Cortical Processing of Respiratory Afferent Stimuli during Sleep in Children with the Obstructive Sleep Apnea Syndrome

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Study Objectives: Children with the obstructive sleep apnea syndrome (OSAS) have blunted upper airway responses to negative pressure, but the underlying cause remains unknown. Cortical processing of respiratory afferent information can be tested by measuring respiratory-related evoked potentials (RREPs). We hypothesized that children with OSAS have blunted RREP responses compared to normal children during sleep.

Design: During sleep, RREPs were obtained from EEG electrodes Fz, Cz, Pz during stage 2 sleep, slow wave sleep (SWS), and REM sleep. RREPs were produced with multiple short occlusions of the upper airway.

Setting: Sleep laboratory.

Participants: 9 children with OSAS and 12 normal controls.

Measurements and Results: Children with OSAS had significantly decreased evoked K-complex production in stage 2 sleep and slow wave sleep and significantly reduced RREP N350 and P900 components in slow wave sleep. There were no significant differences in any of the measured RREP components in stage 2 sleep, and the only REM difference was decreased P2 amplitude.

Conclusions: Results indicate that in children with OSAS, cortical processing of respiratory-related information measured with RREPs persists throughout sleep; however, RREPs during SWS are blunted compared to those seen in control children. Possible causes for this difference include a congenital deficit in neural processing reflective of a predisposition to develop OSAS, or changes in the upper airway rendering the airway less capable of transducing pressure changes following occlusion. Further research is required to evaluate RREPs after effective surgical treatment of OSAS in children, in order to distinguish between these alternatives.

Keywords: RREPs, children, obstructive sleep apnea syndrome

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A COMBINATION OF STRUCTURAL AND NEUROMUSCULAR CONTROL FACTORS CONTRIBUTE TO THE PATHOGENESIS OF CHILDHOOD OBSTRUCTIVE SLEEP APNEA syndrome (OSAS).[1-6] However, the cause of the neuromuscular abnormalities is not well understood. Previous work has shown that, compared to normal controls, children with OSAS have selectively elevated arousal thresholds to respiratory stimuli, such as mechanical and hypercapnic stimuli.[7,8] Children with OSAS also have impaired upper airway reflex responses to subatmospheric pressure during sleep.[1] On the other hand, children with OSAS have normal arousal thresholds to nonrespiratory (e.g., auditory) stimuli.[9] The underlying causes of the altered arousal and upper airway responses to respiratory stimuli in OSAS remain unknown. It is also not known whether these altered responses reflect a cause or effect of the OSAS phenomenology. It is possible that, compared to normal controls, children with OSAS have altered afferent processing of mechanoreceptor responses in the upper airway to the negative pressure generated by breathing against occlusions. Such alterations in processing may be secondary to anatomic differences in the physical properties of upper airway tissue affecting their ability to transduce pressure changes into afferent neural signals. Alternatively, they may reflect alterations in the central processing of the afferent information.

Respiratory related evoked potentials (RREPs) are one way to measure the central nervous system processing of respiratory afferent information.[10-12] RREPs are the averaged surface EEG responses to multiple brief occlusions or loads applied during inspiration.[10,11] During wakefulness, a series of early components is evident in the RREPs, reflecting initial sensory and motor processing[13,14] and a subsequent series of late components reflecting cognitive processing of the stimuli.[15,16] During Non-REM (NREM) sleep, a different series of later components is produced that reflect the elicitation of phasic EEG responses (such as vertex sharp waves and K-complexes) to stimuli.[17-19] Stimuli relating to increases in inspiratory effort reliably induce RREPs,[20] which in turn provide a unique way to investigate the afferent processing pathway for respiratory load mechanoreception during both wakefulness and sleep.[17,21] We have recently demonstrated that inspiratory occlusions reliably produce RREPs in children in stage 2, SWS, and REM sleep.[22] While similar to the sleep RREPs previously reported in adults, the predominant late component in children was the N350 waveform rather than the N550, and the scalp topography of the components was more broadly distributed than typically seen in adults.

Compared to normal adults, adults with OSAS have fewer K-complexes evoked by inspiratory occlusion stimuli during

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NREM sleep,[23,24] with no difference in K-complex responses to auditory stimuli.[24] They also have blunted RREPs during NREM sleep, manifested by a significantly decreased late RREP component N550, which is a reflection of the evoked K-complex in adults.[25] However, nothing is known about RREPs in children with OSAS. Compared to adults with OSAS, children with OSAS have a shorter duration of disease and fewer comorbidities, such as chronic obstructive pulmonary disease, and are often effectively treated with surgery to remove tonsils and adenoids.[26] Thus the pathophysiology of OSAS in children is likely different from that in adults. Based on previous work showing altered arousal thresholds to respiratory stimuli in children with OSAS,[7,8] we hypothesized that children with OSAS would have fewer evoked K-complexes and blunted RREP responses compared to normal children during sleep.

METHODS

Nine subjects with OSAS and 12 controls of similar ages were studied. RREPs were obtained from the surface EEG during stage 2, slow wave sleep (SWS), and REM sleep.

