Effect of sleep stage on breathing in children with central hypoventilation

Huang J, Colrain IM, Panitch HB, Tapia IE, Schwartz MS, Samuel J, Pepe M, Bandla P, Bradford R, Mosse YP, Maris JM, Marcus CL. Effect of sleep stage on breathing in children with central hypoventilation. J Appl Physiol 105: 44–53, 2008. First published May 22, 2008; doi:10.1152/japplphysiol.01269.2007.—The early literature suggests that hypoventilation in infants with congenital central hypoventilation syndrome (CHS) is less severe during rapid eye movement (REM) than during non-REM (NREM) sleep. However, this supposition has not been rigorously tested, and subjects older than infancy have not been studied. Given the differences in anatomy, physiology, and REM sleep distribution between infants and older children, and the reduced number of limb movements during REM sleep, we hypothesized that older subjects with CHS would have more severe hypoventilation during REM than NREM sleep. Nine subjects with CHS, aged (mean ± SD) 13 ± 7 yr, were studied. Spontaneous ventilation was evaluated by briefly disconnecting the ventilator under controlled circumstances. Arousal was common, occurring in 46% of REM vs. 38% of NREM trials (not significant [NS]). Central apnea occurred during 31% of REM and 54% of NREM trials (NS). Although minute ventilation declined precipitously during both REM and NREM trials, hypoventilation was less severe during REM (drop in minute ventilation of 65 ± 23%) than NREM (drop of 87 ± 16%, P = 0.036). Despite large changes in gas exchange during trials, there was no significant change in heart rate during either REM or NREM sleep. We conclude that older patients with CHS frequently have arousal and central apnea, in addition to hypoventilation, when breathing spontaneously during sleep. The hypoventilation in CHS is more severe during NREM than REM sleep. We speculate that this may be due to increased excitatory inputs to the respiratory system during REM sleep.

Ondine’s curse; rapid-eye-movement sleep; PHOX2B gene

CENTRAL HYPOVENTILATION SYNDROME (CHS) is a rare disorder of ventilatory control, characterized by generally adequate ventilation during wakefulness, but severe alveolar hypoventilation during sleep, to the point where patients require mechanical ventilation (2). The congenital form of CHS is now known to be due to mutations of the PHOX2B gene (3, 55), which promotes neuronal differentiation and development of the autonomic nervous system (54).

The early literature reported that infants with CHS breathed better during rapid eye movement (REM) than non-REM (NREM) sleep (12, 19), although this finding has never been tested systematically. REM sleep is characterized by hypotonia of skeletal muscles, with the exception of the extraocular muscles and the diaphragm. The finding of improved ventilatory control (6, 33, 50) further confirmed the supposition that REM sleep during wakefulness is more severe during REM than NREM sleep due to REM-related hypotonia. Furthermore, during REM sleep there is hypotonia of the accessory muscles of respiration and, although controversial (43, 44), some human studies suggest that the ventilatory drive is lower during REM sleep (9). Thus most types of sleep-disordered breathing, such as obstructive sleep apnea, are worse during REM compared with NREM sleep (14).

There are many physiological differences in the respiratory system between infants and older subjects. Infants have a different configuration of the thorax, with ribs orientated more horizontally, as well as a very compliant chest wall. As a result, the rib cage contribution to breathing during sleep is less than in older subjects (22). Infants perform laryngeal braking (active glottic narrowing) to maintain their functional residual capacity, which is lower than that of adults. Muscle mass increases with age, and whereas infants can produce high inspiratory pressures, they tend to function close to the diaphragmatic fatigue threshold (41). Other physiological differences between infants and adults include a higher arousal threshold during sleep (37) and differences in ventilatory control (6, 33, 50). Furthermore, infants with CHS may initially hypoventilate during both wakefulness and sleep (2) but only require ventilatory support during sleep once they have matured. Thus breathing patterns in infants with CHS may differ from older patients. Furthermore, REM sleep changes with age. Infants typically enter sleep via REM and have shorter ultradian cycles with more REM sleep than older individuals. REM density also decreases with age (23). Therefore, it is possible that the breathing pattern during REM sleep in infants differs from REM breathing in older individuals.

