and second overnight PSG

<table>
<thead>
<tr>
<th></th>
<th>First PSG (n = 40)</th>
<th>Second PSG (n = 40)</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.7 ± 2.6</td>
<td>8.2 ± 2.6</td>
<td>−33.1</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI z-score</td>
<td>0.30 ± 0.8</td>
<td>0.22 ± 0.9</td>
<td>0.77</td>
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<tr>
<td>TST (min)</td>
<td>449.85 ± 36.2</td>
<td>464.13 ± 41.7</td>
<td>−1.54</td>
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<tr>
<td>Stage 1 (% TST)</td>
<td>3.33 ± 2.1</td>
<td>2.68 ± 1.8</td>
<td>1.35</td>
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</tr>
<tr>
<td>Stage 2 (% TST)</td>
<td>44.90 ± 6.0</td>
<td>46.0 ± 5.9</td>
<td>−0.85</td>
<td></td>
</tr>
<tr>
<td>SWS (% TST)</td>
<td>31.88 ± 5.8</td>
<td>31.38 ± 5.6</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>REM (% TST)</td>
<td>19.89 ± 4.0</td>
<td>19.96 ± 4.2</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>90.02 ± 21.9</td>
<td>93.4 ± 23.7</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Movement (min)</td>
<td>8.14 ± 4.3</td>
<td>8.28 ± 4.3</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>WASO (min)</td>
<td>40.46 ± 30.0</td>
<td>38.86 ± 33.9</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Arousal (per hour TST)</td>
<td>0.77 ± 0.5</td>
<td>0.59 ± 0.4</td>
<td>1.73</td>
<td></td>
</tr>
<tr>
<td>Stage shifts (per hour TST)</td>
<td>11.78 ± 2.7</td>
<td>11.22 ± 2.4</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>PLMI</td>
<td>2.97 ± 4.0</td>
<td>2.04 ± 3.1</td>
<td>1.28</td>
<td></td>
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<tr>
<td>SAI</td>
<td>9.95 ± 2.6</td>
<td>9.44 ± 2.8</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td>0.88 ± 0.8</td>
<td>1.08 ± 0.9</td>
<td>−1.04</td>
<td></td>
</tr>
</tbody>
</table>

AHI, apnoea and hypopnoea index; BMI, body mass index; PLMI, periodic limb movement index; PSG, polysomnography; REM, rapid eye movement; SAI, spontaneous arousal index; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset.

Figure 1. Averaged (± SEM) ΔRR (% change from prearousal baseline) during spontaneous arousals during stage 2 and rapid eye movement sleep for the first (top) and second (bottom) polysomnography. The dashed vertical line (zero time point) indicates the onset of the cortical arousal as seen visually on the electroencephalogram trace. The arrows indicate the onset of significant R–R interval shortening.

difference in the time from initial sleep onset in the occurrence
of the longest arousal for REM and stage 2 sleep.

There was also a significant interaction between arousal
duration and sleep stage, with the shortest arousal in REM
being longer than the shortest arousal in stage 2 sleep but with
no sleep stage difference in arousal duration for the longest
arousal.

There was no significant difference in baseline R–R or
DRR between short and long arousals in either stage 2 or REM
sleep. However, when all arousals were pooled there was a very
small but statistically significant correlation between arousal
duration and ΔRR ($R^2 = 0.01$, $P < 0.001$), but no significant
association between arousal-related ΔRR and time from initial
sleep onset of arousal ($R^2 = 0.002$, $P > 0.05$).

**Respiratory rate changes associated with arousal**

The average respiratory rate of the three breaths immediately
prior to and the three breaths postarousal onset are shown in
Fig. 3. A total of 419 and 172 arousals met the inclusion
criteria for respiratory frequency analysis from stage 2 and
REM sleep, respectively. There was a marked difference in
respiratory rate before and after arousal, with a significant
increase in respiratory rate immediately after arousal that

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**Table 2** Arousal and arousal-related R–R interval characteristics during stage 2 and REM sleep for the first and second PSG (co-varying for age)

<table>
<thead>
<tr>
<th></th>
<th>First PSG (n = 40)</th>
<th>Second PSG (n = 40)</th>
<th>F-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arousal duration (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>6.53 ± 1.1</td>
<td>6.22 ± 1.0</td>
<td>1.62</td>
</tr>
<tr>
<td>REM</td>
<td>7.47 ± 1.3</td>
<td>7.22 ± 1.5</td>
<td>20.65****</td>
</tr>
<tr>
<td>Prearousal R–R (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>797.4 ± 104.6</td>
<td>822.1 ± 94.2</td>
<td>7.45**</td>
</tr>
<tr>
<td>REM</td>
<td>750.9 ± 87.4</td>
<td>764.8 ± 78.1</td>
<td>9.85***</td>
</tr>
<tr>
<td>ΔRR (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>−14.6 ± 4.7</td>
<td>−15.6 ± 4.2</td>
<td>1.70</td>
</tr>
<tr>
<td>REM</td>
<td>−15.0 ± 5.3</td>
<td>−16.2 ± 4.5</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*P < 0.01; **P < 0.005; ***P < 0.001.