The Institutional Review Board at the Children's Hospital of Philadelphia approved the study. Informed consent was obtained from the parents/legal guardians of the subjects, and assent from subjects older than 7 years of age.

Study Group

(1) Patients with OSAS: Subjects with OSAS were recruited from those referred to the Sleep Center at the Children's Hospital of Philadelphia. Subjects were eligible for this study if they were 5-12 years of age, had no previous upper airway surgery, had no lower respiratory tract diseases except for mild to moderate asthma, and had no significant medical conditions (such as craniofacial anomalies or neuromuscular disease) other than OSAS. The upper age limit was chosen to limit the study to primarily prepubertal or early pubertal children,[27] and the lower age limit to exclude those who were too young to cooperate with the face mask and other aspects of the protocol.

(2) Normal controls: Controls were 5-12 years of age, healthy, non-obese individuals recruited from the general population by means of advertisements. They were all non-snorers, with a negative history for sleep disordered breathing and a negative Brouillette questionnaire for symptoms of OSAS.[28] Patient and control groups were age- and gender-matched on a group-wise basis.

Baseline Polysomnography

All the patients with OSAS, as well as the first four controls, had a baseline polysomnogram (sleep study) to characterize the degree of OSAS. The remaining controls were evaluated during the RREP study night. During the study, a Rembrandt polysomnography system (Embla, Broomfield, CO) recorded the following parameters: EEG (C3/A2, C4/A1, O1/A2, O2/A1); left and right electrooculogram; submental electromyogram; tibial electromyogram; electrocardiogram; oronasal airflow with a 3-pronged thermistor (Pro-Tech Services, Inc., Mukilteo, WA); nasal pressure with a pressure transducer (Pro-Tech Services, Inc., Mukilteo, WA); rib cage and abdominal wall motion using respiratory inductance plethysmography (Viasys Healthcare, Yorba Linda, CA), end-tidal CO_2 (Novametrix Medical Systems, Inc., Wallingford, CT) and arterial oxygen saturation (SpO_2) with pulse waveform (Masimo, Irvine, CA). Subjects were also recorded on digital video. Sleep architecture, respiratory events, and arousals were scored using standard criteria.[29-32] To limit overlap between groups, subjects with OSAS were included only if their apnea hypopnea index (AHI) was ≥5/hr, and controls were included only if their AHI was <1.5/hr.[33-36]

RREP Study

RREPs were obtained during sleep on a separate night using the methods mentioned above, with the following exceptions: EEG was recorded from 3 additional electrodes: Fz, Cz, and Pz. Subjects wore a full face mask connected to a nonrebreathing balloon valve (Hans Rudolph, Inc., Kansas City, MO). The valve was then connected to a continuous positive airway pressure machine. A bias flow with a pressure of 2 cm H_2O was provided to account for the resistance within the circuit and to wash out CO_2 within the mask. Flow was measured using a pneumotachometer (Hans Rudolph, Inc., Kansas City, MO) with a differential pressure transducer (ADInstruments, Colorado Springs, CO) connected to the full face mask. Pressure within the mask was measured using a pressure transducer with a demodulator (Validyne Engineering Corp., Northridge, CA). To reduce leak from the mask, transcutaneous CO_2 was monitored rather than end-tidal CO_2. Transcutaneous CO_2 was calibrated with end-tidal CO_2 before subjects went to sleep. All the subjects wore earplugs to avoid any possibility of being aroused by low level sound associated with the balloon valve closure.

For controls who did not have a baseline polysomnogram, RREPs were obtained using the same method for those who had a baseline sleep study. Their respiration was monitored between occlusions during the RREP sleep study to ensure that they did not have OSAS.

During stage 2, SWS, and REM sleep, multiple (200-400) 400 ms inspiratory occlusions were performed as interruptions of inspiration. Occlusions were separated by ≥2 normal breaths. For OSAS patients, occlusions were triggered only when there were no obstructive events.

Data from the Rembrandt system were converted into European Data Format (EDF) and then read into Scan 4.3 software (Compumedics NeuroScan, El Paso, TX). EEG activity was referenced to A1+A2, band pass filtered (0.3-30 Hz), epoched (500 ms before to 1500 ms after the initiation of each occlusion) and averaged for stage 2 sleep, SWS, and REM sleep, respectively. Occlusions with EEG artifacts and mask leak were excluded. RREPs were then calculated at Fz, Cz, and Pz, for each of stage 2, SWS, and REM sleep. P2, N350, N550, and P900 components were defined as follows: P2 was the maximum positive deflection between 160 and 310 ms; N350 the maximum negative deflection between 310 and 460 ms; N550 the maximum negative deflection between 460 and 810 ms; and P900 the maximum positive deflection between 660 and 1160 ms. The response to each stimulus was evaluated to determine whether or not a K-complex occurred as a response. K-complexes were defined using Rechtschaffen and Kales criteria as "EEG wave forms having a well delineated negative sharp

