Cortical Processing of Respiratory Occlusion Stimuli in Children with Central Hypoventilation Syndrome

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Rationale: **The ability of patients with central hypoventilation syndrome (CHS) to produce and process mechanoreceptor signals is unknown.**

Objectives: **Children with CHS hypoventilate during sleep, although they generally breathe adequately during wakefulness. Previous studies suggest that they have compromised central integration of afferent stimuli, rather than abnormal sensors or receptors. Cortical integration of afferent mechanical stimuli caused by respiratory loading or upper airway occlusion can be tested by measuring respiratory-related evoked potentials (RREPs). We hypothesized that patients with CHS would have blunted RREP during both wakefulness and sleep.**

Methods: **RREPs were produced with multiple upper airway occlusions and were obtained during wakefulness, stage 2, slow-wave, and REM sleep. Ten patients with CHS and 20 control subjects participated in the study, which took place at the Children's Hospital of Philadelphia. Each patient was age- and sex-matched to two control subjects. Wakefulness data were collected from 9 patients and 18 control subjects.**

Measurements and Main Results: **During wakefulness, patients demonstrated reduced Nf and P300 responses compared with control subjects. During non-REM sleep, patients demonstrated a reduced N350 response. In REM sleep, patients had a later P2 response.**

Conclusions: **CHS patients are able to produce cortical responses to mechanical load stimulation during both wakefulness and sleep; however, central integration of the afferent signal is disrupted during wakefulness, and responses during non-REM are damped relative to control subjects. The finding of differences between patients and control subjects during REM may be due to increased intrinsic excitatory inputs to the respiratory system in this state.**

Keywords: central hypoventilation syndrome; respiratory-related evoked potentials; wakefulness; sleep

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Central hypoventilation syndrome is a rare disease characterized by generally adequate breathing during wakefulness but hypoventilation during sleep. Previous studies suggest that people with this syndrome have compromised central integration of afferent stimuli.

What This Study Adds to the Field

In patients with central hypoventilation syndrome, integrated processing of the respiratory stimuli is disrupted during wakefulness, and responses during non-REM are damped relative to responses of control subjects.

Patients with central hypoventilation syndrome (CHS), congenital or late-onset type (1, 2), usually have adequate ventilation during wakefulness but need mechanical ventilation during sleep due to alveolar hypoventilation (3). More severely affected children hypoventilate during both wakefulness and sleep (3). The mechanisms for this breathing abnormality are not yet known.

In normal subjects, afferent signals from a number of mechanoreceptors in the upper airway, lower airway, lung, and chest wall play an important role in the regulation of breathing. Normal subjects readily sense mechanical stimuli, such as upper airway occlusion or a respiratory load, indicating the presence of cortical processing of afferent mechanoreceptor signals (4). The ability of patients with CHS to produce and process these signals is unknown. However, passive motion of the lower extremities in patients with CHS elicits significant increases in alveolar ventilation during non-REM sleep (5). This finding indicates that mechanoreceptor afferent pathways in patients with CHS are at least partially functional. On the other hand, results from functional magnetic resonance imaging studies indicate that patients with CHS may have an abnormal central response to afferent mechanical input caused by forced expiratory loading. Regions responsible for this abnormality are diffuse and include the dorsal and ventral medulla, cerebellum, and dorsal pons (6). In addition, patients with CHS have been shown to have some chemoreceptor function (7, 8), although chemoreception is not normal (9). These data led to the hypothesis that hypoventilation in patients with CHS could be associated with a deficit in the central integration of sensorimotor information (6, 7).

One way to test this hypothesis is to measure respiratory-related evoked potentials (RREPs), the cortical response to rapid application of inspiratory occlusions (4). The RREP method provides a unique way to investigate the neural integration mechanisms mediating respiratory load perception during both wakefulness (4, 10–22) and sleep (12, 14, 16, 23, 24).

During wakefulness, a series of RREP components can be elicited, starting with P1, which is prominent at posterior scalp sites and is believed to reflect activation of the primary somatosensory cortex (10). P1 amplitude is correlated with stimulus intensity (20, 22), and with load magnitude estimation (22, 25). Occurring at approximately the same time as P1, but

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prominent over the frontal scalp, is the Nf (11). This component is believed to be produced in the supplementary motor area (10) and reflects the processing associated with the organization of a motor response to overcome an occlusion or load. A P300 response is a frequent response to inspiratory occlusion stimuli (14–16, 21, 22, 26) even when subjects are not asked to attend to the stimuli (12). As with the P1 and Nf, the P300 only occurs when the stimulus intensity exceeds detection threshold (20), and is believed to represent a higher level of cognitive processing of the stimulus following the integration of lower-order sensory features.

