Peripheral Chemoreceptor Function in Children With Myelomeningocele and Arnold-Chiari Malformation Type 2

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Blunted rebreathing hyperoxic hypercapnic ventilatory and arousal responses are frequent in older children with myelomeningocele (MMC) and Arnold-Chiari malformation type 2 (ACM). In contrast, isocapnic hypoxic rebreathing ventilatory responses are only occasionally affected. Thus, regions mediating the hypoxic ventilatory response appear usually preserved in children with MMC and ACM. Peripheral chemoreceptor function (PCR), however, has not been critically assessed in these children. To study this, PCR was measured in ten children and adolescents with MMC and ACM with normal alveolar ventilation during wakefulness, and in ten sex- and age-matched controls by measuring the ventilatory responses induced by 100% O2 breathing, five tidal breaths of 100% N2, and vital capacity breaths of 15% CO2 in O2. In general, tidal breathing of 100% O2 resulted in smaller decreases in minute ventilation (VE) responses in patients with MMC, although absent VE responses to hyperoxia were found in four patients. Vital capacity breaths of 15% CO2 elicited similar increases in VE in five patients and in ten controls, but no changes in VE were found in the remaining five patients (p<0.02). Acute hypoxia induced by N2 tidal breathing resulted in significant linear regression correlations between VE and SpO2 in five patients with MMC, while absent responses were measured in those same five patients with absent hypercapnic responses. We conclude that PCR, when assessed by acute hypoxia, hyperoxia, or hypercapnia is abnormal in some children with MMC and ACM, particularly in those demonstrating abnormal ventilation during sleep. We postulate that the large interindividual variability of PCR is dependent on the severity of brainstem involvement of PCR afferents or central respiratory integration sites.

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Key words: brainstem; hypercapnia; hyperoxia; hypoxia; respiratory control

Infants with myelomeningocele (MMC), hydrocephalus, and Arnold-Chiari malformation type 2 (ACM) are at increased risk for sleep-disordered breathing.

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ACM=Arnold-Chiari malformation type 2; CCR=central chemoreceptor function; HCVR=rebreathing hypercapnic ventilatory response; MMC=myelomeningocele; PCR=peripheral chemoreceptor function; PFT=pulmonary function test; VC=tidal volume; VE=minute ventilation; Vt=tidal volume

Arousal responses to ventilatory stimuli are frequently abnormal, particularly when sleep apnea is present. Despite adequate alveolar ventilation during wakefulness, older children with MMC and ACM will also frequently demonstrate blunted ventilatory responses to hypercapnia. In these patients, mean ventilatory responses to progressive isocapnic hypoxia are most commonly normal, suggesting that peripheral chemoreceptor function (PCR) is usually preserved in MMC with ACM. However, Swannathan et al. reported blunted responses to hypoxia in more severely affected patients, indicating that peripheral chemoreceptor afferents and integrative pathways of the response to hypoxia may also be involved in the disease process. Further evidence of possible involvement of PCR in patients with MMC was also suggested by the report of a 18-year-old male with ACM and syringomyelia in whom impaired peripheral chemosensitive pathways led to respiratory failure.

Critical assessment of peripheral chemoreceptor function in children with MMC and ACM is lacking. Such information could provide useful insights into
pathophysiologic mechanisms leading to ventilatory disturbances during sleep in patients with MMC.

Therefore, the purpose of this study was to determine peripheral chemoreceptor function in older children and adolescents with MMC and ACM, by assessing the ventilatory response to transient hypoxia, hypercapnia, and hyperoxia.

**Methods**

Ten children with MMC and ACM and ten age- and sex-matched controls participated in the study. Diagnosis of MMC and ACM was confirmed by clinical findings as well as by CT and/or magnetic resonance imaging (MRI) studies. Several years prior to this study, patients underwent posterior fossa surgical decompression, and insertion of ventriculo-peritoneal shunts as clinically indicated, and in subsequent radiologic assessments, no evidence of increased intracranial pressure was present. Mean age was 11.3±1.5 (SEM) years (range, 8 to 20 years), and six were male. Informed consent was obtained, and the study was approved by the Institutional Review Board.