Table 1—Demographic and Polysomnographic Data of Subjects with OSAS and Controls. Medians (range) are Presented for Age, Body Mass Index, Arousal Index, Apnea Hypopnea Index, and O_2 Saturation Nadir

	OSAS	Controls	P Value
N	9	12	
Age (yr)	9 (5-11)	8 (5-10)	NS
Male, N (%)	6 (67%)	8 (67%)	NS
Race			NS
African American	9 (100%)	9 (75%)	
Multiracial		3 (25%)	
Body mass index (Z-score)	2.18 (0.79-2.74)	1.13 (-0.35 - 1.71)	0.002
Arousal Index (N/hr)	18.9 (9-33)	9.7 (8-34)	NS
Apnea hypopnea index (N/hr)	6.3 (5-57)	0 (0-0)	0.001
O_2 saturation nadir (%)	87 (74-91)	95 (92-99)	0.003

wave which is immediately followed by a positive component. The total duration of the complex should exceed 0.5 s."[29]

Statistical Analysis

Nonparametric methods were used to compare data relating to subject characteristics and K-complex proportions, as most of these data were not normally distributed. Age, BMI Z-score, arousal index, apnea hypopnea index, and oxygen saturation nadir were expressed as median and range. Differences were compared between groups using the Mann-Whitney rank sum test. Gender distribution in the 2 groups was compared using the chi square test.

Stimulus intensity was measured as the mean peak difference in mask pressure shown in response to the occlusions used to elicit EEG responses. Data were subjected to two-way ANOVA with sleep state (stage 2, SWS, REM) as a repeated factor and diagnosis (OSAS and control) as a between groups factor.

RREP peak amplitudes and latencies were analyzed with an electrode site (Fz, Cz, Pz) × diagnosis (OSAS, control) analysis of variance (ANOVA). In each analysis the site factor was tested for sphericity with Mauchly's test, and where significant, Greenhouse-Geisser corrections were applied to the degrees of freedom used in the analysis, and probabilities reported accordingly. Planned contrasts were used to compare each of the Fz and Pz values to those from Cz (typically the site of most prominence).

Effects were considered significant using an alpha criterion of $P = 0.05$.

RESULTS

Study Population

Subject characteristics are shown in Table 1.

Stimulus Intensity

The magnitude of the pressure change elicited by occlusions did not vary as a function of diagnosis or sleep stage. The pressure differences for the OSAS patients were 1.5 ± 0.57 cm H_2O for stage 2; 1.4 ± 0.53 cm H_2O for SWS; and 1.9 ± 0.79 cm H_2O for REM sleep. The control subjects had pressure differences of 0.8 ± 2.8 cm H_2O for stage 2 sleep; 2.4 ± 1.7 cm H_2O for SWS; and 2.1 ± 1.5 cm H_2O for REM sleep.

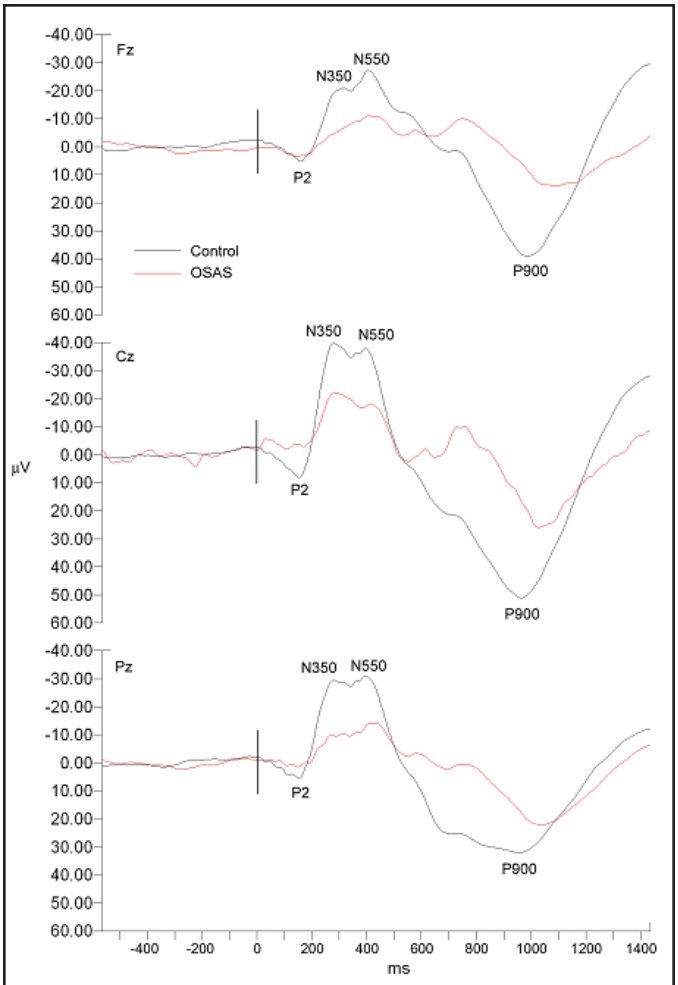

Figure 1—Grand mean RREP waveforms for controls (black lines) and OSAS patients (red lines) during slow wave sleep are shown for Fz, Cz, and Pz leads. The vertical bar represents the time of the occlusion. N350 and P900 were significantly smaller in OSAS than controls ($P < 0.01$ for each). There was a trend for a smaller N550 in OSAS ($P = 0.059$).