During sleep, a series of components are seen that reflect a generalized response to stimuli that are not sufficiently intense to produce an arousal. In non-REM sleep, the RREP waveform consists of a series of late components: the P2, N350, N550, and P900 (12, 16, 20, 23, 24, 27, 28). In adults, the response is dominated by the N550 response (12, 16, 27, 28); in children, the predominant component is the earlier N350 (23, 24). During REM sleep, the N350 is also prominent (23, 24). This pattern of response is common to respiratory and auditory stimuli (27, 28). Although the functional significance of these responses is unknown, they are probably not a reflection of processing within the respiratory somatosensory pathway. It is possible, however, that they are a reflection of a process that enables a response to stimuli compatible with the continuation of sleep, and perhaps protective of sleep maintenance (29).

The present experiment tests the hypothesis that patients with CHS have abnormal processing of afferent mechanoreceptor information during wakefulness and sleep. Some of the results of this study have been previously reported in the form of an abstract (30).

METHODS

Additional detail on the methods is provided in the online supplement.

Patients with CHS and control subjects were studied. Patients with CHS underwent a baseline polysomnogram. All subjects underwent pulmonary function testing, testing of their hypercapnic ventilatory response, and genetic testing. For patients with CHS and control subjects, RREPs were obtained on a separate night from the surface EEG during wakefulness, stage 2 sleep, slow-wave sleep (SWS), and REM sleep. Control subjects did not have a baseline polysomnogram but were screened for the presence of a negative history of sleep-related breathing disorders, and their respiration was closely monitored to ensure normal breathing during the noninterventional portions of the RREP sleep study.

The institutional review board at the Children's Hospital of Philadelphia approved the study. Informed consent was obtained from subjects older than 18 years, or from the parents or legal guardians of younger subjects. In addition, consent was obtained in the presence of a parent or legal guardian if the subject was between 7 and 17 years of age.

Study Group

Patients with CHS. Patients with CHS were recruited from the Children's Hospital of Philadelphia and from those who responded to an advertisement on the Congenital Central Hypoventilation Syndrome (CCHS) family website (www.cchsnetwork.org). The diagnosis of CHS was based on American Thoracic Society criteria, that is, persistent hypoventilation during sleep (P_{CO_2} consistently >60 mm Hg) and absence of primary pulmonary, cardiac, metabolic, or neuromuscular dysfunction (3).

Normal control subjects. Each patient was individually age and sex matched to two control subjects. Controls were healthy individuals recruited from the general population by means of advertisements. They were all nonsnorers and had a negative history of sleep-disordered breathing based on the Brouillette questionnaire (31).

Genetic Testing, Hypercapnic Ventilatory Response Testing, Spirometry, and Baseline Polysomnography

Methods for testing are described in the online supplement.

Inspiratory Occlusions and RREP Assessment

RREP methods during wakefulness and sleep are described in detail in the online supplement.

During wakefulness, patients with CHS and control subjects were studied while seated and breathing through a mouthpiece and wearing nose clips. Patients with tracheostomies had their tracheostomy tubes capped. The mouthpiece was connected to a non–re-breathing balloon valve (9,300 series; Hans Rudolph, Inc., Kansas City, MO) and a heated pneumotachometer (Hans Rudolph, Inc.). Upper airway pressure was measured using a pressure transducer with a demodulator (Validyne Engineering Corp., Northridge, CA) connected to the mouthpiece. Surface EEG was recorded at Fz, Cz, and Pz throughout the study. Multiple (80–100) 400-ms inspiratory occlusions were performed.

During sleep, patients with CHS received assisted ventilation via tracheostomy or through a full face mask. Controls wore a full face mask connected to a continuous positive airway pressure machine at a pressure of 2 cm H_2O to account for the resistance within the circuit and to wash out carbon dioxide within the mask. Flow, pressure, and surface EEG were measured using methods similar to those measured during wakefulness. Multiple (200–400) inspiratory occlusions were performed during stage 2, SWS, and REM sleep.

Statistical Analysis

For each sleep RREP component, the EEG site (Fz, Cz, or Pz) at which that component reached the maximal value was selected for analysis. Independent sample *t* tests were conducted to assess the effect of diagnosis (patients with CHS vs. control subjects) on K complex induction rate, mouth or mask pressure, and each RREP component for wakefulness and sleep stage (stage 2, SWS, and REM) separately. Levene's test for equality of variances was conducted, and when significant, degrees of freedom were adjusted where appropriate.

