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Arousal and upper airway resistance (UAR)

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Abstract

Objective: The objective of this study is to investigate upper airway resistance (UAR) in infants and children and presence/absence of electroencephalogram (EEG) arousal.

Methods: Polysomnography with nasal cannula/pressure transducer and esophageal manometry; pattern recognition of sleep disordered breathing (SDB) in children. Identification of visually scored arousals in response to SDB. Power spectrum analysis of EEG associated with SDB.

Results: Several breathing patterns and change in heart rate (HR) can be seen with abnormal UAR during sleep. SDB may end with or without visual arousal. Power spectrum analysis shows different EEG patterns with termination of UAR and SDB. HR is also variably modified.

Conclusions: Airway reopening and decline in UAR is associated with variable central nervous system activation and only intermittently with arousals.

Keywords: Upper airway resistance; Children; Heart rate; Visual electroencephalogram arousal; Power spectrum; Central nervous system activation

1. Introduction

Airway resistance is a function of the rate of airflow, type of flow (i.e. turbulent or laminar), airway caliber, and the composition of the gas breathed. The amount of airflow resistance through an airway can be calculated by a formula that includes flow per unit time and the pressure difference between the ends of the airway. The units for resistance are cm H_2O/l/s.

The upper airway presents many irregularities and narrowings, which make the flow turbulent and the resistance relatively high. Airway resistance is difficult to measure, particularly during sleep. Pneumotachograph with facemask and esophageal pressure are needed to measure the flow and pressures involved in the airflow resistance formula. Although this equipment disturbs sleep, habituation enables the eventual monitoring of sleep states.

Upper airway resistance (UAR) during sleep has been measured in children and adults on a research basis [1–4]. Results show that some subjects presented 'resistive breathing' during sleep. UAR in these subjects was higher than the resistance noted in control subjects [1–5].

Associations were found between UAR and snoring, and abnormal increase in UAR and arousals, based on visual analysis of central electroencephalograph (EEG) leads. In older children, 'arousal' was defined by alpha/beta rhythms, with or without an electromyograhic (EMG) burst, lasting for a defined unit time. In younger children (from 3 to 24 months), an arousal was defined by faster frequency and lower amplitude of EEG than those associated with sleep (7–12 Hz and beta frequencies), which were often present with EMG burst [1–5].

The technical difficulties associated with measuring increased UAR during sleep, has led to a simpler recording approach. Nasal cannula/pressure transducer system and mouth thermistor to measure mouth flow has been used. Nasal cannula/pressure transducer allows a semi-quantitative determination of nasal flow decrease [6,7]. The measurement of esophageal pressure (Pes) was added to this approach [8,9]. This simplified technology does not measure resistance. It only measures 'respiratory effort' with Pes and nasal flow limitation and does not distinguish between 'resistance' and 'collapsibility'. Several polysomnographic patterns have subsequently been reported.

2. Respiratory effort/flow limitation and sleep stages modulation

Nasal cannula/pressure transducer system demonstrates a clear bell-shaped curve with normal nasal flow. Inspiration and expiration times can be determined and correlated to peak end inspiratory Pes. Inspiratory and expiratory phases

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of a breath and their duration can be easily determined [5–9] during polysomnography.

Normal subjects were monitored during different sleep states. It has been shown that a modulation of respiratory effort was associated with changes in sleep stages [9] when subjects were kept in a standardized position (i.e. supine).

2.1. Methods

We studied 21 normal young children between 6 and 24 months and 40 children between 2 and 11 years. In both groups of subjects, a more negative inspiratory Pes was measured during slow wave sleep (SWS) compared to stages 1 and 2 non-rapid eye movement (NREM) sleep in the same cycle. Children also showed a less negative peak end inspiratory Pes during tonic REM sleep compared to stages 1 and 2 NREM sleep.

These analyses were performed with visual scoring and the simultaneous usage of a computerized system developed in collaboration with the Stanford University Computer Science Department. Breaths with artifacts, based on visual analysis, were deleted prior to usage of the computerized program. The Pes calibration was performed both prior to and after each recording. All the results showed a similar pattern, independent of the subjects' age.