**Overnight Polysomnography**

To determine the presence and severity of sleep-related breathing abnormalities, overnight polysomnographic recordings were obtained in all ten patients with MMC and in eight of ten control children. Children were studied for 8 h, in a quiet, darkened room with an ambient temperature of 24°C, and did not receive any drugs or medications. The following parameters were measured: chest and abdominal wall movement by inductance plethysmography (Respiritrace); heart rate by ECG; air was sampled at the nose or mouth. PetCO2 and PtcO2 were measured by mass spectrometry (1100 medical gas analyzer; Perkin-Elmer; Pomona, Calif); airflow was monitored with a thermistor (Physitemp; Clifton, NJ); transcutaneous Po2 and PCO2 were monitored using heated (43°C), calibrated transcutaneous electrodes (Transcend Cutaneous Gas System; SensorMedics; Yorba Linda, Calif); arterial oxygen saturation was assessed by pulse oximetry (SpO2) (N 200; Nellcor; Hayward, Calif) with simultaneous recording of the pulse waveform; electroculegram, two-channel electroencephalogram, and chin electromyogram were also monitored.

Scoring of respiratory variables during sleep was performed as previously described, using the definition of apnea as cessation of air flow for 10 s or longer. Hypopnea was defined as a decrease of 50% or more in nasal air flow, associated with a fall of 4% or more of baseline SpO2. Nonrespiratory variables were also scored using standard criteria.

**Table 1—Pulmonary Function Tests in Ten Patients With MMC and ACM and Ten Matched Controls* **

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients with MMC</th>
<th>Control Subjects</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC, %pred</td>
<td>85±11</td>
<td>104±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VC, %pred</td>
<td>83±10</td>
<td>103±7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>28±3</td>
<td>25±4</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1, %pred</td>
<td>78±4</td>
<td>107±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEF25%-75%, %pred</td>
<td>67±10</td>
<td>87±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MVV, L/min</td>
<td>84±16</td>
<td>101±17</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Group means±SEM are shown. TLC=total lung capacity; VC=vital capacity; RV/TLC=residual volume/total lung capacity; FEF25%-75%=forced expiratory flow between 25 and 75% of exhaled vital capacity; MVV=maximal voluntary ventilation.

**Table 2—Mean Slopes of Ventilatory Response to Hypercapnic, Hypoxic, and Hyperoxic Challenges in Ten MMC and Ten Matched Controls* **

<table>
<thead>
<tr>
<th>Test</th>
<th>MMC</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCVR, L/min/mm Hg</td>
<td>0.39±0.14</td>
<td>0.74±0.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCVR-CO2</td>
<td>0.45±0.49</td>
<td>0.83±0.19</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>L/min/mm Hg</td>
<td>-0.29±0.39</td>
<td>-0.76±0.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SpO2</td>
<td>-7.6±1.9</td>
<td>-16.9±1.6</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

*Group means±SD are shown; PCVR-CO2=transient hyperoxic hypercapnic challenge; PCVR-N2=transient hypoxic challenge; PCVR-100% O2=transient hyperoxic challenge.

**Pulmonary Function Tests**

To rule out pulmonary mechanical limitation to ventilatory responses that may compromise the validity of this study, pulmonary function tests (PFTs) were performed. Vital capacity (VC), FEV1, FEF25%-75%, and maximal expiratory flow volume curves were obtained (model 3000; Medscience; St. Louis, Mo). Functional residual capacity was measured with a body pressure plethysmograph (2800 Autobox; Sensormedics; Yorba Linda, Calif) by the method of DuBois et al.11 Maximal voluntary ventilation was also measured in all subjects for a period of 12 s, to determine whether mechanical limitation or muscle weakness was present. Individual test results were analyzed, and if considered markedly abnormal,12 led to exclusion from the study.