RESULTS

Study Population

Ten patients with CHS and 20 control subjects were studied. Participant characteristics are shown in Table 1. Two patients had late-onset CHS, as described in detail in the literature (2, 32), including one subject with late-onset CHS associated with hypothalamic abnormalities and consistent with previously described cases (2). This subject was asymptomatic until 4 years of age, and subsequently developed central hypoventilation during sleep requiring nocturnal ventilatory support, as well as obesity, an abdominal ganglioneuroma, hypothyroidism, diabetes insipidus, and growth hormone deficiency. The other child with atypical disease presented at 5years of age with severe nocturnal hypoventilation requiring ventilatory support but did not have obesity or hypothalamic disease. His case has been described in detail in the literature (32). None of the subjects received ventilation during wakefulness, although 24-hour ventilation had been recommended for, but refused by, a 20-year-old subject. All patients with CHS had flat hypercapnic ventilatory responses (Table 1). Pulmonary function tests were not obtained from the two youngest patients with congenital CHS (CCHS) (aged 5 and 6 yr) because of inadequate cooperation. Patients with CHS had a slightly lower predicted percentage of FEV_1 ($P = 0.046$), but values were still well within the normal range. All patients with CCHS had heterozygous polyalanine repeat expansion mutations within exon 3 of the *PHOX2B* gene (25–27 repeats), whereas the two patients with late-onset CHS and the control subjects did not have a mutation, consistent with the current literature (1). All control subjects had normal breathing during the noninterventional portions of the RREP sleep study.

TABLE 1. DEMOGRAPHIC, HYPERCAPNIC VENTILATORY RESPONSE TESTING, SPIROMETRY, AND PHOX2B POLYALANINE REPEAT DATA OF PATIENTS WITH CENTRAL HYPOVENTILATION SYNDROME AND CONTROL SUBJECTS

	CHS	Control Subjects
n	10	20
Male	4	8
Age, yr (range)	13 ± 6 (5–20)	13 ± 6 (5–20)
BMI *z*-score	1.44 ± 0.73	0.92 ± 0.81
Associated conditions		
Hirschsprung's disease	2	0
Wake hypoventilation	1	0
Cardiac pacemaker	1	0
Developmental delay	1	0
Neural tumor	1	0
Hypothalamic dysfunction	1	0
Ventilation method		
Tracheostomy	5	0
Mask	5	0
Slope of hypercapnic ventilatory response testing, L/min/mm Hg	0.14 ± 0.23	3.29 ± 1.34*
Correlation coefficient of hypercapnic ventilatory response testing	0.04 ± 0.22	0.83 ± 0.13*
Spirometry		
FEV_1, % predicted	90 ± 10	99 ± 11†
FVC, % predicted	91 ± 9	101 ± 14
FEV_1/FVC, % predicted	91 ± 9	90 ± 5
PHOX2B mutation, number of polyalanine repeats		
20/20 (normal)	2	20
20/25–27	8	

Definition of abbreviations: CHS = central hypoventilation syndrome; BMI = body mass index.

Spirometry was obtained in eight patients with CHS and their respective control subjects. Values are n, mean ± SD, and range.

* $P < 0.05$.

† $P < 0.001$.

TABLE 2. RESPIRATORY-RELATED EVOKED POTENTIAL COMPONENT AMPLITUDES AND LATENCIES AND MOUTH PRESSURE CHANGES AFTER OCCLUSION DURING WAKEFULNESS IN 9 SUBJECTS WITH CENTRAL HYPOVENTILATION SYNDROME AND 18 MATCHED CONTROL SUBJECTS

Group	Component	Site	Amplitude (μV)	Latency (*ms*)
Controls	P1	Pz	2.4 ± 2.8	89.7 ± 15.0
CHS			1.6 ± 1.3	83.9 ± 32.1
Controls	Nf	Fz	−3.5 ± 4.1*	60.3 ± 7.3*
CHS			−1.7 ± 1.5	66.6 ± 8.1
Controls	P300	Cz	5.5 ± 3.3*	215.9 ± 37.2
CHS			2.2 ± 2.4	230.9 ± 31.1
	Mouth pressure (*cm* H_2O)			
Controls	3.7 ± 0.7			
CHS	3.1 ± 1.2			

Definition of abbreviation: CHS = central hypoventilation syndrome.

Values are mean ± SD.

* $P < 0.05$ control subjects versus patients with CHS.