2.2. Results

The computerized program indicated a mean Pes variation of 0.5 ± 0.5 cm H_2O during tonic REM sleep and 1 ± 0.7 cm H_2O during SWS compared to the mean Pes during stage 2 NREM sleep. The mean breath duration was 3.49 ± 0.41 s during stage 2 sleep and 3.17 ± 0.16 s in tonic REM sleep. The respiratory frequency in tonic REM sleep was a mean of 1.8 breaths/min higher than in stage 2 NREM sleep, which had a mean breathing frequency of 17 breaths/min. In addition, during REM, there was decreased respiratory effort and decreased amplitude of the nasal cannula pressure transducer bell-shaped curve amplitude without flattening. Oxygen saturation measured with pulse-oximetry (Nelcor Inc., Alameda, CA, USA; taken as an approximate index of minute ventilation) was stable at greater than 99.5% during all measurements.

These data demonstrate modulation of respiratory effort with sleep stages. This modulation is not reflected in the shape of the nasal cannula/pressure transducer recording. In this study, we see a decrease in nasal flow curve amplitude during tonic REM sleep, simultaneous with a decrease Pes amplitude from end expiration to peak inspiration.

The simultaneous investigation of EEG central leads does not indicate abrupt EEG frequency changes in association with the sleep stage modulation of effort.

In summary, breathing modulation is associated with a more negative peak end inspiratory Pes during SWS and less negative peak end inspiratory Pes during REM sleep compared to stage 2 NREM sleep. This Pes curve change is not reflected in the nasal cannula curve bell shape but is reflected in the shorter breath duration during tonic REM sleep.

3. Abnormal breathing during sleep

3.1. Pes patterns

Studies have been performed on infants, toddlers, and prepubertal children with signs and symptoms of sleep disordered breathing (SDB) [3–5]. Several patterns have been described. Patterns called 'Pes crescendo' and 'continuous sustained efforts' have been defined. They have been investigated in normal as well as SDB children. Pes crescendo is a sequence of at least four breaths with successively more negative peak end inspiratory pressure. A 'Pes crescendo' [8] ends with a 'Pes reversal' [8,9], which is defined as an abrupt decrease in respiratory effort and less negative peak end inspiratory Pes. 'Continuous sustained effort' [9] is defined by the presence of several successive breaths of abnormal peak end inspiratory Pes that do not become increasingly more negative. This pattern also ends with an abrupt Pes reversal. Both patterns indicate the presence of increased respiratory effort.

3.2. Nasal cannula/pressure transducer patterns

Studies demonstrate several associations between the above-described patterns and the shape of the nasal cannula/pressure transducer curve. With these Pes patterns, the nasal cannula curve may decrease in amplitude by 50% or more. Simultaneous flattening of the curve demonstrates flow limitation and partial collapse of the upper airway. SaO_2 may remain unchanged or drop from 1 to 3%. This pattern is called 'hypopnea', and is commonly associated with mouth breathing as indicated by the mouth thermistor.

The shape of the curve can be affected with a change in amplitude between 20 and 50%. With only moderate changes in nasal flow, changes in amplitude of nasal cannula curve are more difficult to visually assess, especially when the amplitude decreases by less than 20% and when there is a flattening pattern without much change in amplitude. This flattening pattern is similar to what is seen with facemask and pneumotachograph, which is associated with UAR without demonstration of airway collapse.

3.3. Dissociation between Pes and nasal cannula patterns

The Pes pattern of 'continuous sustained effort', is often associated with a flattening of the nasal cannula curve. Absence of 'flattening' is associated with an increased breathing frequency in NREM sleep and clear tachypnea in REM sleep. These patterns are also associated with UAR, without collapsibility, when subjects are studied with facemask and pneumotachograph. They are seen without clear visual changes in SaO_2.

All the above reported abnormal breathing patterns termi-

nate with either a Pes reversal and return to normal nasal cannula curve bell shape or a decrease in breathing frequency without Pes reversal (when tachypnea is present).

4. EEG analysis in association with reversal from SDB patterns during sleep

4.1. Method

Sleep recordings of ten 3–14-month-old infants and 15 2–11-year-old prepubertal children were analyzed. Five infants and five children without signs or symptoms of SDB were control subjects. The mean infant age was 6 ± 2 months, and the mean child age was 7.2 ± 2.5 years. All abnormal breathing patterns were determined and sleep EEG was monitored in the central leads.