**Ventilatory Response Tests**

Subjects were studied while awake, comfortably sitting, wearing nose clips, and spontaneously breathing through a mouthpiece. Studies were always performed at least 3 h after last meal, and children were instructed to avoid any caffeinated products 12 h before testing. Children were connected via the mouthpiece to a pneumotachograph (Hans Rudolph; Kansas City, Mo), and to a one-way or two-way breathing valve (Hans Rudolph) as appropriate.

<table>
<thead>
<tr>
<th>L/min/Torr PETCO2</th>
<th>CONTROL</th>
<th>MMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
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</tr>
<tr>
<td>1.0</td>
<td></td>
<td></td>
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<tr>
<td>1.2</td>
<td></td>
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</tbody>
</table>

**Figure 1.** Summary of the individual slopes of the ventilatory response to rebreathing hyperoxic hypercapnia by the Read method in ten patients with MMC and ten matched controls. Solid lines indicate mean values and dotted lines show SD values for each group.
At the inlet of the breathing port, a Douglas bag containing the test gas mixture was attached. Air was sampled at the expiratory port of the breathing valve. Breath-by-breath PO2 and PCO2 were measured by mass spectrometry (Perkin-Elmer 1100 medical gas analyzer; Pomona, Calif). Dead space of the system was approximately 40 mL, and resistance to airflow was determined at less than 0.012 cm H2O/L/min for flow rates ranging from 0 to 200 L/min. Flow was measured using a heated pneumotach and a pressure transducer (Valyndie; Northridge, Calif), and tidal volume (VT) was obtained by analog integration of the flow signal. All outputs were recorded on a polygraph strip chart recorder (Gould Inc; Rolling Meadows, Ill).

Inspiratory time, total time, VT, and end-expiratory carbon dioxide tension (PETCO2) were measured for each breath. From these, expiratory time, respiratory rate, minute ventilation (VE), mean inspiratory flow rate, and duty cycle were calculated.

**Rebreathing Hyperoxic Hypercapnic Ventilatory Responses**

To determine central chemoreceptor sensitivity during wakefulness, we examined the ventilatory responses to rebreathing hypercapnia in an hyperoxic background as described by Read. Subjects rebreathed from a 13-L bag filled with 70 mL/kg of a gas mixture with an initial composition of 95% O2 and 5% CO2. Subjects breathed room air for several minutes to establish baseline values and were then switched into the bag at the end of a normal expiration. Each rebreathing test was maintained until subjects could no longer continue, or when PaCO2 reached 65 to 70 mm Hg. The final PaCO2 was greater than 60 mm Hg in all cases. All tests were completed within 4 min. Ventilatory responses to hypercapnia (HCRV) were expressed as the slope of VE vs PETCO2. Normative values for HCRV in children have been recently established in our laboratory.

**Peripheral Chemoreceptor Ventilatory Responses**

The following tests in gas mixtures were administered: (A) the subject breathed for at least 3 min on room air to establish a baseline; (B) 3 min of tidal breathing with 100% oxygen; (C) one vital capacity breath from residual volume of 15% CO2 in 85% oxygen; and (D) five tidal breaths of 100% nitrogen to allow a decrease in oxygen saturation (SpO2) for a few seconds to 65 to 75%.

Tests C and D were performed in duplicate or triplicate as allowed by each subject, and results were averaged. For test C, VC breaths with room air were randomly introduced to serve as placebo, and were analyzed in the same fashion as hypercapnic transient stimuli.

For tests C and D, the immediate peripheral chemoreceptor ventilatory response (PCVR) was measured as the mean breath-by-breath computed minute volume from the second to the sixth breaths following application of the stimulus. In test B, the percent change in VE was calculated for the period of 30 s preceding and following administration of 100% O2.