In view of these differences in physiology between infants and older individuals, we thought it likely that spontaneous breathing during sleep in older individuals with CHS would differ from that of infants. Considering that sleep-disordered breathing in most conditions is typically worse during REM than NREM sleep and that limb movement is less common during REM, we hypothesized that subjects with CHS who were past infancy would have more severe hypoventilation during REM than NREM sleep. Further, we sought to resolve the controversy regarding whether arousal occurred in response to endogenous gas exchange abnormalities in CHS (2, 32).

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PATIENTS AND METHODS

Subjects with CHS and controls underwent genetic testing, pulmonary function testing, and testing of hypercapnic ventilatory responses during wakefulness. Subjects with CHS then underwent polysomnography during which their spontaneous ventilation was assessed in REM vs. NREM sleep. Control sleep data were obtained from baseline polysomnography data obtained as part of another study evaluating respiratory-related evoked potentials during sleep (24).

Study Group

Subjects with both CHS and atypical forms of central hypoventilation syndromes were recruited from The Children’s Hospital of Philadelphia. In addition, a study advertisement was displayed on the Congenital Central Hypoventilation Syndrome family website. The diagnosis of CHS was made using American Thoracic Society criteria, i.e., persistent hypoventilation during sleep (PCO₂ consistently >60 mmHg) and absence of primary pulmonary, cardiac, metabolic, or neuromuscular dysfunction (2). Subjects were studied at a time when they were in good health, without any concurrent infections or recent changes in ventilator settings.

Each subject with CHS was individually age- and sex-matched to a normal control recruited from the community by means of advertisements.

The study was approved by The Children’s Hospital of Philadelphia Institutional Review Board. Informed consent was obtained from subjects older than 18 yr of age and from the parents/legal guardians of the younger subjects. In addition, assent was obtained from the subject him/herself in the presence of a parent/legal guardian if the subject was between 7 and 17 yr of age.

Genetic Testing

Resequencing of PHOX2B genomic DNA was performed unless results from prior clinical testing (performed at Rush University Medical Center) were available. Bidirectional sequencing of PHOX2B coding sequence was performed as previously described (40). Briefly, oligonucleotide primer pairs flanking the coding regions of exons 1, 2, and 3 of PHOX2B were designed using Primer 3.0 and used for PCR amplification and bidirectional sequencing of purified PCR products (primer sequences available on request). All sequence aberrations were confirmed by repeat sequencing after cloning of purified PCR products (TOPO TA Cloning; Invitrogen Life Technologies, Carlsbad, CA).

Hypercapnic Ventilatory Response Testing

Hyperoxic hypercapnic ventilatory response testing was performed during wakefulness in the morning using the Read rebreathing technique (47), modified for children, as previously described (13, 15, 33–35). All tests were performed with the subjects seated comfortably, breathing through a mouthpiece and wearing nose clips, while being monitored by a physician. The mouthpiece was connected via a three-way nonrebreathing valve (Hans Rudolph, Kansas City, MO) to an anesthesia bag. For patients with tracheostomies, the tracheostomy was capped (which was standard practice for these subjects during wakefulness). Flow was measured at the mouthpiece using a heated pneumotachograph (Hans Rudolph) and pressure transducer (Validyne Engineering, Northridge, CA). Arterial oxygen saturation (SpO₂) and heart rate were measured using a pulse oximeter (Masimo, Irvine, CA). All signals were recorded digitally (PowerLab, ADInstruments, Colorado Springs, CO). Subjects rebreathed from a 13-liter bag filled with 70 ml/kg of a gas mixture with the initial composition of 95% O₂-5% CO₂. The test was continued until end-tidal PCO₂ reached 65–75 mmHg. All tests were completed within 4 min so that significant respiratory acidosis would not occur. Ventilatory responses were analyzed by performing a least-squares linear regression of minute ventilation vs. end-tidal PCO₂. The slope and correlation coefficient of the line were used to characterize each subject’s response.

Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines (38) to ensure that there was no mechanical limitation affecting ventilatory response testing.