All infants and children were monitored all night with a minimum of 9 h of time in bed. The following variables were systematically monitored: C_z/A_2, C_4/A_1, O_1/A_1, O_2/A_2, electrooculogram (EOG), child and leg EMG, ECG (modified V_2 leads), nasal cannula/pressure transducer, mouth thermistor, uncalibrated thoracic and abdominal inductive respiratory plethysmography bands, Pes, pulse-oximetry, neck microphone, intercostal EMG, and position sensor. All subjects were simultaneously video-monitored.

4.2. Analysis

Recordings were visually scored using the Rechschaffen and Kales criteria [10]. Short arousals were scored using the American Sleep Disorders Association criteria [11]. Respiratory event related arousals (RERAS) [12] and other abnormal breathing patterns were scored using the American Academy of Sleep Medicine recommendation [12]. EEG arousals were scored when there was an increased frequency of 7–12 Hz with or without presence of beta activity in central leads. Arousals were also scored with a burst of EMG activity with decrease in EEG amplitude and passage to faster frequency between 7 and 12 Hz with or without mixed beta activity.

Once all records had been visually scored for sleep stages and arousals, they were re-scored to identify presence of abnormal respiratory events and their end points, indicated by a Pes reversal and return to normal flow or by end of tachypnea. Once abnormal respiratory events and their endings had been defined, EEG arousals and ends of abnormal breathing events were visually checked. When there was no visually scored arousal associated with termination of a respiratory event, a new visual evaluation was performed with a description of the EEG pattern in the central lead.

Each identified abnormal breathing event was clearly marked on the computer and examined for artifacts in the EEG central leads to submit to spectrum analysis. Heart rate (HR) was also analyzed for each 4-s segment, from 30 s before to 30 s after abnormal respiratory event termination. The HR 30 s before the termination of the event was considered 'baseline' HR, and the percentage of HR change in each successive 4-s windows was calculated. An increase in HR was assigned a positive percentage; a decrease in HR, a negative percentage.

4.3. Results

In the ten SDB children, 54 abnormal breathing events were identified during a mean of 452 ± 24 min of total sleep time. Forty-eight occurred in NREM sleep. There were three abnormal breathing events scored in the five control subjects with only one in NREM sleep. Seventeen out of the 48 events in SDB subjects during NREM were scored without arousals of 3 s or longer; 31 events were scored with arousals. Only seven events were associated with arousals lasting longer than 15 s. The distribution of the events is presented in Table 1. HR increase was calculated based on the HR measured 30 s before the end of the event and after the Pes reversal.

Seven out of 17 events without EEG arousals were associated with a burst of delta wave. Two were associated with cessation of tachypnea, three were associated with the cessation of 'sustained effort', and two were associated with the cessation of 'Pes crescendos'.

Analysis of infants identified 36 abnormal breathing events during a mean of 468 ± 31 min of total sleep time. Twenty-eight were in NREM sleep. One was seen in a control infant during REM sleep, and all others were in the SDB infants. Twenty out of 28 NREM and 5/8 REM sleep events were scored with 'EEG arousal'. Nine events were associated with a burst of delta waves. Seven were not associated with an obvious EEG change on visual inspection.

Table 1
Analysis of 48 'non-apneic, non hypopneic' sleep disordered breathing events seen during NREM sleep

	n
(a) Termination of non-apneic, non-hypopneic SDB events	
With EEG arousal	31
Without EEG arousal	17
• with delta burst	7 *
• without visual EEG change	10 *
Total	48
(b) Type of non-apneic, non-hypopneic SDB events	
Tachypnea ($n = 6$)	
• ending with EEG arousal	2
• ending with delta burst	2
• ending without EEG change	2
Pes Crescendo ($n = 19$)	
• ending with EEG arousal	16
• ending with delta burst	2
• ending without EEG change	1
Continuous Sustained Effort ($n = 23$)	
• ending with EEG arousal	13
• ending with delta burst	3
• ending without EEG change	7
Total	48

