24-Hour BP in Children With Congenital Central Hypoventilation Syndrome*

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Objective: To study circadian BP patterns in patients with congenital central hypoventilation syndrome (CCHS).

Design: Case-control study.

Setting: Teaching hospital in Paris, France.

Patients: Eleven patients with CCHS (median age, 13 years; range, 6 to 18 years) and 11 sex- and height-matched control subjects.

Intervention: None.

Methods: Each subject underwent 24-h ambulatory BP monitoring. Oxygen saturation and end-tidal PCO₂ were monitored noninvasively. Polysomnography was performed to determine sleep times. All patients with CCHS received mechanical ventilation during sleep. Mean values for systolic BP (SBP) and diastolic BP (DBP) during wakefulness and sleep were analyzed. Nocturnal BP “dipping” was defined as the difference in mean SBP (and/or DBP) between wakefulness and sleep, divided by individual waking mean values. BP “dippers” were defined as subjects showing at least 10% nocturnal dipping.

Results: Patients with CCHS had BPs in the low normal range of normative data. As compared to control subjects, patients with CCHS had lower BP during wakefulness (p < 0.003 and p < 0.016 for SBP and DBP, respectively), and higher BP during sleep (p = 0.016 and p = 0.002). Nocturnal BP dipping was abnormally reduced in patients with CCHS (p < 0.000). Ten of the 11 patients with CCHS were BP nondippers, compared to none of the control subjects.

Conclusion: The abnormal circadian BP pattern observed in children and adolescents with CCHS may be related to autonomic nervous dysfunction. Lifelong cardiovascular follow-up is recommended for patients with CCHS.

Key words: autonomic nervous function; BP; respiratory control; sleep

Abbreviations: CCHS = congenital central hypoventilation syndrome; DBP = diastolic BP; GDNF = glial-cell derived neurotrophic factor; HR = heart rate; NREM = non-rapid eye movement; PETCO₂ = end-tidal PCO₂; REM = rapid eye movement; SBP = systolic BP; SpO₂ = oxygen saturation

Congenital central hypoventilation syndrome (CCHS) is a rare disease characterized by impaired central control of breathing. CCHS manifests as alveolar hypoventilation, which is typically more severe during sleep than during wakefulness and is most marked during non-rapid eye movement (NREM) sleep.¹⁻³ Although the cause of CCHS is unknown, a growing body of data suggests that CCHS may be related to abnormal development of neural crest-derived cells.²⁻⁸ Nearly 20% of patients with CCHS have Hirschsprung disease.²⁻⁴ Autonomic nervous dysfunction has been suggested to explain heart rate (HR) dysregulation,⁵,⁶ esophageal dysmotility,⁷ or ocular disorders⁸ observed in patients with CCHS. Mutations in genes involved in the RET/glial-cell derived neurotrophic factor (GDNF) and endothelin pathways have been identified in a few patients with CCHS.⁹⁻¹¹ Also, widespread dysfunction of brain stem structures is thought to exist.²,³ Studies¹²,¹³ have provided evidence of complex interactions between central control of respiration and central control of cardiovascular or GI tract function, which may be largely dependent on brain structures located in the ventral medullary surface.

Patients with CCHS sometimes experience dizziness or syncopes, which have been ascribed to sinus
bradycardia and sinus pauses. Decreased HR variability has been reported. Long-term BP control has not been studied. We hypothesized that BP control may be altered in CCHS and that this may contribute to the occurrence of dizziness or lightheadedness. To investigate this hypothesis, we evaluated the circadian BP pattern in a group of patients with CCHS. We used ambulatory BP monitoring, which has been found reliable for evaluating BP in children and adolescents, and is being increasingly used for clinical management and research in a variety of diseases.

**Patients and Methods**

**Patients With CCHS**

Eleven children and adolescents with CCHS (9 girls and 2 boys; median age, 13 years; range, 6 to 18 years) underwent 24-h ambulatory BP monitoring. Four patients (patients 1, 3, 6, and 8) reported a history of infrequent episodes of dizziness or lightheadedness (fewer than two episodes per year) [Table 1]. All patients had been evaluated at the Department of Physiology, Robert Debré Teaching Hospital, Paris, France, and found to fulfill criteria for idiopathic CCHS: (1) persistent central alveolar hypoventilation (PaCO₂ > 60 mm Hg) during sleep detected by polysomnography while the patient spontaneously breathed room air; (2) lack of ventilatory response to inhaled CO₂; and (3) absence of lung, cardiac, neuromuscular, or brain stem disorders known to cause hypoventilation. All the study patients were of French or Italian descent.