Awake RREP Data

Wakeful RREP data could not be obtained in one young, developmentally delayed child with CCHS due to lack of cooperation, and data from his two matched control subjects were also excluded. Mouth pressure changes induced by occlusions did not differ significantly between patients with CHS and control subjects. Amplitude and latency values for P1, Nf, and P300 are presented in Table 2. P1 was a reliably observed component in 11 of 18 (61%) control subjects and 6 of 9 (67%) patients with CHS. There was no difference in the amplitude or the latency of P1 between the two groups. Nf was observed in all control subjects and 7 of 9 (78%) patients with CHS. In those subjects in whom Nf was detected, the Nf amplitude was significantly smaller and Nf latency significantly longer in subjects with CHS. P300 was observed as a component in 16 of 18 (89%) control subjects and 8 of 9 (89%) patients with CHS. In those subjects in whom it was detected, P300 amplitude was significantly smaller in CHS, with no difference in P300 latency between the two groups (Figure 1).

To assess whether RREP generation differed when stimuli were presented via mask or tracheostomy, three of the patients with CHS were studied with occlusions presented via tracheostomy in addition to those presented via mouthpiece. Average pressure responses to occlusions were 3.27 ± 1.11 cm H_2O in the mouthpiece condition and 2.89 ± 0.41 cm H_2O in the tracheostomy condition. Nf at Fz had an average amplitude of -3.23 ± 0.76 μV in the mouthpiece condition and 0.58 ± 3.01 μV in the tracheostomy condition. P1 at Pz had an average amplitude of 2.53 ± 0.78 μV in the mouthpiece condition and 2.09 ± 1.58 μV in the tracheostomy condition. P300 at Cz had an average amplitude of 2.72 ± 3.15 μV in the mouthpiece condition and 1.92 ± 0.59 μV in the tracheostomy condition.

Sleep RREP Data

K complex proportions. In stage 2 sleep, K complexes were produced by 22.9 ± 15.8% of stimuli in control subjects (range, 4.0–46.5%), and 15.0 ± 15.2% of stimuli in patients with CHS (range, 0–41.6%) (not significant). In SWS, the K complex rate was 19.3 ± 14.6% in control subjects (range, 7.2–66.7%) and 11.9 ± 5.0% in patients with CHS (range, 4.2–21.1%) ($P < 0.01$). K complexes were rarely seen in REM sleep (<3% of stimuli overall) and group differences were not evaluated.

Stage 2 RREPs

Airway pressure change induced by occlusions was significantly higher in patients with CHS (all of whom were receiving positive-pressure ventilation). For both groups, the averaged amplitude reached maximal values at Cz for P2 and N350 and at Fz for N550 and P900. Patients with CHS had a significantly smaller N350 component, but the latency was not significantly different between patients with CHS and control subjects. Neither amplitude nor latency for P2, N550, or P900 displayed any effects of diagnosis (*see* Table 3).

SWS RREPs

Airway pressure change induced by occlusions was significantly higher in patients with CHS. For P2, N350, N550, and P900, the averaged maximal values appeared at Cz for both groups. The N350 amplitude was smaller for patients with CHS than control subjects and there was no difference for N350 latency between these two groups. For P2, N550, and P900, neither amplitude nor latency was different between the two groups (*see* Table 3).

REM RREPs

Airway pressure change induced by occlusions was significantly higher in patients with CHS. In REM sleep, patients with CHS had a significantly later P2 component. No difference was observed in P2 amplitude or the amplitude/latency of N350, N550, or P900 components between patients with CHS and control subjects (*see* Table 3).