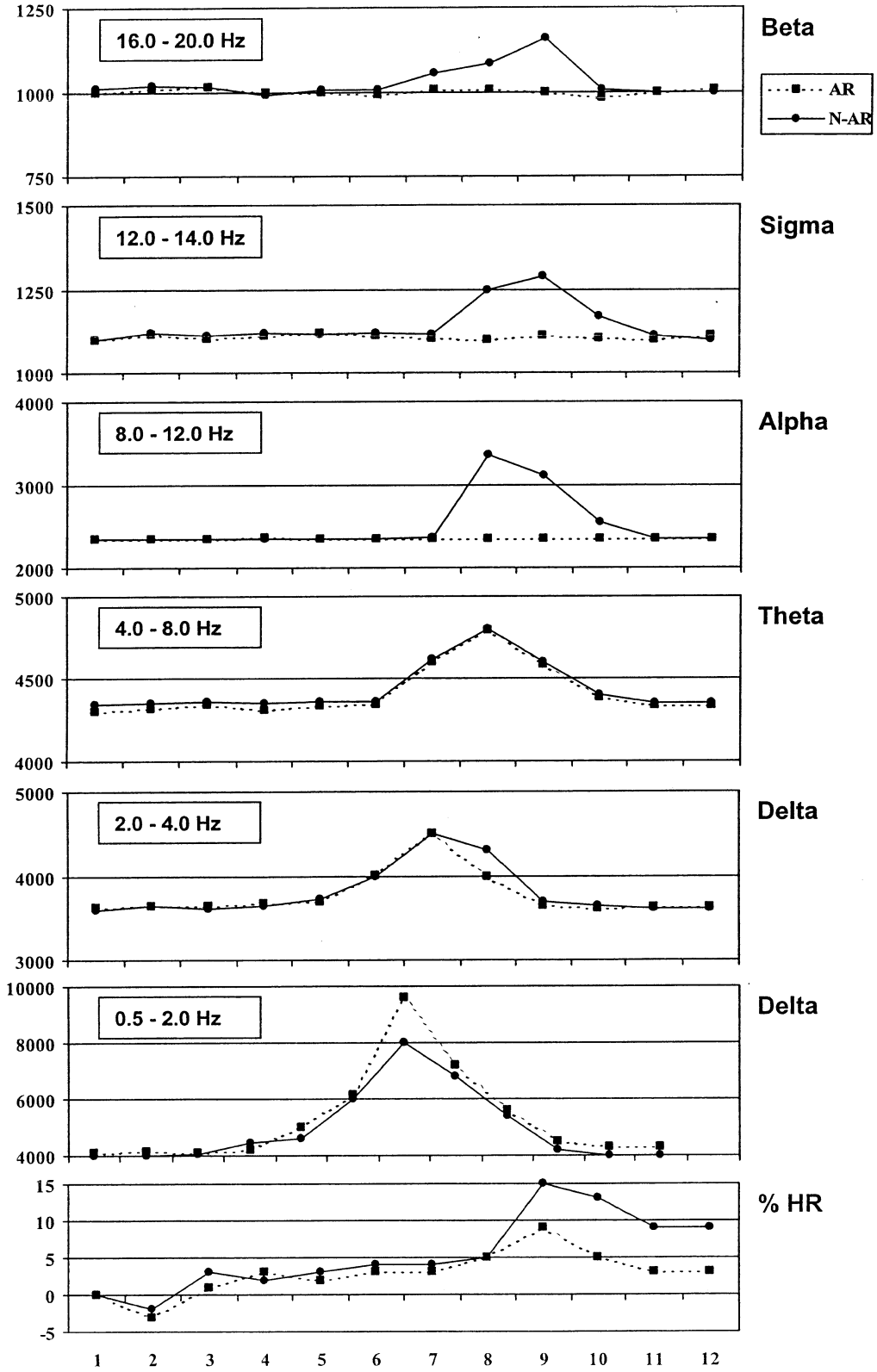

Fig. 1. Absolute power spectrum EEG analysis. Mean data obtained from abnormal breathing events during NREM sleep of 15 children are presented. EEG analysis was performed on 4-s windows. The central lead EEG data are the mean absolute power within each band (microV 2). The reopening of the airway is in the mid part of window 8. The lowest panel presents the mean percentage of HR change in each window compared to window 1. AR, arousal; N-AR, non-arousal.