As shown in Table 1, 10 of the 11 patients had an isolated CCHS phenotype (the exception was patient 8). Nocturnal ventilation was delivered via a nasal mask in seven patients and a tracheostomy cannula in the other three patients. None of these patients were receiving medications known to affect BP or HR. All breathed room air spontaneously during the day and at night.

Two patients (patient 1 and patient 6) had human achaete-scute homologue 1 gene mutations, which were de novo in one patient and inherited from a healthy father in the other patient. None had mutations in genes encoding RET, GDNF, endothelin-3, or endothelin B receptor.

**Control Subjects**

Eleven healthy sex- and height-matched control subjects were recruited among the children of the hospital staff. Median age was 11 years (range, 6 to 17 years). All the control subjects were of French descent. None were obese or had known respiratory, cardiovascular, or renal disease. None were receiving medications known to affect BP or HR. All breathed room air spontaneously during the day and at night.

**Methods**

The study was approved by the appropriate ethics committee, and informed consent was obtained from the parents. Each subject underwent 24-h ambulatory BP monitoring using an oscillometric device (SpaceLabs 90207; SpaceLabs Medical; Redmond, WA). The cuff was chosen to match arm size and placed around the nondominant arm, as recommended by the 1987 Task Force on BP Control in Children. The monitor was programmed to read BP every 20 min during daytime (8 am to 8 pm) and every 30 min during nighttime (10 pm to 8 am), and to take one additional measurement 3 min after a failed reading. Systolic BP (SBP) and diastolic BP (DBP) and HR were recorded and stored in the monitor device.

Each subject had also oxygen saturation (SpO₂) and end-tidal PCO₂ (PETCO₂) monitored noninvasively using a portable pulse oximetry/capnography (Tidal Wave; Novametrix; Wallingford, CT) and an actigraphic recording (Activwatch; Cambridge, UK) during daytime. An attended full-night polysomnography was performed to determine sleep times and gas exchange status during sleep. The attended variables were EEG, electrooculogram, submental electromyogram, nasobuccal or tracheal airflow using thermistors, thoracoabdominal respiratory movements using strain gauges, SpO₂ and PETCO₂ (Novametrix), and ECG. Behavior and activity diaries were completed by the children or parents. All children engaged in their usual activities and went to sleep at their preferred time. All patients with CCHS received mechanical ventilation during nocturnal sleep.

**Analysis**

Polysomnography was analyzed as recommended by guidelines for pediatric sleep studies. Sleep was staged based on criteria of Rechtschaffen and Kales. Apneas were scored on polysomnographic recordings.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>CCHS Phenotype</th>
<th>Nighttime Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>6</td>
<td>Isolated</td>
<td>Tracheostomy</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>6</td>
<td>Isolated</td>
<td>Tracheostomy</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>7</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>12</td>
<td>Isolated</td>
<td>Tracheostomy</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>12</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>13</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>13</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>15</td>
<td>CCHS + Hirschsprung disease + ganglioneuroma</td>
<td>Tracheostomy (+ daytime pacer)</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>16</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>17</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>18</td>
<td>Isolated</td>
<td>Mask</td>
</tr>
</tbody>
</table>
graphic traces of the control subjects. SpO₂ and PETCO₂ were determined in the early morning (9 to 10 AM), in the late afternoon (6 to 7 PM), and during sleep.

SBP, DBP, and HR obtained from ambulatory monitoring were analyzed. Single measurement values for each variable were extracted into the SPSS software (SPSS; Chicago, IL) that read the ASCII text files generated by the monitor device. One-hour mean values were calculated and used to determine means during wakefulness and during sleep.

BPs of patients with CCHS were compared to those in the sex- and height-matched control subjects, and to normative data previously obtained in a large group of healthy European children and adolescents.¹⁶ The percentages of BP readings below the 50th percentiles of normative data were calculated. The difference in mean SBP (and/or DBP) between wakefulness and sleep was calculated and divided by individual waking mean values. A value of ≥10% defined nocturnal BP dipping; thus, a nondipping pattern was defined as a value of <10%.

Data are shown as medians and ranges, unless stated otherwise. Differences between patients with CCHS and control subjects and between sleep stages in each study group were evaluated using nonparametric Wilcoxon signed-rank tests. Correlations between BP and demographic or gas exchange data in patients with CCHS were evaluated using Spearman tests; p < 0.05 was considered significant. All statistical analyses were performed using SPSS software (SPSS).

**Results**

Table 2 compares sleep and BP data between patients with CCHS and control subjects. Representative 24-h BP patterns obtained in one patient and one control subject are shown in Figure 1.