K-complex proportions

In stage 2 sleep, K-complexes were produced by 15.3% ± 11.5% of stimuli in control subjects (range of 4% to 44%), and 6.9% ± 11.5% of stimuli in OSAS patients (range of 0% in two subjects to 35%) ($P < 0.01$, with Mann-Whitney rank sum test). A similar pattern of results was seen for SWS, with the control subjects having K-complexes produced in response to 19.2% ± 11.3% of stimuli (range of 7% to 40%) as compared with 6.5% ± 8.2% for OSAS patients (range of 1% to 27%) ($P < 0.01$). As would be expected, K-complexes were rarely seen in REM sleep (<3% of stimuli overall) and group differences were not evaluated.

Given the large effect of diagnosis, a multiple regression model was assessed to determine the extent to which markers of

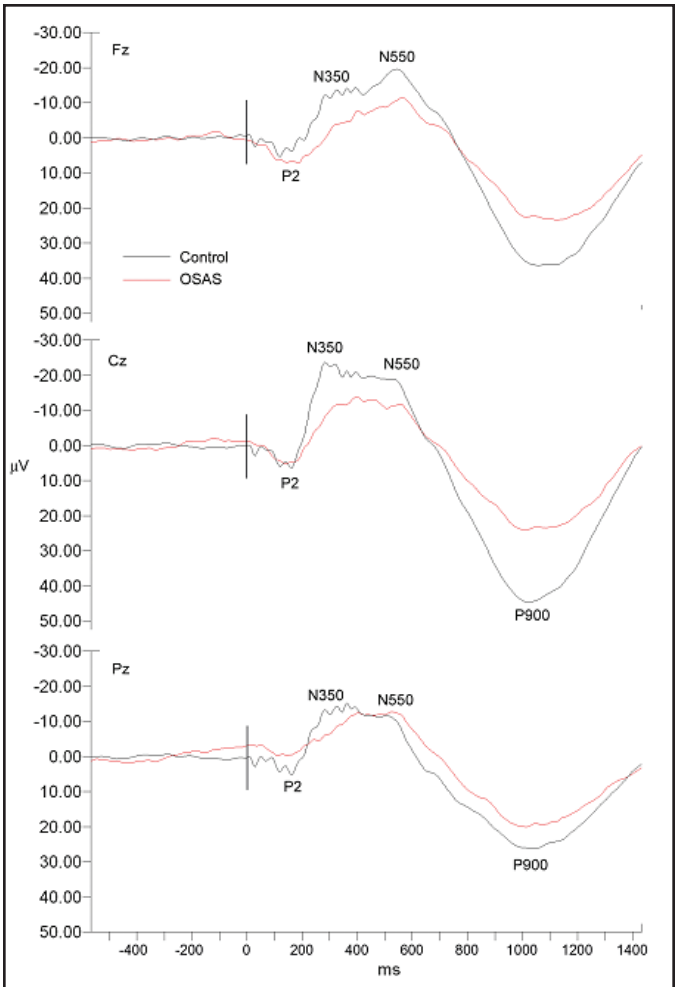

Figure 2—Grand mean RREP waveforms for controls (black lines) and OSAS patients (red lines) during stage 2 sleep are shown for Fz, Cz, and Pz leads. The vertical bar represents the time of the occlusion. Note the reduced scale relative to Figure 1.

disease severity (BMI z-score, AHI, arousal index, and oxygen saturation nadir) predicted the K-complex proportion in each of stage 2 and SWS. The linear regression model accounted for 34.7% of the variance in stage 2 sleep and 34.2% of the variance in SWS. Neither model was significant.

SWS (Figure 1 and Table 2)

Neither P2 amplitude nor latency displayed any effects of diagnosis or electrode site. N350 displayed a significant effect of diagnosis, with OSAS values being significantly smaller than those of controls ($F_{1,19}$ = 13.97, P < 0.001). There was also a significant effect of electrode site ($F_{2,38}$ = 7.58, P < 0.01), and amplitudes at Fz ($F_{1,19}$ = 11.6, P < 0.01) and Pz ($F_{1,19}$ = 10.6, P < 0.01) were significantly smaller than at Cz. There was no significant site × diagnosis interaction effect. N350 latency was not impacted by diagnosis or electrode site.

There was a trend for N550 amplitude to be smaller in OSAS patients ($F_{1,19}$ = 4.1, P = 0.059) but no effect of electrode site. There was also a trend for N550 to be later in OSAS patients ($F_{1,19}$ = 3.5, P = 0.076), with latency displaying a significant effect of site ($F_{2,38}$ = 3.7, P < 0.05), and Cz latencies being longer than those at Fz ($F_{1,19}$ = 4.9, P < 0.05).