All events from the children's group were then submitted to power spectrum analysis using a 4-s window from 30 s before to 30 s after event termination. Window 8 was selected to contain the termination of abnormal breathing event, indicated by Pes reversal [13], in its middle. When tachypnea was the marker, the middle of window 8 contained the peak end inspiratory Pes of the breath in which tachypnea ended (i.e. with longer duration).

The spectral analysis indicated an increase in delta power, which began in window 2 for all events, became statistically significant in window 5, and was maximal in window 7. (See Fig. 1.) There was a simultaneous increase in theta in window 6 that was significant in window 8, but only subjects with a visual arousal presented an increase in alpha and beta power that was statistically significant compared to window 1 in windows 8 and 9 with peak in window 9. There was a significant increase in delta power in windows 8 and 9 compared to window 1 which was noted for all subjects. HR increased in association with Pes changes. There was a HR increase, compared to window 1, in window 9 in all subjects (see Fig. 1). The increase was the smallest with tachypnea. The HR increase compared to window 1 was 15% in window 9 with a visual arousal, 7% with sustained effort, and 6% with tachypnea. The EEG analysis showed that breathing events may terminate without high theta alpha and beta EEG frequencies seen with arousal. Termination of breathing events were always associated with HR changes but of various proportions.

5. Discussion

Nasal cannula/pressure transducer systems with esophageal manometry allows the investigation of several abnormal breathing patterns during sleep.

An abnormally negative peak end inspiratory Pes can be seen with several successive breaths. This succession of breaths, with more important respiratory effort, and more important pleural pressure at end inspiration, may increase the shift of the interventricular cardiac septum, change the volumes of ventricles, and at times cause pulsus paradoxus [14].

Reopening of the airway at wakefulness and disappearance of abnormal UAR, are not necessarily associated with an arousal. Mono- and poly-synaptic reflexes are involved in the regulation of upper airway patency. Respiratory patterns that need correction activate the central nervous system (CNS). This activation varies, depending on the sensory recruitment and the adequacy of the response. The thalamus is the gate that filters information destined for the cortex to obtain a stronger and better-directed response to a specific challenge. Sleep is a cortical function that needs protection, as lack of sleep has negative behavioral and cognitive consequences. A respiratory challenge is usually resolved by CNS activation without cortical arousal as demonstrated by change in EEG pattern. Arousal should be only triggered when sub-thalamic structures involved in the modulation of breathing have failed.

EEG arousal leads to a more important and focused response. The respiratory and cardio-vascular system continuously interact, and the CNS structures must be informed to cause adjustments by appropriate organs. The Nucleus Tractus Solitarius (NTS) is one of the locations where coordination occurs for an integrated response with change in HR. The autonomic nervous system (ANS) response is enhanced when an arousal occurs, which explains the greater increase in HR with EEG arousal than without EEG arousal. Depending on the amount of recruitment and numbers of sub-thalamic structures involved, the CNS activation will be variable, but the NTS is always stimulated and HR change is seen independent of resolution of the problem. But HR is always a limited indicator of CNS activation. It is difficult to dissociate the responses that are secondary to stimulation to the thalamus and those that cause cortical activation, based on HR analysis. In addition, HR increase triggers changes in stroke volume, baro-receptors stimulation, and other reflex adjustments. These responses explain the poor correlation between analysis of HR and arousal and the limited sensitivity and specificity of technique such as pulse-transit time in recognizing arousals [15].

The possibility of limiting the activation of the CNS at the brain stem and resolving the challenge without involving the cortex will protect sleep.

Coordination of different organs responses to a challenge requires continuous reflex integration: lung inflation for example impacts muscle nerve sympathetic activity, blood pressure, HR, and splanchnic circulation. To base the notion of 'arousal' on investigation of one autonomic effector such as HR is obviously a very simplistic view that does not allow distinction of 'activation' from 'arousal' and does not take into consideration the adjustments that request only brain-stem reflexes.

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