Ventilatory and Cardiovascular Responses to Hypercapnia and Hypoxia in Multiple-System Atrophy

Axel Lipp, MD; James D. Schmelzer, BS; Phillip A. Low, MD; Bruce D. Johnson, PhD; Eduardo E. Benarroch, MD

Background: Loss of medullary sympathoexcitatory neurons may contribute to baroreflex failure, leading to orthostatic hypotension in multiple-system atrophy (MSA). The cardiovascular responses to chemoreflex activation in MSA have not been explored to date.

Objectives: To determine whether ventilatory and cardiovascular responses to hypercapnia and hypoxia during wakefulness are systematically impaired in MSA.

Design: Case-control study.

Setting: Mayo Clinic, Rochester, Minnesota.

Patients: Sixteen patients with probable MSA (cases) and 14 age-matched control subjects (controls).

Main Outcome Measures: Minute ventilation, blood pressure, and heart rate responses to hypercapnia and hypoxia during wakefulness. Hypercapnia was induced by a rebreathing technique and was limited to a maximal expiratory partial pressure of carbon dioxide of 65 mm Hg. Hypoxia was induced by a stepwise increase in inspiratory partial pressure of nitrogen and was limited to a minimal arterial oxygen saturation of 80%. Ventilatory responses were assessed as slopes of the regression line relating minute ventilation to changes in arterial oxygen saturation and partial pressure of carbon dioxide.

Results: In cases, ventilatory responses to hypercapnia and hypoxia were preserved, despite the presence of severe autonomic failure, while cardiovascular responses to these stimuli were impaired. Among cases, hypercapnia elicited a less robust increase in arterial pressure than among controls, and hypoxia elicited a depressor response rather than the normal pressor responses (P < .001 for both).

Conclusions: Ventilatory responses to hypercapnia and hypoxia during wakefulness may be preserved in patients with MSA, despite the presence of autonomic failure and impaired cardiovascular responses to these stimuli. A critical number of chemosensitive medullary neurons may need to be lost before development of impaired automatic ventilation during wakefulness in MSA, whereas earlier loss of medullary sympathoexcitatory neurons may contribute to the impaired cardiovascular responses in these patients.

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MULTIPLE-SYSTEM ATROPHY (MSA) is a sporadic progressive adult-onset disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in various combinations. Respiratory manifestations, including alveolar hypoventilation and central sleep apnea, are prominent complications of this disorder and may occur as the initial feature or may develop in later stages of the disease. These manifestations likely reflect involvement of neuronal groups associated with ventilatory chemosensitivity and automatic ventilation in this disease. Automatic breathing depends on the activity of central and peripheral chemoreceptive cells that respond to changes in oxygen, carbon dioxide, and pH levels in the blood and cerebrospinal fluid.

Results of experimental studies indicate that central chemosensitive neurons are widely distributed in the brainstem and include glutamatergic neurons located close to the ventromedullary surface and serotonergic neurons of the medullary raphe. Findings from our laboratory demonstrate a loss of glutamatergic and serotonergic neurons in the arcuate nucleus at the ventromedullary surface in patients with MSA. It is suggested that these neurons have respiratory chemosensitive function in humans. Although pathologic evidence suggests that neurons involved in respiratory chemosensitivity are vulnerable in MSA, the association with autonomic failure has not been explored to date. Patients with
Subjects were excluded if they had clinical histories of cardiovascular or pulmonary diseases, including asthma and tobacco use. Subjects refrained from exercise, alcohol, and caffeine for 24 hours before testing. All vasoactive medications, including levodopa and fludrocoritonsone, were discontinued at least 5 half-lives before the study. Before the study, all subjects underwent clinical autonomic testing to assess cardiovagal function (heart rate response to deep breathing), adrenergic function (blood pressure responses to passive head-up tilt and to Valsalva maneuver), and sudomotor function (quantitative sudomotor axon reflex test and thermoregulatory sweat test). The combined results of these tests were scored on the Composite Autonomic Scoring Scale (CASS) (eBox: http://www.archneurol.com), an objective scale ranging from 0 (no deficit) to 10 (maximal deficit). Subjects with a summed score of 3 or less on the CASS have mild autonomic failure; those with a summed score of 7 to 10 have severe autonomic failure. Subjects reported their autonomic symptoms using the Autonomic Symptom Profile, a self-reported questionnaire of 169 questions. The Autonomic Symptom Profile yields a total score reflecting the overall severity of autonomic symptoms and 11 weighted subscale scores that assess the severity of symptoms within the following domains: orthostatic intolerance, syncope, sexual failure (men only), bladder dysfunction, diarrhea, constipation, upper gastrointestinal tract symptoms, secretomotor dysfunction, sleep dysfunction, vasomotor symptoms, and pupillomotor symptoms. Clinical motor impairment in cases was rated using the Unified Multiple System Atrophy Rating Scale.22