PSG, polysomnography; REM, rapid eye movement; S2, stage 2 sleep.

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**Table 3** Arousal-related R–R interval characteristics during stage 2 and REM sleep divided by individual shortest and longest cortical arousals (co-varying for age)

<table>
<thead>
<tr>
<th></th>
<th>Shortest arousal</th>
<th>Longest arousal</th>
<th>F-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage 2</td>
<td>REM</td>
<td>Stage 2</td>
</tr>
<tr>
<td>Arousal onset (min)†</td>
<td>28.23 ± 36.2</td>
<td>149.93 ± 65.38</td>
<td>406.07 ± 62.5</td>
</tr>
<tr>
<td>Arousal duration (s)</td>
<td>3.21 ± 0.7</td>
<td>4.88 ± 1.1</td>
<td>10.67 ± 2.3</td>
</tr>
<tr>
<td>Prearousal R–R (ms)</td>
<td>738.85 ± 106.4</td>
<td>732.64 ± 118.3</td>
<td>795.73 ± 123.9</td>
</tr>
<tr>
<td>ΔRR (%)</td>
<td>−16.23 ± 8.1</td>
<td>−16.51 ± 8.0</td>
<td>−21.12 ± 9.7</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.001.

REM, rapid eye movement.

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**Figure 2.** Arousal duration as a function of sleep time in stage 2 (left) and rapid eye movement (right) sleep. The x-axis represents time elapsed since sleep onset. Data are presented for the first polysomnogram only.

normalized within three breaths. Post hoc analysis showed that the respiratory rate was highest for the breath immediately following arousal compared with all other cycles, with the exception of the second breath following arousal (see Fig. 3). There were no sleep stage differences in respiratory rate for the three breath cycles immediately before or following arousal. These results remained unchanged after co-varying for child age.

Gender effects on polysomnography parameters and arousal-related heart rate characteristics

Males were older than females (8.77 ± 2.7 versus 6.99 ± 2.3 years, \( t_{38} = 2.25, P < 0.05 \)), but matched for BMI z-score (0.39 ± 0.5 versus 0.23 ± 1.0, \( t_{38} = 0.56, P > 0.05 \)). After co-varying for age there was no significant difference in arousal duration, prearousal baseline R–R, ARR or any other PSG measure between males and females.

Age effects on polysomnography parameters and arousal-related heart rate characteristics

To examine the effect of age on sleep variables and arousal-related heart rate characteristics, the study group was divided into three groups according to arbitrarily defined age ranges, which ensured adequate cell size: (i) 3–6.5 years (mean age = 4.92 ± 1.3 years, \( n = 14 \)); (ii) >6.5–9 years (mean age = 7.79 ± 0.7 years, \( n = 13 \)); and (iii) >9–12 years (mean age = 10.61 ± 1.2 years, \( n = 13 \)).

Children aged 3–6.5 years had a lower percentage of stage 2 sleep (42.1 ± 5.7 versus 48.3 ± 5.3, \( P < 0.05 \)), and fewer awakenings per hour of sleep (0.5 ± 0.5 versus 1.0 ± 0.4, \( P < 0.05 \)) compared with 9–12 year olds. Both 3–6.5-year-old and > 6.5–8-year-old children had a greater percentage of SWS compared with 9–12-year olds (33.7 ± 5.6, 33.5 ± 4.7, 28.3 ± 5.7, respectively, \( P < 0.05 \)). Children 3–6.5 years old had a greater percentage of REM sleep compared with > 6.5–8-year-old children (21.8 ± 4.1 versus 17.8 ± 4.1, \( P < 0.05 \)) and a greater rate of spontaneous arousals compared with > 6.5–8-year-old and 9–12-year-old children (12.0 ± 1.6, 8.8 ± 2.5 and 8.9 ± 2.4, respectively, \( P < 0.005 \)). No other age group differences were observed for the PSG-derived sleep parameters.