**Data Analysis**

Data are presented as mean±SEM unless indicated otherwise. The change in respiratory parameters measured for 100% O2 was expressed in percentage change for patients with MMC and controls. These, as well as the ventilatory responses obtained using different gas mixtures in patients with MMC were compared by analysis of variance procedures, two-tailed unpaired t tests, or the Wilcoxon signed rank test as appropriate, using a statistical package (BMDP). Linear regression analysis was performed to assess the correlation between VE and SpO2 and VE and PETCO2. A p value of <0.05 was considered as statistically significant.

**RESULTS**

Ten patients with MMC and ten age- and sex-matched controls completed the study. Of these, five patients with MMC (50%) had significant ventilatory abnormalities during sleep requiring ventilatory support by positive pressure mechanical ventilation in two patients, supplemental oxygen in two, and occasional...
hypopneas, obstructive apneas, and 15 to 20 s duration central apneas associated with mild oxygen desaturation (nadir SpO2-87%) in the fifth patient.

Breathing abnormalities in those patients necessitating mechanical ventilation during sleep consisted of prolonged periods of alveolar hypoventilation and hypoxemia with frequent central apneas and periodic breathing, as well as occasional obstructive apneas. In the other two patients, mild to moderate intermittent alveolar hypoventilation, with occasional central, mixed, and obstructive sleep apneas associated with significant oxygen desaturation (nadir SpO2-60%) were observed.

All patients with MMC had adequate alveolar ventilation during the waking state, as evidenced by PETCO2 values consistently below 45 mm Hg.

Radiologic evidence of syringobulbia and hydromyelia was present in all five patients with MMC displaying some degree of ventilatory abnormality during sleep.

Pulmonary function tests showed evidence of mild restrictive lung disease in most patients with MMC.
(Table 1). Maximum voluntary ventilation (MVV) was also lower in patients with MMC than in control children (Table 1). However, maximal ventilation measured during HVCR testing (see below) was always <70% of MVV, indicating the absence of significant mechanical limitation imposing on measured ventilatory responses.

Mean HCVRs in patients with MMC were lower than in controls (Fig 1; Table 2; p<0.001). However, in all but three patients with MMC, HVCR fell within 2 SDs of mean HVCR measured in control children.

The mean ventilatory decrease following the hyperoxic switch was 7.6±1.9% in patients with MMC and 16.9±1.6% in controls (Table 2; p<0.002). However, the response was was either absent or smaller than any response in controls in four patients with MMC with abnormal results of sleep studies (Fig 2). In the remaining six patients with MMC, 100% O₂-induced reduction in ventilation was comparable to control values.

Significant linear regressions were found for \( V_E \) and PetCO₂ in five patients with MMC and in all controls during hypercapnic transients (Fig 3). Five patients lacked a significant ventilatory response to transient hypercapnia. These included all five patients who demonstrated respiratory disturbances during sleep. Mean slopes of the linear relationship between \( V_E \) and PetCO₂ were lower in patients with MMC than in controls (p<0.04); however, significant overlap was present (Table 2; Fig 4).

Similarly, significant responses to five tidal breaths of 100% N₂ were measured in five patients with MMC and again, were absent in those five patients who either required ventilatory support during sleep or had evidence of sleep-disordered breathing (Fig 5 and 6). In patients with MMC, mean slopes of the linear relationship between \( V_E \) and SpO₂ were lower than in controls (Table 2; p<0.01).

Discussion

In this study, we demonstrate that some children and adolescents with MMC and ACM have absent PCVR when assessed by the ventilatory responses to transient hyperoxia, hypoxia, or hypercapnia. Although the absence of PCVR is not exclusive of patients requiring ventilatory support during sleep, our data suggest that evidence for PCVR dysfunction is more likely to occur in those patients with MMC with sleep-associated respiratory abnormalities.