Polysomnography

Overnight polysomnography was performed with the subjects receiving ventilatory support from their home ventilators via tracheostomy or nasal mask. The following parameters were recorded simultaneously on Rembrandt (Medcare, Buffalo, NY) and PowerLab (ADInstruments) systems: electroencephalogram (C3/A2, C4/A1, O1/A2, O2/A1), submental electromyogram (EMG), tibial EMG; electrocardiogram, chest and abdominal wall motion by respiratory inductance plethysmography (Respitrace Systems, Ambulatory Monitoring, Ardsley, NY), transcutaneous PCO₂ (TCM4, Radiometer, Bronshoj, Denmark), end-tidal PCO₂ (Novametrix 7000); SpO₂ (Masimo, Irvine, CA), oximeter pulse waveform, and digital video. The transcutaneous CO₂ monitor was calibrated at the beginning of each study using a calibration-grade 7.5% CO₂, 20.9% O₂, balance N₂ gas mixture, in accordance with the manufacturer’s instructions. To minimize drift as well as the possibility of skin burn, the sensor position was changed after 4 h. Flow was measured from the tracheostomy/mask using a heated pneumotachograph (Hans Rudolph) and pressure transducer (Validyne Engineering). Airway pressure was measured at the tracheostomy/mask, using a differential pressure transducer (Validyne Engineering) referenced to atmosphere. Control subjects were studied while wearing a nasal mask and breathing through a similar respiratory circuit as the CHS subjects receiving noninvasive ventilation; continuous positive airway pressure (CPAP) of 2 cmH₂O was provided as a bias flow. Sleep architecture was scored using standard techniques (48). Arousals were scored by a blinded registered polysomnography technologist viewing only EEG, electrooculogram, and EMG channels, using the American Sleep Disorders Association criteria (1). In brief, arousals were scored if there was an abrupt shift of EEG frequency lasting at least 3 s. In REM, this EEG shift had to be accompanied by an increase in submental EMG (1).

Spontaneous Breathing Trials

Subjects were allowed to fall asleep while using their ventilators on their home settings. In some cases, ventilator settings were adjusted to improve gas exchange. Each individual’s baseline end-tidal CO₂ was similar between REM and NREM challenges (group mean CO₂ was 42 ± 7 mmHg during REM and 41 ± 7 mmHg during NREM, P = 0.381). Once the patient was stable, spontaneous ventilation was evaluated by briefly disconnecting the ventilator. All testing was performed in the presence of a respiratory therapist and a pulmonary physician. The protocol called for the trial to be discontinued once the end-tidal PCO₂ rose to >55 mmHg for more than 5 min, or >60 mmHg for any duration, or the subject aroused. Following the trial, the subject was reconnected to the ventilator until baseline settings were reached. If necessary, the subject was hand-ventilated with supplemental oxygen and an Ambu bag. Two trials were attempted during NREM and REM sleep, respectively. Trials were separated by at least 15 min. For data analysis, the transcutaneous CO₂ peak following interventions was used to account for the transcutaneous monitor lag time.

Data Analysis

Respiratory parameters were analyzed on the PowerLab system. Tidal volume was calculated by integrating the flow signal, and minute ventilation by multiplying tidal volume by respiratory rate. Baseline parameters were determined for 1 min before each trial (mean of 20 ± 5 breaths). During the challenge, all breaths before the patient either awoke or was reconnected to the ventilator were assessed (mean of 12 ± 7 breaths).
Data are presented as means ± SD unless otherwise stated. Statistical analyses were performed using Sigmastat For Windows version 2.03 (SPSS). Parameters that would be expected to change with age or body size (respiratory rate, tidal volume, minute ventilation, heart rate) were compared under different conditions as a percentage of baseline, whereas other parameters (such as gas exchange values) were compared using absolute values. Data were tested for normality using the Kolmogorov-Smirnov test. Parametric tests were used when data conformed to parametric assumptions. When these assumptions were violated, appropriate nonparametric tests were performed. Parameters from REM vs. NREM sleep were compared using McNemar’s, Wilcoxon signed rank, or paired t-tests as appropriate. Data from subjects before and after ventilator disconnection were compared using the paired t-test. As the number of subjects arousing during trials differed between REM and NREM, gas exchange parameters at arousal were compared using the unpaired t-test. A P value <0.05 was considered significant.