Arousal duration was not significantly correlated with age. The prearousal baseline R–R interval was significantly associated with age during both stage 2 (\( r = 0.65, P < 0.001 \)) and REM sleep (\( r = 0.69, P < 0.001 \); Fig. 4), but ARR showed no relationship to age in either sleep stage. In particular, children 3–6.5 years old were found to have a significantly smaller prearousal baseline R–R (i.e. faster heart rate) when compared with 9- to 12-year-olds during both stage 2 (742.0 ± 102.6 versus 844.1 ± 91.0, \( P < 0.05 \), Fig. 3) and REM sleep (703.0 ± 90.2 versus 789.6 ± 62.1, \( P < 0.05 \), Fig. 5). No other age-related differences were found with respect to arousal-related heart rate characteristics.

DISCUSSION

This is the first study to extensively investigate the heart rate and ventilatory responses associated with spontaneous cortical arousals during sleep in healthy children. Our major findings are: (i) the baseline prearousal heart rate, but not the magnitude in arousal response (ΔRR), decreases with age; (ii) the prearousal baseline heart rate, but not the magnitude of arousal response (ΔRR), is higher during REM compared with stage 2 sleep; (iii) there are no significant gender differences in heart rate response associated with arousals in preadolescent children; (iv) the changes in R–R interval typically precede the cortical arousal by about 3 s; (v) breathing rate increases immediately after cortical arousal.

Heart rate pattern during arousal

Spontaneous arousals in children were typically associated with a biphasic increase/decrease in heart rate of approximately 10 s duration, similar to that reported in adults (Sforza et al., 2000) and consistent with one brief report for healthy children of similar age (O’Driscoll et al., 2008). Individual arousal heart rate patterns, however, varied substantially with each single arousal event. This might be due to superimposed regulatory processes such as respiratory sinus arrhythmia or cardiac baroreflex response. In healthy adults and patients with obstructive sleep apnoea it has been demonstrated that, while the majority of arousals are associated with an R–R shortening, a smaller number of arousals may coincide with R–R prolongations (Nalivaiko et al., 2007). Due to the expected high inter-individual variation, we restricted our analysis to the hallmarks of arousal-related heart rate responses: the prearousal baseline R–R interval and the magnitude of R–R interval change, i.e. the shortest R–R interval following baseline activity.
Effect of sleep stage

The prearousal baseline heart rate was significantly higher during REM sleep compared with stage 2 sleep. This finding is well known in adults and has been associated with increased sympathetic activity during REM sleep. Intraneural recordings of efferent sympathetic nerve activity in the peroneal nerve of healthy adults during different sleep stages showed an increased amplitude and frequency of bursts during REM sleep. This increase of neural outflow to skeletal muscle may be paralleled by increased outflow to sympathetic terminals at the heart (Somers et al., 1993).

The relative arousal-related increase in heart rate during REM sleep was not different to that observed in stage 2 sleep, despite the fact that arousals were significantly longer in REM sleep. This finding supports the view that the increased cardiac activity seen during arousal is due to reflex activation of the cardiorespiratory system (Trinder et al., 2001a, 2006).

The neural mechanisms involved in cardiac arousal activation are not fully understood. The rapid increase in heart rate appears to be predominantly mediated by vagal efferents (Horner, 2003). Besides vagal withdrawal, sympathetic activation might contribute to this increase in heart rate. A study investigating the peroneal nerve traffic after auditory-induced arousal during non-REM sleep in healthy volunteers found a burst in sympathetic activity 2 s after stimulus, lasting 2–3 s (Morgan et al., 1996). Further, the QT interval of the ECG has shown to shorten immediately after arousal, suggesting increased sympathetic outflow to the myocardium (Nalivaiko et al., 2007; Smith et al., 2009).

Figure 5. Averaged (± SEM) R–R interval characteristics for stage 2 (left) and rapid eye movement (right) sleep during the first polysomnogram for three age groups.

**Heart rate and respiratory response to arousals in children**

Onset of arousal response

Due to notable variations among arousal heart rate responses, we were not able to quantify the onset of each single arousal response. Instead the group-averaged heart rate arousal response was assessed. CUSUM analysis revealed that the average heart rate changes precede the onset of EEG changes arousal by at least 3 s. Our finding that arousal-associated heart rate accelerations precede cortical activation is in line with observations in adults, where heart rate changes have been found to precede the cortical arousal onset. Sforza et al. (2004) described a slight rise in heart rate at the second and first beat before the onset of the cortical arousal, supporting the hypothesis of a hierarchical arousal response, where subcortical areas involving autonomic control are activated before cortical regions.