P900 amplitude was significantly smaller in OSAS patients than controls ($F_{1,19}$ = 10.5, P < 0.01), and displayed a significant site effect ($F_{2,38}$ = 4.8, P < 0.05), with Cz values significantly larger than those at Fz ($F_{1,19}$ = 13.8, P < 0.01). P900 was significantly later in OSAS patients ($F_{1,19}$ = 5.6, P < 0.05), with a significant overall effect of site ($F_{2,38}$ = 4.0, P < 0.05).

Stage 2 Sleep (Figure 2 and Table 3)

In stage 2 sleep, P2 amplitudes did not differ with diagnosis and there was no significant diagnosis × site interaction effect. There was a significant main effect of electrode site ($F_{2,36}$ = 4.5, P < 0.05), with values at Cz being similar to those at Fz but larger than those at Pz ($F_{1,18}$ = 7.5, P < 0.05). P2 latency displayed no significant effects in the ANOVA model.

N350 amplitudes for stage 2 sleep displayed a trend for OSAS values to be smaller than those of controls ($F_{1,18}$ = 3.75, P = 0.069). There was, however, a significant effect of electrode site ($F_{2,36}$ = 9.39, P = 0.001), with amplitudes at Fz ($F_{1,18}$ = 20.85, P < 0.001) and Pz ($F_{1,19}$ = 9.31, P < 0.01) being significantly smaller than at Cz. The site × diagnosis interaction effect was not significant. N350 latency displayed no significant effects.

N550 amplitude did not differ significantly between OSAS patients and controls and did not display an overall effect of electrode site; however, Cz values were significantly larger than those at Pz ($F_{1,17}$ = 4.6, P < 0.05). N550 latency did not differ between groups, but did show an overall effect of electrode site ($F_{2,34}$ = 3.5, P < 0.05).

P900 amplitude displayed a trend to be smaller in the OSAS patients ($F_{1,18}$ = 3.2, P = 0.09), with no effect of electrode site. There were no significant group or site effects for P900 latency.

REM Sleep (Figure 3 and Table 4)

P2 amplitude was significantly smaller in OSAS patients than controls ($F_{1,18}$ = 7.1, P < 0.05). There was a significant effect of electrode site ($F_{2,36}$ = 4.1, P < 0.05), with Cz values similar to Fz but larger than Pz ($F_{1,18}$ = 7.5, P < 0.05). P2 latency in REM was significantly later in OSAS patients ($F_{1,17}$ = 13.6, P < 0.01), but did not show any effect of site. There was no difference between OSAS patients and controls for N350. There was, however, a significant effect of site ($F_{2,32}$ = 10.91, P < 0.001). While there was no difference between the Fz and Cz amplitudes, N350 at Cz was larger than that at Pz ($F_{1,16}$ = 12.3, P < 0.01). There was no significant site by diagnosis interaction effect for amplitude and no site or diagnosis or interaction effects for N350 latency. N550 amplitude showed no effects of diagnosis or electrode site. N550 latency displayed a trend to be later in the OSAS patients ($F_{1,13}$ = 4.5, P = 0.059), with no impact of electrode site. P900 amplitude did not differ between groups, but did show a significant effect of electrode site ($F_{2,32}$ = 4.2, P < 0.05), with Cz values being smaller than those at Fz ($F_{1,16}$ = 7.7, P < 0.05) and Pz ($F_{1,16}$ = 5.1, P < 0.05). P900 latency showed no effects in the ANOVA model.

DISCUSSION

This is the first study to evaluate cortical responsiveness to inspiratory loading during sleep in children with OSAS, and