None of the patients with CCHS or control subjects experienced dizziness during the recordings. No significant differences were found for total or rapid eye movement (REM) sleep times. SpO₂, or PETCO₂ between the two groups. Control subjects had an apnea index of 0.2 (range, 0 to 0.4) and normal SpO₂ and PETCO₂. Patients with CCHS slightly increased their PETCO₂ in the late afternoon (p = 0.009; Table 3).

In each group, mean SBP and DBP during wakefulness and sleep were between 10th and 90th percentiles of normative data, and no differences were found between REM and NREM sleep. However, as compared to control subjects, patients with CCHS had lower BPs during wakefulness (p = 0.003 and p = 0.016 for SBP and DBP, respectively) and higher BPs during sleep (p = 0.016, and p = 0.002; Fig 2). BPs did not correlate with SpO₂ or PETCO₂ in patients with CCHS.

In the patients with CCHS, 79% (range, 60 to 100%) of the SBP and 76% (range, 53 to 95%) of the DBP readings were below the 50th percentile during wakefulness. These percentages were significantly higher than in the control subjects (p = 0.001; Fig 3). Conversely, the corresponding percentages during sleep were similar in the two groups. The percentage of DBP readings below the 50th percentile during wakefulness increased with age (r = 0.64, p = 0.046) and height (r = 0.701, p = 0.024) in the CCHS group. Data were similar in tracheostomized and nontracheostomized patients with CCHS. Results from patient 8 were within the range of those in the other patients.

Nocturnal dipping was less marked in the patients with CCHS than in the control subjects (Table 2), for both SBP and DBP (p = 0.000) and for HR (p = 0.012; Fig 4). Ten of the 11 patients with CCHS were nondippers, compared to none of the control subjects. Five patients with CCHS were systolic nondippers, and five were systolic and diastolic nondippers. Four patients had higher BPs during sleep.

**Table 2—Demographic and Sleep Data, BP, and Heart Rate in CCHS Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Variables</th>
<th>CCHS</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>13 (6–18)</td>
<td>11 (6–17)</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>151 (115–174)</td>
<td>144 (120–174)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>42 (18–67)</td>
<td>43 (23–67)</td>
<td>NS</td>
</tr>
<tr>
<td>Awake time, h</td>
<td>14 (11–18)</td>
<td>14 (12–16)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>109 (97–112)</td>
<td>117 (104–123)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>66 (60–75)</td>
<td>71 (63–77)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean HR, beats/min</td>
<td>96 (68–115)</td>
<td>92 (77–101)</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep time, h</td>
<td>8 (5–12)</td>
<td>10 (7.5–10.5)</td>
<td>NS</td>
</tr>
<tr>
<td>REM sleep time, % sleep time</td>
<td>18 (10–24)</td>
<td>16 (13–23)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>104 (91–109)</td>
<td>95 (90–103)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>63 (54–70)</td>
<td>55 (46–55)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean HR, beats/min</td>
<td>84 (51–97)</td>
<td>73 (58–85)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP nocturnal dipping, %</td>
<td>3 (–1–12)</td>
<td>15 (10–20)</td>
<td>0.000</td>
</tr>
<tr>
<td>DBP nocturnal dipping, %</td>
<td>8 (–21–19)</td>
<td>27 (22–29)</td>
<td>0.000</td>
</tr>
<tr>
<td>Nocturnal fall in HR, %</td>
<td>14 (5–25)</td>
<td>21 (14–23)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Data are presented as median (range) unless otherwise indicated. NS = not significant.
during sleep than during wakefulness (for both SBP and DBP in two cases, SBP only in one case, and DBP only in one case).

**Discussion**

The main finding from this study was that children and adolescents with CCHS exhibited a nondipping circadian BP pattern. They had lower BPs during wakefulness and higher BPs during sleep than did the control subjects. Ten of the 11 patients with CCHS were nondippers, compared to none of the control subjects. Four patients had higher BPs while asleep than while awake.

Over the last few years, ambulatory BP monitoring has been increasingly used in various populations of

![Table 3 — Spo2 and PetCO2 in Patients With CCHS*](https://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20384/)

Table 3—Spo2 and PetCO2 in Patients With CCHS*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early Morning (9 to 10 AM), Spontaneous Ventilation</th>
<th>Late Afternoon (6 to 7 PM), Spontaneous Ventilation</th>
<th>Sleep, Mechanical Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spo2, %</td>
<td>96 (95–98)</td>
<td>95 (91–99)</td>
<td>98 (93–98)</td>
</tr>
<tr>
<td>PetCO2, mm Hg</td>
<td>36 (33–39)</td>
<td>43 (35–50)†</td>
<td>39 (37–42)</td>
</tr>
</tbody>
</table>

*Data are presented as median (range).