Gender effects

In our study, we did not find differences in arousal-related heart rate characteristics between boys and girls. This is in contrast to adults, where prearousal baseline heart rate has been found to be increased in females compared with males (Agelink et al., 2001; Bonnemeier et al., 2003; Nalivaiko et al., 2007). Gender differences may emerge following pubertal development.

Effect of age

With increasing age the baseline heart rate reduced, which is a common observation (Silvetti et al., 2001). In contrast, the magnitude of arousal-related heart rate increase (ARR) showed no significant age dependence. Although subgroup analysis showed significant differences in sleep architecture between three age groups, the magnitude of heart rate arousal response was unaffected. Overall heart rate variability in children has found to increase with age, which has been explained as ‘maturation’ of the autonomic nervous system (Kazuma et al., 2002). In adults, overall heart rate variability was found to reduce with age, indicating a loss of autonomic cardiac control (Umetani et al., 1998).

Effect of arousal duration

The duration of spontaneous arousals increased with the progress of sleep for both stage 2 and REM sleep (Fig. 2), possibly indicating a loss in sleep drive. During stage 2 sleep, both the prearousal baseline R–R interval and magnitude of R–R arousal response was greater for longest arousal compared with shortest arousal. Because the longest arousal occurred later at night than the shortest arousal, the increase in prearousal baseline R–R might be the result of a circadian variation in vagal tone. In adults, heart rate was found to fall asymptotically during the night, and has been interpreted as the result of an increase of vagal tone with the progress of sleep (Trinder et al., 2001a). In view of this, the heart rate arousal response – more pronounced later at night – might be an effect of the increased absolute vagal tone, which results in a relatively stronger heart rate response to withdrawal. During REM sleep, the prearousal baseline R–R interval was similar for short and long arousals, although the time of onset was significantly different. This might be due to a relatively lower vagal influence on heart rate during REM compared with stage 2 sleep.

An important limitation of our comparison between shortest and longest arousals is imposed by the scoring criteria. Spontaneous arousals last per definition between 3 and 15 s, making the classifications ‘shortest’ and ‘longest’ potentially redundant. From our data we can only speculate to which degree cortical indicators of arousal that do not fulfil these criteria are associated with heart rate changes.

Respiratory rate response to arousal

As shown in adults, respiratory rate significantly increased for a brief period following arousal before returning to baseline. Typically this increase in adults is maximal at the second breath following arousal (Khoo et al., 1996; O’Driscoll et al., 2004, 2005). However, the children in our study demonstrated the maximal response at the first breath following arousal with a return to baseline levels by the third breath postarousal. Interestingly, while the patterns of respiratory rate change before and after arousal were similar between sleep stages, the effects were only significant during stage 2 sleep and not REM sleep. To our knowledge sleep stage effects have not been reported previously in children or adults. The results may reflect a blunted neuromuscular response during REM sleep (Wellman et al., 2004); however, this is yet to be confirmed. Differences in arousal response may also be apparent among children with specific sleep disorders, as has been suggested for adults (O’Driscoll et al., 2004), which in turn may be attenuated in specific sleep stages.

Heart rate as a marker of autonomic arousals

In contrast to adults where disruptions from sleep are usually accompanied by cortical arousals, EEG changes are poor markers of sleep disturbance in children (Lopes and Marcus, 2007). Given the hierarchical nature of arousals, measures assessing the activation of the autonomic nervous system have been suggested to be more sensitive to sleep disturbance in children (Tauman et al., 2004). Heart rate pattern analysis might provide such an autonomic marker. It can be easily derived from body surface ECG, and there is some evidence suggesting that heart rate analysis is suited to detect autonomic arousals: auditory stimulation during sleep results in a heart rate increase that is not necessarily associated with EEG arousals in the alpha band. However, if the stimulus is strong enough to cause a cortical arousal, the heart rate response is pronounced (Guilleminault et al., 2006). In a different study of adults, tachycardia–bradycardia heart rate patterns typical of arousal
have been found to occur more frequently during stage 2 sleep than cortical arousals, whereas the magnitude of the bouts was bigger when associated with a cortical arousal (Togo et al., 2006). Our data indicate that cortical arousals are preceded by marked heart rate bouts, reflecting autonomic cardiac activation, and screening for these bouts may better quantify sleep disruption in children.

CONCLUSION

Cortical arousals in healthy children are associated with significant heart rate accelerations, which typically precede arousal onset by several seconds. These accelerations appear independent of age and gender in preadolescent children. Analysis of heart rate pattern may provide a more sensitive measure of sleep fragmentation in children than traditional EEG-based scoring of cortical arousals.

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