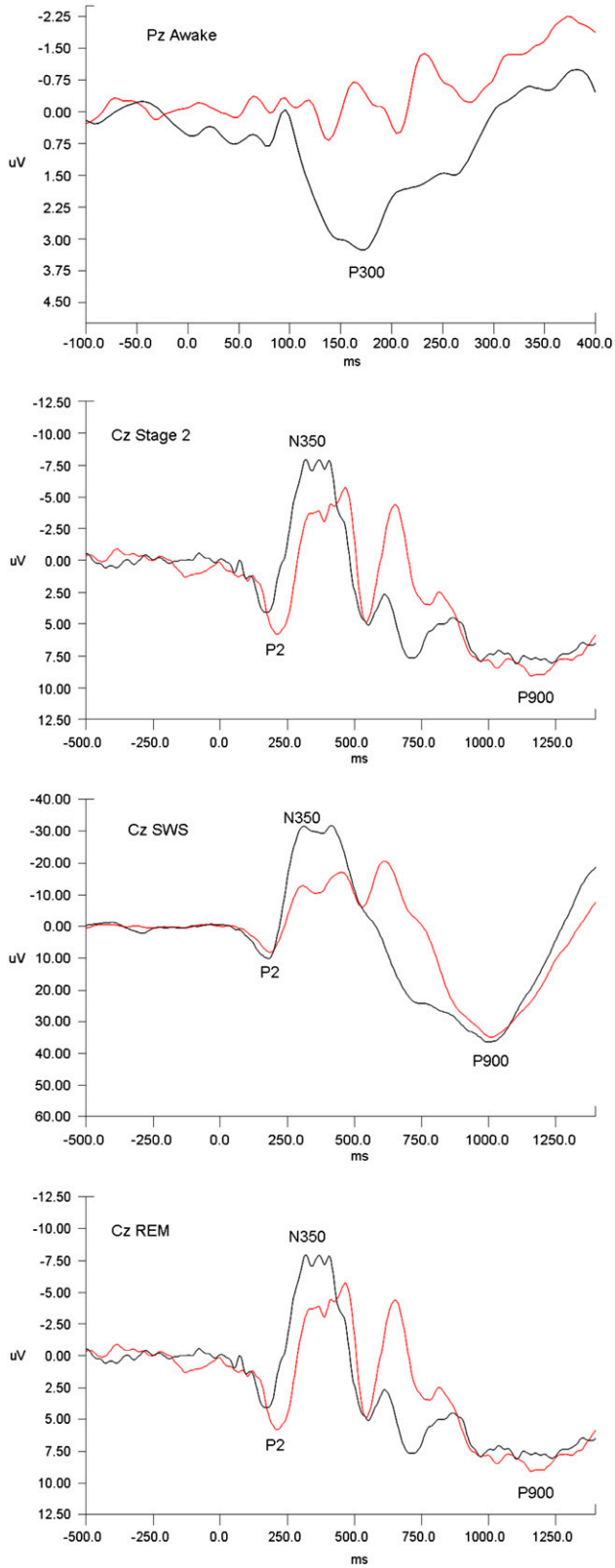

Figure 1. Grand mean respiratory-related evoked potential (RREP) waveforms for control subjects (*black lines*) and patients with central hypoventilation syndrome (CHS) (*red lines*) during wakefulness (Pz), stage 2 (Cz), slow-wave sleep (SWS) (Cz), and REM sleep (Cz).

Patients with Mechanical Ventilation via Face Mask versus Control Subjects

Five of 10 patients with CHS received mechanical ventilation via tracheostomy during sleep, whereas the other 5 received mechanical ventilation via face masks. Because it is possible that RREP generation differed in subjects ventilated via face mask versus tracheostomy, we analyzed the subgroup of patients with CHS receiving mask ventilation compared with their respective control subjects. Patients with CHS demonstrated reduced amplitude of N350 ($P = 0.004$), N550 ($P = 0.011$), and P900 ($P = 0.002$) components in stage 2 sleep with no differences in the latency of any components. There were no differences seen in SWS. In REM sleep, P2 latency was significantly later in CHS ($P = 0.011$), whereas no other components differed between the groups.

Late-Onset versus CCHS

Two patients with late-onset CHS had blunted RREPs similar to that of patients with CCHS during wakefulness, stage 2, and SWS; removal of the two patients with late-onset CHS did not alter the general pattern of significant differences seen between control subjects and patients with CHS. For the 8 patients with CCHS and the 16 matched control subjects during wakefulness, Nf at Fz was smaller in patients with CCHS than in control subjects (-1.5 ± 1.6 μV vs. -4.7 ± 3.4 μV, $P = 0.016$). No difference in the latency of Nf was observed. Patients with CCHS had a smaller and later P300 at Cz than control subjects (amplitude: 2.5 ± 2.3 μV vs. 5.7 ± 3.4 μV, $P = 0.030$; latency: 217.6 ± 38.5 ms versus 234.3 ± 35.7 ms, $P = 0.028$). During non-REM sleep, patients with CCHS had a smaller but not later N350 response than controls (stage 2: -17.9 ± 7.2 μV vs. -35.7 ± 16.4 μV, $P = 0.021$; SWS: -28.9 ± 11.1 μV vs. -40.2 ± 21.0 μV, $P = 0.020$). In REM, no difference was observed between patients with CCHS and control subjects.