In a previous study, the mean central chemoreceptor response to hypercapnia was blunted in 14 patients with MMC and ACM. However, only two patients had HCVR slope values that were 2 SDs below those of control children. These results are in close concordance with current findings and suggest that some degree of residual central chemosensitivity is present in most patients with MMC who are able to sustain adequate ventilation during wakefulness. Also, Worley et al found increased incidence of abnormal HCVR in younger patients with evidence of brainstem dysfunction. Therefore, although traction and compression of brainstem structures probably occur in all patients with MMC, such processes will affect the HCVR more severely in those patients with MMC with more extensive brainstem involvement. Widespread location of central chemoreceptive structures has been suggested in the cat and more recently documented in humans, using noninvasive, functional MRI techniques. Such widespread distribution of chemosensitive regions across rostral, midbrain, and brainstem structures may lead to sparing of some of these structures by the disease process in MMC and explain why the HCVR may be within the normative range in most patients with MMC. Accordingly, only in patients with more extensive involvement of critical chemosensitive brain regions, would one expect to observe markedly blunted or absent central chemosensitivity in wakefulness.

Similarly, it could be anticipated that peripheral chemoreceptor afferents or brainstem regions mediating peripheral chemoreceptor integration would more likely be involved in those patients with MMC with respiratory disturbances during sleep. Indeed, during sleep, a loss or decreased cortical and rostral efferent input occurs, and a more preponderant role is played by brainstem respiratory regions in maintaining ventilatory homeostasis. If damage to peripheral chemosensitive pathways occurs in addition to partial/extensive damage to central chemoreceptor regions (ie, low normal or blunted HCVR, respectively), transition from waking to sleep states would increase the susceptibility to the occurrence of clinical respiratory manifestations such as apnea and/or alveolar hypoven-
tillation. During wakefulness, such evidence would be concealed by compensatory mechanisms originating from more rostral brain regions, and would be demonstrable only with use of specific tests such as those employed in this and previous studies.4,5

In addition, PCVR could also be abnormal without concomitant involvement of central chemoreceptive regions. This possibility is suggested by two of our patients in whom the HCVR was well within normative values, while the PCVR was absent, irrespective of the transient ventilatory challenge employed. In these two patients, polysomnographic recordings revealed mild breathing abnormalities in both, leading to the need for supplemental oxygen during sleep in one patient. It is possible that the degree and extension of structural damage and the interaction between central and peripheral chemoreceptor pathways is critical in determining the adequacy of respiratory adjustments during sleep in patients with MMC. Partial validation of such assumption may also be inferred from similar studies in patients with the congenital central hypoventilation syndrome who characteristically demonstrate severe hypoventilation during sleep, while maintaining adequate alveolar ventilation during wakefulness.25,26 Despite the absence of detectable radiologic or anatomic abnormalities,27 central chemosensation is absent both during sleep and wakefulness,28 while PCVR appears to be intact.29 Altogether, our findings suggest that in patients with MMC, extent of structural disruption within neural structures in the brainstem will translate into a spectrum of HCVR and PCVR disturbance, the degree of which will, in turn, establish the ability to sustain adequate ventilation during sleep (Fig 7).

Although data are mostly anecdotal at present, syringobulbia and/or hydromyelia were identified only in patients with significant disturbance of ventilatory response to the various ventilatory stimuli employed, suggesting that gradual deterioration of function in hindbrain structures may occur over time, and lead to the onset of sleep-associated breathing abnormalities,30 and in extreme cases, to respiratory insufficiency.6

In summary, our study confirms that, as a group, patients with MMC have lower central chemoreceptor drive. However, only in a minority of patients, true blunting of central chemoreceptor function occurs. In contrast, we demonstrate that PCVR is frequently absent in patients with MMC and that this finding coincides with sleep-associated breathing abnormalities. We postulate that periodic assessment of ventilation during sleep may be useful in identifying patients with HCVR and/or PCVR abnormalities, and thereby, may provide important anatomic and functional correlates in furthering our understanding of respiratory control.

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