RESULTS

Study Group

Demographic data are shown in Table 1. The study group included all patients with CHS who were older than infancy and were followed at The Children’s Hospital of Philadelphia, plus three subjects recruited via the congenital central hypoventilation syndrome website. Seven subjects had classic congenital CHS, and two were atypical. The latter included a subject (Table 1, subject 4) with late-onset central hypoventilation syndrome associated with hypothalamic abnormalities, consistent with previously described cases (26). He was asymptomatic until 4 yr 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 (subject 5) with atypical disease presented at 5 yr 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 (8). None of the subjects was receiving ventilation during wakefulness, although 24-h ventilation had been recommended for but refused by a 20-yr-old subject (subject 9).

All 7 subjects with classic congenital CHS had a polyalanine expansion mutation, with 25–27 polyalanine repeats (Table 1). Both of the children with atypical hypoventilation syndromes had normal genetic testing, consistent with the literature (8, 25, 36). No controls had mutations.

Pulmonary function tests were normal in all subjects, except one subject with CHS who had very mild obstructive disease [forced expiratory volume in 1 s (FEV₁) = 78% predicted; FEV₁/(forced vital capacity) = 77%]. All subjects with CHS had a totally flat response to hypercapnic testing, indicating very abnormal hypercapnic ventilatory drives, whereas all control subjects evidenced a vigorous ventilatory response (Table 1).

Polysomnography

Most patients were adequately ventilated during sleep on their home settings. In two subjects, minor changes were made in ventilator settings to improve ventilation. A third subject, recruited via the website, was usually ventilated at home using diaphragm pacers without a tracheostomy, supplemented by facemask noninvasive ventilation as needed. She was noted to have obstructive sleep apnea, which resolved when the pacers were switched off and she was ventilated using noninvasive face mask ventilation alone. All ventilator changes were performed at the beginning of the night before the disconnection challenges. Thus there were no large, abrupt swings in oxygenation or ventilation that would be expected to affect study outcomes.

Spontaneous Breathing Trials

Some subjects awoke immediately when the ventilator was disconnected [i.e., EEG changes consistent with wakefulness for >15 s (48), as well as behavioral changes]. This was most likely due to the disconnect maneuver itself, and thus no data were collected and the trials were repeated. However, in three trials, the subjects had American Sleep Disorders Association-defined microarousals (1) on disconnection and then immediately fell asleep again; these trials were included in the analysis. Similarly, trials where microarousals occurred during the

Table 1. Subject demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Sex</th>
<th>BMI Z-Score</th>
<th>Mode of Ventilation</th>
<th>Other Clinical</th>
<th>PHOX2B Mutation</th>
<th>HCVR, slope in l·min⁻¹·mmHg⁻¹ (correlation coefficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>5</td>
<td>F</td>
<td>1.80</td>
<td>NIPPV</td>
<td>Developmental delay; Hirschsprung’s disease</td>
<td>20/26; -0.17 (-0.37)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>6</td>
<td>M</td>
<td>1.15</td>
<td>Trache</td>
<td></td>
<td>20/27; 0.62 (0.17)</td>
</tr>
<tr>
<td>Subject 3</td>
<td>8</td>
<td>M</td>
<td>0.69</td>
<td>NIPPV</td>
<td>Hirschsprung’s disease</td>
<td>20/27; 0.22 (0.17)</td>
</tr>
<tr>
<td>Subject 4</td>
<td>8</td>
<td>M</td>
<td>2.60</td>
<td>NIPPV</td>
<td>Late-onset, hypothalamic abnormalities, ganglioneuroma</td>
<td>20/20; 0.10 (-0.20)</td>
</tr>
<tr>
<td>Subject 5</td>
<td>8</td>
<td>M</td>
<td>1.86</td>
<td>Trache</td>
<td>Late onset</td>
<td>20/20; 0.08 (0.28)</td>
</tr>
<tr>
<td>Subject 6</td>
<td>17</td>
<td>F</td>
<td>0.42</td>
<td>Trache</td>
<td></td>
<td>20/25; 0.13 (0.06)</td>
</tr>
<tr>
<td>Subject 7</td>
<td>20</td>
<td>F</td>
<td>2.45</td>
<td>Trache</td>
<td></td>
<td>20/25; 0.37 (0.14)</td>
</tr>
<tr>
<td>Subject 8</td>
<td>20</td>
<td>F</td>
<td>1.42</td>
<td>Trache</td>
<td></td>
<td>20/26; -0.08 (-0.19)</td>
</tr>
<tr>
<td>Subject 9</td>
<td>20</td>
<td>M</td>
<td>0.77</td>
<td>NIPPV</td>
<td></td>
<td>20/27; 0.00 (0.02)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13±7</td>
<td>F; M 4</td>
<td>1.5±0.8</td>
<td>NIPPV</td>
<td></td>
<td>slope 0.14±0.24; correlation coefficient 0.01±0.22</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20/20; 3.41±1.48*; correlation coefficient 0.81±0.13*</td>
</tr>
</tbody>
</table>