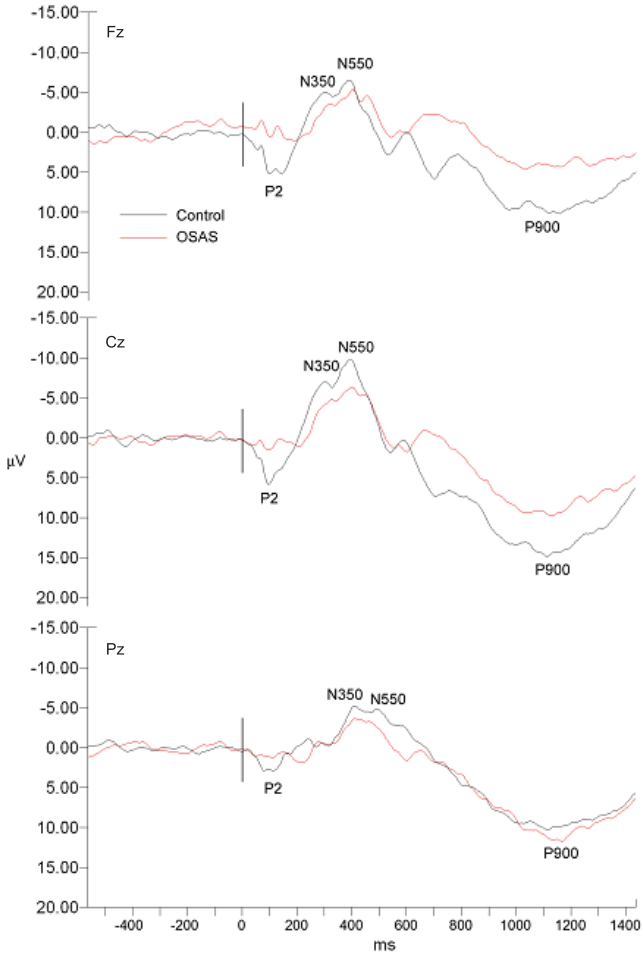

Figure 3—Grand mean RREP waveforms for controls (black lines) and OSAS patients (red lines) during rapid eye movement (REM) sleep are shown for Fz, Cz, and Pz leads. The vertical bar represents the time of the occlusion. Note the further reduced scale relative to Figures 1 and 2.

only the second to investigate RREPs during sleep in children.[22] Similar to adults with OSAS,[23,24] children with OSAS produced significantly fewer K-complex responses to inspiratory occlusions than did age-matched controls. Unlike adults with OSAS,[23,24] there were no significant differences in the amplitude of RREP components during stage 2 sleep, with only N350 and P900 being affected in SWS. Despite REM sleep being the state in which most OSAS pathology is manifest in children,[37] relative few RREP differences between OSAS patients and controls were apparent in this state, with the exception of OSAS having a smaller and later P2 component.

The source of the afferent signals for the cortex processing is not definitively known, but is thought to include the diaphragm, chest wall and upper airway.[38] Increases in inspiratory effort can reliably elicit RREPs.[24] Thus, RREPs reflect the response of the central nervous system to mechanical stimulation of the respiratory system. The two studies of RREPs in adults with OSAS reported that these adults had both a reduced incidence of K-complex production and a lower amplitude of N550 in the averaged K-complex responses, compared with controls.[23,24] Neither study showed a difference in RREPs between OSAS and controls during wakefulness. This suggests that sleep RREP differences are not due to altered mechanoreceptor function, unless the deficit in mechanoreceptor function is state specific. In the study conducted by Afifi et al, there was no difference in K-complex elicitation or N550 amplitude in response to auditory stimuli presented during sleep.[24] This indicates that the OSAS-related evoked potential difference is specific to the processing of respiratory afferent signals during sleep.

Several hypotheses can be postulated to explain the abnormal RREPs in patients with OSAS. The abnormal RREPs may be (i) a secondary abnormality induced by OSAS, or (ii) a primary abnormality that predisposes individuals to OSAS. For the first hypothesis, it is possible that the abnormal RREPs are an adaptive response to sleep fragmentation, in order to protect the integrity of sleep. Alternatively, the mechanoreceptors may be blunted due to vibrational damage resulting from snoring.[39] If there is indeed a mechanoreceptor abnormality in OSAS, it may not be apparent during wakefulness due to the multiple redundant afferent pathways for respiratory information. This theory requires a reasonable assumption that the afferent pathways are gated during sleep, thus unmasking the abnormality. The second hypothesis is that the abnormal RREPs may reflect a congenital predisposition to develop OSAS. In this scenario, patients with OSAS have subclinical abnormalities in cortical processing of respiratory afferent stimuli that predispose them to develop OSAS. Patients may remain asymptomatic until they develop a structural load that narrows the airway, such as adenotonsillar hypertrophy or obesity. The structural load results in upper airway collapse during sleep. Because the patients do not detect the load, they do not activate their upper airway muscles to widen the airway, and therefore OSAS develops. (iii) A third hypothesis is that the increased collapsibility of the upper airway in OSAS during sleep[1,40] renders the airway less capable of transducing occlusion related pressure change into an afferent signal. Thus, in this theory, the RREP deficit is secondary to mechanical differences in upper airway properties.

Studying children with OSAS is helpful in starting the process of sorting through these various hypotheses. Children with OSAS frequently fail to have cortical arousals in response to obstructive apneas,[41,42] and tend to have normal sleep architecture.[37] Furthermore, in the current study, RREP abnormalities did not correlate with the arousal index. Thus, it is unlikely that the abnormal RREP responses in the children with OSAS were secondary to sleep fragmentation. Vibrational nerve damage is probably less severe in children with OSAS than adults, as the duration of snoring will be less in children.[43] Nevertheless, we think it most likely that the abnormal RREPs in children with OSAS are due to either a congenital abnormality of processing of respiratory afferent stimuli or to abnormal transduction of occlusion related pressure changes secondary to changes in upper airway properties (such as changes in airway stiffness, edema etc.).