There was, however, a major difference between congenital and late-onset subjects during REM sleep. The two late-onset subjects had greater P2 (30.1 and 19.2 μV) and N350 (-38.1 and -20.9 μV) amplitudes than the remainder of the patients with CHS (P2: amplitude of 6.0 ± 4.1 μV; and N350: -7.4 ± 3.0 μV). Indeed, their responses were also larger than those seen in the control subjects for both P2 (6.7 ± 4.5 μV) and N350 (-11.9 ± 9.6 μV).

DISCUSSION

In support of the hypotheses being tested, patients with CHS demonstrated reduced Nf and P300 responses during wakefulness and a reduced N350 response during non-REM sleep compared with age- and sex-matched control subjects. The only difference between patients with CHS and control subjects during REM sleep was that patients with CHS had a later P2 response.

RREPs during Wakefulness

The awake response in patients with CHS did not show a significantly decreased P1 response. This is consistent with the patients having functioning mechanoreceptors and transmission of the output of these receptors to the cortex. However, the failure to find a significant difference needs to be interpreted with caution because of the small number of subjects. There was, however, a significantly reduced Nf component. Nf has not been as extensively studied as P1, as its measurement requires the measurement of EEG from frontal sites with a linked ear reference, and many studies have only reported RREP responses at C3 or C4 referenced to Cz. A source localization

TABLE 3. RESPIRATORY-RELATED EVOKED POTENTIAL COMPONENT AMPLITUDES AND LATENCIES AND MOUTH PRESSURE CHANGES AFTER OCCLUSION DURING STAGE 2, SLOW-WAVE SLEEP, AND REM SLEEP

	Stage 2				SWS				REM			
Group	Component	Site	Amplitude (μV)	Latency (ms)	Component	Site	Amplitude (μV)	Latency (ms)	Component	Site	Amplitude (μV)	Latency (ms)
Controls	P2	Cz	9.9 ± 6.7	160.7 ± 34.0	P2	Cz	11.6 ± 10.4	159.3 ± 24.3	P2	Cz	6.7 ± 4.5	142.2 ± 38.8*
CHS			8.1 ± 8.8	226.5 ± 127.9			10.1 ± 7.7	179.6 ± 55.1			10.1 ± 9.3	235.1 ± 129.3
Controls	N350	Cz	−34.5 ± 15.2*	330.2 ± 60.3	N350	Cz	−39.8 ± 22.7*	335.1 ± 75.7	N350	Cz	−11.9 ± 9.6	320.2 ± 44.8
CHS			−21.4 ± 12.4	371.4 ± 106.4			−25.6 ± 13.3	368.3 ± 64.3			−13.4 ± 14.0	378.8 ± 111.3
Controls	N550	Fz	−33.6 ± 26.6	553.2 ± 62.6	N550	Cz	−33.6 ± 25.9	504.4 ± 153.6	P900	Cz	12.9 ± 8.5	886.4 ± 212.4
CHS			−26.4 ± 19.2	628.8 ± 102.0			−28.5 ± 17.9	569.4 ± 114.0			13.7 ± 8.6	946.5 ± 142.9
Controls	P900	Fz	57.0 ± 36.2	1,017.9 ± 80.8	P900	Cz	52.3 ± 21.5	826.3 ± 218.2*				
CHS			41.9 ± 40.3	1,075.3 ± 140.8			40.7 ± 23.0	930.4 ± 105.7				
	Mask/tracheostomy pressure ($cm\ H_2O$)				Mask/tracheostomy pressure ($cm\ H_2O$)				Mask/tracheostomy pressure ($cm\ H_2O$)			
Controls	2.5 ± 1.4†				2.2 ± 1.3†				2.3 ± 1.3*			
CHS	9.8 ± 3.0				10.8 ± 4.8				7.5 ± 6.3			

Definitions of abbreviations: SWS = slow-wave sleep; CHS = central hypoventilation syndrome.
Values are mean ± SD.
* $P < 0.05$.
† $P < 0.01$ control subjects versus CHS.

study (10) reported a significant fit for Nf with bilateral dipoles in the left and right supplementary motor areas. This region is involved in the coordination of motor responses (33) and has been shown to be activated in speech, another condition involving the coordinated action of respiratory motor systems (34). The reduced amplitude of Nf in patients with CHS is evidence of disrupted motor processing in the face of an occlusion. This interpretation also needs to be considered with caution, however, as patients with CHS were able to mount the same motor response to the occlusion as control subjects, as indicated by the absence of any difference in the mouth pressure change produced by the occlusion stimulus.