CHS, central hypoventilation syndrome; M, male; F, female; BMI, body mass index; HCVR, hypercapnic ventilatory response; NIPPV, noninvasive positive pressure ventilation; Trache, positive-pressure ventilation via tracheostomy. *P < 0.001.
time the subject was disconnected, but where the subject resumed sleep, were included, although breaths during the arousal period were excluded from analysis. This occurred on 5 of the 26 trials (NREM: 1 arousal occurred in each of 4 trials; REM: 1 arousal occurred in 1 trial). A state change from a deeper to lighter stage of NREM sleep occurred in one trial following arousal. In no case did the state change from REM to NREM or vice versa.

Thirteen paired (REM/NREM) trials were performed successfully. Of the NREM trials, seven were initiated in slow-wave sleep, five in stage 2 sleep, and one in stage 1 sleep. In subjects with multiple NREM trials, all NREM trials were the same sleep stage. There was no significant difference in any analyzed parameter between NREM sleep stages (although the study was not powered to address differences between NREM stages). The length of the disconnect trial averaged 82 ± 62 s. Figure 1 shows an example of a central apnea and arousal following ventilator disconnection during NREM sleep.

Arousal. Excluding the immediate arousals on ventilator disconnection, arousal occurred in 46% of REM trials and 38% of NREM trials ($P = 0.789$, not significant [NS]). Time to arousal was 34 ± 72 s (range 11–272 s). For those who aroused, the SpO2 (mean ± SD) was 96 ± 3% and 98 ± 3%, and the transcutaneous PCO2 was 37 ± 3 mmHg and 37 ± 11 mmHg, during REM and NREM, respectively. There were no significant differences in time to arousal ($P = 0.583$) or in SpO2 ($P = 0.525$) or transcutaneous PCO2 ($P = 0.995$) at arousal, in REM vs. NREM sleep.

Central apnea. Central apneas ≥ 5 s duration (~2 missed breaths) were scored. Central apnea occurred in 42% of trials.
In all cases, the central apnea occurred at the beginning of the ventilator disconnect; two subjects each had an additional central apnea later in the same trial. The duration of central apnea was 25 ± 19 s. In two subjects, the trial was ended by the physician because of desaturation before any spontaneous breathing occurred; these central apneas ranged from 38 to 54 s. In most cases, central apneas were not associated with arousal. Although proportionately more central apneas occurred during NREM (54% of trials) than REM (31% of trials), this difference was not significant (P = 0.752).

The relationship between end-tidal PCO2 on the ventilator and the length of central apnea was assessed. There was substantial variation in the baseline levels of PCO2 when the subjects were mechanically ventilated during sleep (note that subjects were managed clinically at 4 different institutions), ranging from PCO2 values in the 20s to 60s. It was found that those with the highest end-tidal PCO2 had the longest central apneas (Fig. 2). In addition, data were examined to determine whether ventilating subjects at or below their awake PCO2 affected the occurrence of central apnea on ventilator disconnection. Most subjects had an elevated end-tidal PCO2 when breathing spontaneously during wakefulness, with a group mean wake PCO2 of 50 ± 8 mmHg. The difference in PCO2 between wakefulness and mechanical ventilation during sleep varied from 5 to 40 mmHg. Linear regression showed no significant relationship between the length of central apnea and the difference between wake and sleep PCO2 at the time of the trial (r = 0.26; P = 0.204).