As with adults, the children with OSAS in the present study displayed much lower K-complex elicitation rates in both stage 2 sleep and SWS than controls. Although a trend was observed for patients with OSAS to have a smaller N550 than controls, no significant difference was observed between the patients and controls in different sleep stages. Instead, patients had smaller N350 and P900 in SWS. However, recent work by Melendres

Table 2—Mean Amplitude and Latency Values for the P2, N350, and P900 Components for the OSAS and Control Groups in Response to the Midinspiratory Occlusion Stimulus in SWS. Means (SD) are Presented for Each Group at Fz, Cz, and Pz

		Fz		Cz		Pz	
Site		OSAS	Control	OSAS	Control	OSAS	Control
P_2	Amplitude, μV	4.02 (7.22)	6.72 (6.47)	2.95 (10.17)	9.27 (5.24)	2.11 (8.84)	6.87 (5.35)
	Latency, ms	206.16 (29.28)	218.10 (43.72)	206.16 (39.58)	216.80 (19.88)	207.47 (35.50)	211.26 (28.53)
N_{350}	Amplitude, μV ** ††	-11.84 (5.97)	-29.57 (15.04)	-20.23 (10.68)	-50.97 (25.77)	-17.43 (12.24)	-37.52 (23.69)
	Latency, ms	410.16 (84.39)	392.58 (60.85)	389.32 (75.87)	384.12 (60.61)	382.38 (82.99)	401.69 (63.94)
N_{550}	Amplitude, μV	-16.97 (11.16)	-32.28 (20.68)	-15.07 (8.41)	-32.52 (24.61)	-12.42 (13.45)	-23.70 (25.29)
	Latency, ms †	736.98 (148.03)	579.43 (126.22)	692.71 (164.31)	572.59 (127.91)	645.83 (154.26)	585.29 (140.33)
P_{900}	Amplitude, μV * †	17.44 (16.07)	44.94 (21.27)	27.01 (26.62)	60.70 (25.04)	25.87 (24.04)	44.17 (14.46)
	Latency, ms * †	1148.44 (137.29)	1007.49 (121.05)	1134.98 (111.59)	960.94 (137.30)	1036.46 (226.10)	952.80 (149.49)

* diagnosis effect at $P < 0.05$; ** at $P < 0.001$
† electrode site effect at $P < 0.05$; †† at $P < 0.01$

Table 3—Mean Amplitude and Latency Values for the P2, N350, and P900 Components for the OSAS and Control Groups in Response to the Midinspiratory Occlusion Stimulus in Stage 2 Sleep. Means (SD) are Presented for Each Group at Fz, Cz, and Pz

		F_z		C_z		P_z	
Site		OSAS	Control	OSAS	Control	OSAS	Control
P_2	Amplitude, μV†	5.71 (6.18)	5.25 (5.77)	5.55 (5.21)	6.45 (5.01)	1.09 (6.97)	5.05 (3.07)
	Latency, ms	216.80 (35.25)	209.96 (47.23)	203.13 (34.94)	209.64 (24.16)	208.01 (38.49)	220.38 (26.78)
N_{350}	Amplitude, μV††	-8.75 (10.14)	-19.93 (12.61)	-15.82 (15.04)	-32.19 (19.45)	-11.79 (14.70)	-17.49 (9.40)
	Latency, ms	406.25 (58.61)	400.72 (49.03)	405.76 (65.28)	392.58 (45.75)	403.32 (47.78)	388.35 (42.28)
N_{550}	Amplitude, μV	-15.97 (17.72)	-24.10 (23.39)	-15.60 (13.12)	-25.87 (18.18)	-14.69 (13.78)	-15.06 (13.52)
	Latency, ms †	604.35 (84.29)	617.19 (79.34)	603.80 (91.19)	573.24 (62.50)	582.59 (103.16)	568.03 (82.59)
P_{900}	Amplitude, μV	21.54 (20.08)	47.45 (43.17)	25.04 (27.49)	53.23 (34.76)	23.16 (21.90)	28.48 (10.07)
	Latency, ms	1109.38 (59.32)	1106.45 (83.23)	1073.73 (50.95)	1087.24 (110.22)	1084.47 (51.86)	1066.08 (124.48)

† electrode site effect at $P < 0.05$; †† at $P < 0.01$

et al.[22] highlights that the N350 component is more prominent than the N550 in children. In adults during NREM sleep, N550 is clearly related to K-complexes,[25] which in turn are suggested to be a precursor to the delta waves produced in SWS.[44] However, Melendres et al.[22] showed N350 and N550 as 2 peaks on a broad negative deflection, rather than as 2 distinct peaks in the waveform. The N350 was later and the N550 earlier than that seen in adults, and there was no intervening P450 component. The scalp topography of the N550 was also different from that seen in adults, with no evidence of the clear front-to-back amplitude gradient present in adults of all ages. The waveforms in the present study were similar to those of Melendres et al.,[22] with the N550 largest at Cz in stage 2 (rather than Fz as in adults) with no effect of scalp site at all in SWS. The lack of an N550 difference between OSAS and control children is thus more likely to be reflective of differences between children and adults in the pattern of EEG response seen to stimuli during sleep than of a difference between children and adults with OSAS. Nonetheless, OSAS appears to have much less of an impact on RREPs during sleep in children than that reported previously in adults.