Several studies have reliably shown a relatively short latency P300 response in the wakefulness RREPs (12, 15, 22, 26). P300 is believed to reflect the activation of a network of different brain regions (35) involved in the "cognitive" processing of sensory signals that have particular relevance or salience to the subject. The production of P300 in response to auditory or visual stimuli typically requires the presentation of different types of stimuli in the presence of a psychological manipulation where one type is labeled important and the other(s) irrelevant. The reduced P300 amplitude in CHS reflects some distributed processing deficit, although there are insufficient data to conclude that such a deficit is specific to the processing of respiratory mechanoreceptor information. Webster and Colrain (21) reported a similar deficit in adult subjects with asthma, but with further investigation they found that a similar deficit was present in the P300 to auditory stimuli in the same patients. The two studies investigating RREP P300 in patients with the obstructive sleep apnea syndrome (14, 16) did not find any difference between these patients and control subjects. This finding reduces the possibility that the P300 result in the present study is due to respiratory-related sleep disruption in the CHS group. The wakefulness data are thus generally supportive of the presence of functionally intact mechanoreception in patients with CHS to the point of afferent stimuli reaching the primary somatosensory cortex, but with subsequent disruption of the later processing of the signal. Whether similar deficits are also present in the processing of auditory or visual stimuli, or the processing problem is specific to respiratory information processing, remains to be determined.

The limited data collected comparing responses to occlusions administered via face mask with those administered via tracheostomy are worthy of comment. Such a comparison informs the discussion as to the role of pharyngeal receptors in the generation of the RREPs, because occlusions administered via a tracheostomy presumably do not stimulate the pharyngeal airway. Only two studies have examined this issue. The first study reported data from eight patients, four with high cervical spine lesions and four with chronic respiratory failure (17). The RREP was present in all patients when occlusions were administered via mouthpiece, but absent when administered via tracheostomy. The authors concluded that upper airway afferents were necessary for the RREP to be evoked. Interestingly, however, the same group reported no impact of upper airway anesthesia on the RREP (18). Davenport and colleagues (19) reported data from two double-lung transplant patients and compared mouthpiece with tracheostomy occlusions in the patients and with mouthpiece occlusions in nine control subjects. Patients demonstrated P1, Nf, and P300 components in response to the tracheostomy occlusions, although they had reduced amplitudes relative to the components seen in response to mouthpiece occlusions, a result that the authors attributed to the reduced occlusion-related pressure change elicited in the tracheostomy condition. The results from the present study are more supportive of those reported by Davenport and colleagues, because P1 and Nf components were visible in both conditions in all three patients. As reported in Davenport and colleagues' study (19), there appeared to be a tendency for the components to be smaller in the tracheostomy condition, although this could not be tested statistically due to the small sample size. Also in agreement with the study conducted by Davenport and colleagues (19), the average occlusion pressure response was slightly smaller in the tracheotomy condition, and thus may have contributed to the smaller RREP components.

RREPs during Sleep

It should be emphasized that the components measured during sleep reflect a more generalized response to the presence of a stimulus, rather than specific processing of afferent respiratory somatosensory signals *per se*. In adults, the N350 is believed to be associated with the presence of evoked vertex sharp waves as well as K complexes during non-REM sleep (28), reflecting the output of an active inhibitory process to facilitate sleep onset (29). N350 has also been hypothesized to act as a trigger for K complexes and N550 (29). N550 is produced when evoked K complexes are present in an averaged response (27, 29). Studies

have indicated that K complexes and the N550 reflect delta frequency EEG generation (36–38). As with the N550, the P900 component is more prominent when more stimuli are able to induce K complexes (39). RREP data from normal children support the finding that P900 has the same origin as N550 and represents the repolarization phase of the cortex activation (23). In children, the N350 rather than the N550 appears as the predominant evoked response potential component in non-REM sleep, with the N350 also prominent during REM sleep (23, 24). The significantly smaller N350 in patients with CHS thus reflects a reduction in general responsiveness to stimulation during non-REM sleep.

During REM sleep, the only difference discerned between the patients with CHS and control subjects was that patients with CHS had a later P2. A possible reason for this is that the tonic cholinergic activation present in REM makes the elicitation of delta frequency responses more difficult, and the overall amplitude of the N350 response is substantially reduced relative to that seen in non-REM sleep (23, 24). Another possibility is that breathing during REM sleep is modulated primarily by intrinsic excitatory inputs to the respiratory system (40), rather than chemo- and mechanoreceptor input. Hence, hypoventilation is less severe in REM sleep in patients with CHS (41).