†p = 0.009 vs early morning.
adults and children, and circadian BP patterns been assessed based on changes between daytime and nighttime values.\textsuperscript{16–20} In most investigations, the study periods were either predetermined using clock times or defined based on patient diaries or actigraphic recordings.\textsuperscript{22} We used polysomnography to identify periods of wakefulness and sleep in each individual and therefore obtained a more accurate assessment of the circadian BP pattern.

Definitions of BP dipping have varied across studies. Normal dipping was initially defined as a pressure decrease by at least 10 mm Hg systolic or 5 mm
Hg diastolic at night as compared to daytime values.23 In this study, we took the definition used in numerous studies16–20 conducted in large groups of adults, children, and adolescents with a variety of diseases, such as arterial hypertension, diabetes, or renal diseases. Nocturnal BP dipping was expressed as a percentage of individual daytime values, and normal dipping defined as a fall by ≥10%.16–20

Our main finding was that BP dipping was reduced in patients with CCHS. BPs in these patients were significantly lower during wakefulness and higher during sleep, as compared to the control subjects. Ten of the 11 patients with CCHS showed no BP dipping; among these 10 patients, 4 patients had higher SBP and/or DBP during sleep than during wakefulness.

One limitation of our study was the difference between the two groups in ventilatory conditions during sleep: all patients with CCHS received mechanical ventilation at night, whereas all control subjects spontaneously breathed room air. Although we were aware of this issue when designing the study, we believed that depriving the patients with CCHS of their usual nighttime ventilation or ventilating the control subjects during sleep would be unethical. Moreover, in patients with CCHS, absence of mechanical ventilation during sleep would result in BP changes related to severe hypoxemia and hypercapnia. Finally, it is unlikely that differences in BP patterns between patients with CCHS and control subjects were caused by differences in ventilatory conditions. Positive airway pressure ventilation at night would be expected to decrease arterial BP by decreasing preload and, subsequently, cardiac output.24,25 Instead, the opposite effects were observed in our patients with CCHS, who were unable to lower their BP during sleep, despite mechanical ventilation. Their BP values were higher during sleep than those in control subjects, and four patients with CCHS had higher SBP and/or DBP while asleep than while awake. These paradoxical findings strongly suggest that the nondipping pattern was an intrinsic characteristic of CCHS.

There is evidence that a nondipping pattern may be of adverse prognostic significance, reflecting and/or predicting progressive target-organ damage due to various conditions such as arterial hypertension or renal insufficiency, and being associated with increased cardiovascular morbidity.18–20,26,27 Another hypothesis involves a role for autonomic nervous dysfunction, as suggested by studies26–30 in both animals and humans, under physiologic conditions and in disease states. Control of BP and HR is mediated by the balance between vagal and sympathetic activities, with both autonomic divisions being essential.28–30 As previously suggested for HR,5,6 the nondipping pattern with elevated BPs during sleep and the absence of differences in BPs between REM and NREM sleep in patients with CCHS may indicate autonomic dysfunction. Several lines of evidence point to abnormal development of the autonomic nervous system in CCHS. CCHS is strongly associated with other neurocristopathies, Hirschsprung disease, and neural crest tumors.2,3 Mutations found in CCHS involve genes of the RET/GDNF and endothelin pathways known to be essential for both the migration and maturation of crest-derived cells, as well as the development of central respiratory structures.9,10 Many studies12,13,30,31 have demonstrated complex interconnections among brain structures in the medulla involved both in central regulation of breathing and in central regulation of cardiovascular reflexes. Thus, a reasonable hypothesis is that the nondipping pattern in CCHS may reflect abnormalities in central autonomic regulation which produced a disrupted vagal-sympathetic balance, with depressed vagal activity and/or increased sympathetic activity. The autonomic disorder is probably a congenital feature in CCHS,1–3 whereas it may be acquired in other diseases such as hypertension, diabetes, or sleep apnea.18,25–27

Another important result in this study was that our young children and adolescents with CCHS had nearly 80% of their daytime BP readings below the 50th percentiles, and this percentage increased with age. Episodes of dizziness, lightheadedness, or fainting may occur as a result of sustained hypotension caused by failure in BP control, particularly when combined with bradycardia.32 Since patients with CCHS may have abnormal control of both BP and

![Figure 4. Percentage of nocturnal fall in BP and HR in patients with CCHS and control subjects. *p < 0.05, ***p = 0.000.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20384/ on 06/26/2017)
HR, we believe that in a clinical setting, long-term cardiovascular assessment is an important part of the routine evaluation of children, adolescents, and adults with CCHS.

In conclusion, our group of children and adolescents with CCHS showed BPs in the low normal range during daytime and a nondipping pattern probably related to autonomic nervous dysfunction. The need for lifelong cardiovascular follow-up in patients with CCHS should be emphasized.

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