An intriguing finding was that the largest differences in evoked responses between OSAS and controls occurred during SWS when children typically have few respiratory events,[37] whereas during REM, when obstructive events are very common,[37] the RREPs were more similar. Again, in stage 2, where the majority of NREM events occur,[37] the only variable that differed with diagnosis was the percentage of K-complexes produced, with none of the RREP components showing a significant difference between groups. The presence of evoked K-complexes in the SWS RREP increases the overall size of the RREP components and thus increases the likelihood of seeing differences in the amplitude of components between patients and controls, given the observed difference in K-complex elicitation. The overall smaller amplitude of EEG responses during REM and the inability of the nervous system to produce K-complexes in this state reduce the statistical power to measure differences between groups. Thus, the presence of a trend only in stage 2 sleep may be due to the reduced number of K-complexes in stage 2 relative to SWS.

The only difference between OSAS and control children in REM involved the P2 component. While the P2 component is apparent in all sleep stages, with a vertex maximal distribution, remarkably little is known about its neural generation or functional significance.[45] The fact that it is seen to be reduced in OSAS in REM, but not in stage 2 or SWS, is thus difficult to interpret, but may reflect that P2 has a different functional significance in REM.

In adults, N350 is thought to reflect the presence of evoked vertex sharp waves in the averaged response, although it is also seen as a component in the averages of K-complexes during stage 2 sleep and SWS.[17] N350 has been hypothesized to act

Table 4—Mean Amplitude and Latency Values for the P2, N350, and P900 Components for the OSAS and Control Groups in Response to the Midinspiratory Occlusion Stimulus in REM Sleep. Means (SD) are Presented for Each Group at Fz, Cz, and Pz

	F_Z		C_Z		P_Z	
Site	**OSAS**	**Control**	**OSAS**	**Control**	**OSAS**	**Control**
P_2 Amplitude, μV* †	1.44 (3.98)	7.16 (4.82)	1.67 (4.52)	7.09 (4.88)	1.57 (4.12)	4.29 (3.26)
Latency, ms*	231.59 (58.10)	206.38 (36.68)	253.91 (51.58)	189.13 (39.19)	230.47 (55.24)	186.20 (34.67)
N_{350} Amplitude, μV †††	-7.85 (8.71)	-11.06 (7.75)	-8.05 (8.14)	-12.77 (10.61)	-3.71 (7.50)	-5.43 (4.23)
Latency, ms	424.66 (55.09)	380.21 (51.02)	406.81 (71.23)	371.42 (48.83)	414.62 (60.49)	403.00 (71.02)
N_{550} Amplitude, μV	-4.72 (6.15)	-5.06 (4.87)	-4.69 (5.89)	-7.07 (6.68)	0.63 (6.19)	-7.50 (6.52)
Latency, ms	707.03 (124.31)	596.24 (121.75)	654.30 (139.48)	601.56 (126.48)	830.08 (266.51)	627.49 (90.81)
P_{900} Amplitude, μV †	6.77 (6.88)	12.75 (5.43)	11.55 (10.26)	16.46 (8.48)	11.35 (10.78)	11.50 (5.03)
Latency, ms	959.27 (209.81)	1002.28 (213.71)	1017.86 (198.84)	1066.08 (143.41)	959.82 (256.66)	1115.56 (69.15)

* diagnosis effect at $P < 0.05$;
† electrode site effect at $P < 0.05$; ††† at $P < 0.001$

as a trigger for K-complexes and N550.[46] In adults, it has been assumed that P900 and N550 reflect different phases of activity originating from the same generator mechanism.[47] However, the limited scalp topography data (Fz, Cz, and Pz) from a recent study of RREPs in normal children during sleep indicated a different amplitude pattern for P900 than for N550,[22] raising the possibility that children have a different pattern of generator activity for N550 and P900 than adults. Nonetheless, it is likely that the P900 reflects some form of repolarization process following the activation of whichever generators are responsible for the N350/N550 and K-complex in children. The significant effect of OSAS diagnosis on amplitude and latency in SWS, and the trend for an amplitude effect in stage 2, are consistent with this interpretation.

The present study has some limitations that could have affected the data. The BMI z-score of the subjects with OSAS group was higher than the control group; however, there are no data suggesting that obesity affects RREPs directly, and a regression analysis failed to show BMI as a significant predictor of the K-complex effect. Most of the controls (8 of 12) did not have a baseline polysomnogram, but their medical history had been strictly screened to exclude OSAS. During the RREP night, none of them had obstructive apneas, desaturation, or hypercapnia. Finally, the interstimulus interval between occlusions was slightly shorter in patients than controls by 2.8 seconds in SWS, 2.1 seconds in stage 2, and by 1.8 seconds in REM. However, using the median interstimulus interval as a covariate did not eradicate the significant findings for N350 amplitude in SWS.

In summary, this study showed that children with OSAS have significantly decreased evoked K-complex production in stage 2 and SWS and significantly reduced RREP N350 and P900 components in SWS. There were no significant differences in any of the measured RREP components in stage 2 sleep, and the only REM difference was a decreased P2 amplitude. Future studies evaluating RREPs after effective surgical treatment of OSAS in children are needed.

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