Minute ventilation. Minute ventilation during ventilator disconnection was compared with the mean minute ventilation for the 60 s preceding disconnection. The change in respiratory rate was calculated both including and excluding periods of central apnea. Flow data were not obtained for subject 1 and for REM runs for subject 3 as the pneumotachometer was disconnected during the trial. There was a highly significant decrease in respiratory rate, including periods of central apnea, tidal volume, and minute ventilation when subjects were breathing spontaneously compared with when they were mechanically ventilated (Table 2). However, the decrease in tidal volume was much larger than the decrease in respiratory rate. An example of a subject breathing spontaneously during REM and NREM sleep is shown in Fig. 3.

When subjects receiving mask ventilation (N = 4) were compared with those with tracheostomies (N = 5), subjects with mask ventilation had a greater drop in tidal volume (85 ± 11% vs. 67 ± 22%, P = 0.034) and minute ventilation (91 ± 8% vs. 67 ± 25%, P = 0.012) than those receiving mask ventilation. The difference in respiratory rate changes between the two groups was not significant (38 ± 29% vs. 19 ± 25%, P = 0.264).

There was a greater decrease in minute ventilation during NREM compared with REM sleep (Table 3). Tidal volume fell more during NREM than REM, but this difference was not statistically significant. There was also a significant decrease in respiratory rate as a percentage of baseline during NREM vs. REM sleep when central apnea time was included in the calculation; this difference was not significant when central apneas were excluded.

Minute ventilation during REM vs. NREM sleep after ventilator disconnection was also compared with spontaneous breathing during quiet wakefulness, rather than breathing while asleep during mechanical ventilation, as a baseline. A similar trend was observed, with a greater decrease in minute ventilation, tidal volume, and respiratory rate when central apnea time was included during NREM vs. REM sleep, although only the latter was statistically significant (P = 0.014).

Gas exchange. The initial study design called for discontinuation of the challenge once significant elevation of end-tidal PCO2 occurred. In practice, this rarely occurred. In many cases, good end-tidal PCO2 waveforms were present when the subject was mechanically ventilated, but were inadequate following ventilator disconnection because the diminution of tidal volumes resulted in nondetectable waveforms. Thus the transcutaneous PCO2 value was the primary outcome used to evaluate for hypercapnia. Following disconnection of the ventilator, most subjects had a period of stable hypoventilation, followed by a very rapid decrease in arterial oxygen saturation. In all cases, the duration of desaturation was very brief (seconds) before the ventilator was reconnected. Overall, 42% of trials were terminated because of subject arousal, 54% because of desaturation, and only 4% because of hypercapnia. Retrospectively, those trials terminated due to arousal or desaturation did not have clinically important hypercapnia, based on the end-tidal PCO2 reading of the first breaths after ventilator reconnection as well as the transcutaneous PCO2 reading within several minutes after reconnection. Only one subject required ventilatory assistance via Ambu bag, due to precipitous desaturation. There was a significant decrease in SpO2 and increase in hypercapnia during the trials (Table 2). However, there was no significant difference in the drop in SpO2 or the increase in transcutaneous PCO2 between REM and NREM sleep (Table 3). At challenge termination, SpO2 was 85 ± 11% and 80 ± 13%.
and transcutaneous $PCO_2$ was 49 ± 15 mmHg and 47 ± 17 mmHg during REM and NREM, respectively.

Heart rate. Heart rate was calculated for the last 10 s of the trial compared with 1 min of baseline. There was no significant change in heart rate, with a mean change of only −1% (Table 2), or −1 ± 12 beats/min in absolute value ($P = 0.537$). There was no difference in the change in heart rate between REM and NREM sleep (Table 3).

Late-onset central hypoventilation subjects. There were no clear differences in any of the parameters between the two subjects with late-onset central hypoventilation and the remainder of the group. Excluding these two subjects from analysis did not alter the significance of any of the findings, with the exception of the decline in minute ventilation between REM and NREM sleep, which was still a trend with this smaller sample size ($P = 0.081$).

Control data. There were no significant differences in any respiratory or cardiac parameters in NREM vs. REM sleep in the controls (Fig. 4).

**DISCUSSION**

In summary, this study showed that older patients with CHS had more severe hypoventilation during NREM than REM sleep, although breathing during REM was still severely impaired. There was also a trend for more central apnea during NREM sleep. In addition, and contrary to common expectation, this study showed that subjects with CHS had frequent arousals associated with gas exchange abnormalities during sleep, and that central apnea was relatively common.