Ventilatory Control in CHS

The reason why patients with CHS have hypoventilation during sleep (and in severe cases, even during wakefulness) is far from clear. During wakefulness, even when minute ventilation is adequate, the ventilatory responsiveness to hypercarbia and hypoxemia, measured using rebreathing methods, is absent (9). However, patients with CHS have ventilatory sensitivity to acute hypoxia and hypercapnia during wakefulness (8). Similarly, during sleep, patients with CHS have no ventilatory response to progressive hypoxia and hypercarbia (41), but show arousal to hypercapnia (7). Functional magnetic resonance imaging studies investigating brain responses to hypoxia, hyperoxia, and hypercapnia in patients with CHS also suggest diffuse deficits in neural processing of chemical afferent stimuli (42, 43). The above evidence supports the hypothesis that compromised chemoreception in patients with CHS is due to an abnormality of the chemoreceptor input integration rather than to abnormalities of the chemoreceptors themselves. Studies investigating the cough reflex in patients with CHS have also yielded controversial yet interesting results. Patients with CHS coughed when they had pneumonia (44). However, when inhaling fog at a concentration known to induce cough, patients with CHS presented a compromised awareness of airway irritation with no change in breathing pattern (45). These findings indicate that the abnormality in CHS is at the central nervous system integration level, rather than at the irritant receptor level.

The manifestation of varying defects in different respiratory sensory modalities in patients with CHS leads to the logical hypothesis that these patients have compromised integral processing of afferent stimuli rather than abnormal sensors or receptors (6, 7). The findings from our study support this hypothesis.

Results from the present study are helpful in better understanding breathing mechanisms during sleep in patients with CHS. Multiple and redundant mechanisms are involved in the regulation of breathing. For subjects with CHS, mechanoreception, together with chemoreception, is important in the control of ventilation (5, 46, 47). During non-REM sleep, when hypoventilation is most severe in patients with CHS (41, 48), significant abnormalities of the RREP response were observed. The above findings support at least an association between compromised mechanoreception and hypoventilation in patients with CHS during non-REM sleep.

Late-Onset versus Congenital Central Hypoventilation

CHS is very heterogeneous (e.g., some patients with CHS have Hirschsprung's disease, some need ventilatory support during wakefulness as well as sleep) and occurs along a spectrum (e.g., some patients with late-onset CHS have neural tumors similar to those with CCHS). Thus, we believe that including all subjects with CHS, and illustrating the similarities and differences between those with classic CCHS and those with atypical CHS, will be useful to the field. Also, CHS is a rare disease with an incidence of only 1 per 200,000 live births. Therefore, we elected to study all patients with CHS. However, the difference in RREP responses between the CCHS and control groups were still valid after we excluded the two late-onset cases. The *PHOX2B* gene promotes neuronal differentiation and development of the autonomic nervous system, and thus could potentially play a role in ventilatory control (49). In our study, however, the late-onset CHS subjects had blunted RREP, similar to the congenital CHS, during wakefulness and all stages of non-REM sleep. This suggests that the altered cortical processing of afferent stimuli reported in this study is not related to abnormalities of the *PHOX2B* gene. Interestingly, the late-onset patients had increased RREP during REM sleep. The reason for this is unclear but may be related to the relative preservation of breathing during REM sleep in patients with CHS (48).

Study Limitations

Although interpretation of data from the present study is clearly limited by the small sample size, this is an inherent problem in studying CHS because it is a rare disease with an estimated incidence of only 1 per 200,000 live births (50).

In tracheotomized subjects, awake RREPs were obtained with the tracheostomy capped, which may have increased upper airway resistance. However, this was unlikely to be an important factor as all of these subjects had small bore tracheostomy tubes that they routinely capped during the day, and the pressures they generated during RREPs when awake did not differ from those of control subjects.

We did not investigate the evoked potential responses of patients with CHS to non–respiratory-related stimuli (such as auditory stimuli) in this study. Further investigations using different stimuli in the same patients with CHS will lead to a better understanding of whether the central integration impairments in CHS are specific to respiratory stimuli or reflect a nonspecific impairment of central nervous system functioning.

Conclusions

These data indicate that patients with CHS clearly generate an RREP response to brief upper airway occlusions during wakefulness and sleep, but that this RREP response is blunted compared with age- and sex-matched control subjects. During wakefulness, there was disruption of higher-order integrated processing of the stimuli. During non-REM sleep, the major component of the RREP was reduced relative to control subjects, a finding that did not extend to REM sleep, when breathing tends to be less affected in this disease. Results from this study support the hypothesis that patients with CHS have abnormalities of central integration of afferent stimuli during wakefulness, and have diminished responses to mechanoreceptor stimuli during non-REM sleep.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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