Reviews of CHS frequently mention that patients breathe better during REM than NREM sleep (2). However, this assumption has been based primarily on case reports, and in all cases, only infants were studied. In 1980, Fleming et al. (12) described a single infant with CHS, noting a greater decrease in both respiratory rate and tidal volume during quiet (NREM) compared with active (REM) sleep (12). Arousal in response to severe hypoxemia ($PO_2 < 30$ mmHg) occurred during active but not quiet sleep. Surprisingly, however, they detected a steady-state ventilatory response to hypercapnia during quiet sleep but not during active sleep or wakefulness. Cornwell et al. (7) reported more apnea during quiet than active sleep in a single infant, but minute ventilation was not measured and statistical analyses were not provided. Takahashi et al. (51) studied another infant and reported more severe hypoventilation during NREM than during some REM cycles. However, it was noted that the patient had severe hypoventilation during sleep-onset REM periods. Guilleminault et al. (19) studied six infants, although minute ventilation was not measured in this study and group data were not provided. They noted that arousals occurred in response to central apneas during active but not quiet sleep in some infants, and that central apneas were longer during quiet sleep than active sleep. They also noted that several infants had more severe gas exchange abnormalities during quiet sleep than during active sleep. In contrast to the earlier studies, the present study is the first to systematically study a group of older subjects. It also supplies a systematic evaluation of minute ventilation in addition to gas exchange and arousals.

In normal subjects, breathing is more irregular during REM than NREM sleep, and $SpO_2$ is lower. Human studies suggest that ventilatory responses to hypoxia and hypercapnia are lowest during REM sleep (10, 21). Central apneas are more common during REM than NREM sleep in children (49), although in adults central apneas frequently occur during stage 1 sleep. Obstructive apnea occurs primarily during REM sleep in children (14, 39) and tends to be most severe during REM sleep in adults (11). Thus CHS appears unique in being the only respiratory disorder in which breathing is better during
according to the level of end-tidal PCO2, as well as the patient’s leminault et al. (19) reported one case where arousal varied neurotically for long periods, hypoxemia may cause central ner-

evous hypercapnia and hypoxia. What can explain this who were well-ventilated during sleep aroused in response to contrast, Marcus et al. (32) showed that children with CHS based on case reports or studies where patients with CHS were

is in contrast to the literature, where it is often stated that the normal central integration of chemoreceptor function (16, 20, 31, 32, 46). The reason why most patients with CHS breathe adequately during wakefulness but not during sleep is unclear. Studies indicate that movement, probably mediated through mechanoreceptor stimulation, is a key factor in increasing ventilation during wakefulness in this population (17, 18, 45). However, during REM sleep, most skeletal muscles are atonic, so mechanoreceptor activation cannot explain the improved breathing during REM. Thus other factors must also play a role in stimulating breathing in this population. In many ways, the central nervous system is similarly activated during REM sleep and wakefulness. During both wakefulness and REM sleep, there are tonic excitatory inputs to the respiratory system; these inputs decline during NREM sleep (5, 42–44). Studies using single-neuron recordings of medullary respira-
tory cells have demonstrated increased firing rates during REM compared with non-REM sleep, even during hyperventilation-induced apnea in intubated animals, when most chemical and mechanical afferents to the respiratory control centers have been eliminated (44). This intrinsic REM-related ventilatory drive may explain why ventilation in subjects with CHS is greater during REM than NREM sleep. However, the breathing during REM sleep in these subjects is still markedly depressed compared with wakefulness, presumably due to the absence of certain excitatory effects on the respiratory system that are strictly limited to the awake state, and possibly also due to REM sleep-specific inhibitory effects on skeletal muscles.

The pathophysiology of the abnormal ventilatory control in CHS is not fully understood but is thought to be due to abnormal central nervous system abnormality in patients with CHS is such that it overrides the normal impact of sleep state on breathing and is relatively insensitive to developmental stage. As a similar pattern was observed in the patients with and without the PHOX2B mutation, this central nervous system abnormality is unlikely to be due to the specific PHOX2B genetic abnormality.

In this study, we included trials during which arousal occurred, although arousal breaths were not included. However, it is possible that on reinitiation of sleep, the level of ventila-

tion may have changed compared with during sleep before the arousal. The limited data, combined with the highly variable nature of breathing during REM, make this difficult to deter-

mine. However, if it were occurring it would translate into increased within-state variance and make it more difficult to see significant between-state (i.e., REM vs. NREM) differ-

ences. Thus any error introduced would be highly conservative. Furthermore, most of these arousals occurred during NREM sleep, and thus any potential error would be in the opposite direction of the study results.

Central apnea was common during this study, occurring in approximately one-third of trials and often resulting in sudden drops in SpO2. This illustrates the hazards of accidental ven-
tilator disconnection in the home environment and the need for appropriate alarms. We were concerned that the common practice of hyperventilating patients with CHS (2) may have exacerbated the degree of central apnea, by lowering the PCO2 below the apneic threshold. However, there was no significant correlation between the wake-sleep PCO2 difference and the length of central apnea. Indeed, it is possible that patients with CHS, by virtue of their impaired ventilatory control, may not even have an apneic threshold. In fact, we found that patients who were hypoventilated during sleep were most likely to have central apneas, suggesting that tight control of the PCO2 during mechanical ventilation is optimal.

Subjects receiving ventilation via tracheostomy tolerated spontaneous breathing better than patients receiving noninva-
sive ventilation. This may have been because of the added load of upper airway resistance (29) in the mask group.

The subjects with CHS in this study did not develop tachy-
cardia or bradycardia in response to hypoxemia. This is in concordance with the known autonomic dysfunction present in patients with CHS (27, 30, 56, 57) and with the function of the PHOX2B gene.

In this study, we chose to compare parameters during the ventilator disconnection trials to baseline parameters with the subjects asleep and receiving mechanical ventilation. We con-

sidered this a valid technique as both REM and NREM dis-

connection trials were initiated from the same ventilator set-

tings. However, it can be argued that a baseline on mechanical ventilation was an artificial baseline, determined by the physi-
cian rather than by the subjects’ physiology. An alternative would be to compare ventilatory parameters during REM vs. NREM sleep to a baseline of spontaneous breathing during quiet wakefulness. Although these data are provided (and show similar results), we consider the latter technique less valid as normal subjects have a decrease in ventilation of 13–15% from wakefulness to either REM or NREM sleep (28). It was not possible to conduct the trials by simply allowing the subjects to fall asleep while breathing spontaneously, as severe hypoxemia would ensue before the subjects entered REM sleep.

There are several limitations to this study. The study sample was small and heterogeneous. CHS is a very rare condition; in 1999, it was estimated that there were only 180 patients with congenital CHS worldwide (2), whereas a recent study sug-

gests an incidence of 1 per 200,000 live births (52). Thus some analyses, such as the difference in central apnea between REM and NREM sleep, may have been underpowered. As CHS is rare and the study population was therefore limited, we also included children with late-onset CHS who did not have mutations in the PHOX2B gene. We considered this valid as these subjects had a similar phenotype to the children with classic congenital CHS, including central hypoventilation with
absent hypercapnic ventilatory responses. Furthermore, this allowed us to evaluate whether study findings were related to the genetic abnormality per se or not. However, excluding these two subjects did not alter our findings. It should be noted that some children with late-onset CHS, particularly those without hypothalamic manifestations, have been reported to have PHOX2B mutations, whereas others have not, suggesting overlap between the syndromes (25, 36, 53).

It should be noted that, although there was a greater decrease in minute ventilation during NREM compared with REM trials, there was no significant difference in transcutaneous PCO2 values between the two conditions. Considering the decrease in minute ventilation, the lack of a difference in CO2 trials, there was no significant difference in transcutaneous PCO2 values between the two conditions. The average length of trials was 82 s, which may not have been long enough for a change in transcutaneous PCO2 to become manifest.

In summary, this study has shown that patients with CHS breathe better during REM than NREM sleep and frequently arouse in response to desaturation. This sheds some light on our understanding of the pathophysiology of this rare condition but does not alter clinical management, as hypoventilation is nonetheless severe during REM sleep, and arousal does not always occur.

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REFERENCES