MEASUREMENTS

Studies were conducted at early morning in a temperature-controlled room with the subject in a sitting position. Heart rate was measured using 3-lead electrocardiography. Arterial blood pressure was measured on a beat-to-beat basis by finger photoplethysmography (Finometer model 1, Finapres, Amsterdam, the Netherlands) and was regularly verified by manual sphygmomanometry on the contralateral arm. Ventilation (tidal volume, minute ventilation [VE], and respiratory rate) was assessed on a breath-to-breath basis using a bidirectional Pitot tube pneumotachograph (Ultima CPX; MedGraphics, St Paul, Minnesota). End-tidal partial pressures of oxygen (P02) and carbon dioxide (PCO2) were continuously measured using a gas analyzer (zirconia oxide sensor for oxygen and nondispersive infrared sensor for carbon dioxide [Ultima CPX]). Oxygen saturation (Sao2) was measured by pulse oximetry at the forehead (Max-Fast Sensor, OxiMax N-600x; Nellcor, Boulder, Colorado).

Hypercapnic ventilatory response was determined using slight modifications to a rebreathing method previously described by Read.23 Subjects were comfortably seated in a quiet and temperature-controlled environment while breathing from a mouthpiece or mask connected to the pneumotachograph. After quietly breathing room air for 5 minutes, the inspiratory port was switched (pneumatic sliding valve, series 2730; Hans Rudolph, Inc, Shawnee, Kansas) to a 6-L rebreathing bag containing 5% carbon dioxide and 95% oxygen. While continuously monitoring P02, PCO2, and breath-to-breath changes in VE, rebreathing was continued until PCO2 reached 65 mm Hg or the patient requested to stop because of dyspnea (approximately 4 minutes). The slope of the plot of VE vs PCO2 was used as an index of carbon dioxide sensitivity. Subjects performed 3 rebreathing tasks, with a 15-minute rest period between studies.

Hypoxic ventilatory response was determined by a modification of methods previously described by Simon et al24 and current consensus criteria1 (cases) and 14 predominantly sedentary control subjects of similar age (8 men and 6 women [mean age, 59.7 years]) (controls) (Table 1).

Abbreviations: bpm, Beats per minute; ΔHR, change in heart rate; ΔSBP, change in systolic blood pressure; PCO2, partial pressure of carbon dioxide; SBP, systolic blood pressure; VE, minute ventilation.

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Table 1. Ventilatory and Hemodynamic Responses to Hypercapnia and Hypoxia in Patients With Probable Multiple-System Atrophy (MSA) and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SEM)</th>
<th>Controls (n=14)</th>
<th>Cases (n=16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic ventilatory response, (L/min⁻¹) × 10⁻¹</td>
<td>-0.34 (0.06)</td>
<td>-0.38 (0.04)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>ΔVE, L/min⁻¹</td>
<td>8.4 (1.7)</td>
<td>6.4 (0.8)</td>
<td>0.52a</td>
<td></td>
</tr>
<tr>
<td>ΔSBP, mm Hg</td>
<td>15.0 (4.1)</td>
<td>-13.0 (4.8)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>ΔHR, bpm</td>
<td>11.7 (1.2)</td>
<td>8.3 (1.1)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Hypercapnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercapnic ventilatory response, (L/min⁻¹) × mm Hg⁻¹</td>
<td>2.1 (0.3)</td>
<td>3.2 (0.3)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>ΔVE, L/min⁻¹</td>
<td>33.7 (3.3)</td>
<td>42.1 (3.8)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>ΔSBP, mm Hg</td>
<td>40.6 (3.7)</td>
<td>17.7 (3.3)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>ΔHR, bpm</td>
<td>7.8 (1.4)</td>
<td>4.0 (1.3)</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bpm, Beats per minute; ΔHR, change in heart rate; ΔSBP, change in systolic blood pressure; PCO2, partial pressure of carbon dioxide; SBP, systolic blood pressure; VE, minute ventilation.

aMann-Whitney test (all other comparisons are by unpaired t test).
Table 2. Autonomic and Motor Impairment According to Multiple-System Atrophy (MSA) Subtype

<table>
<thead>
<tr>
<th>Case No./ Sex/Age, y</th>
<th>MSA Subtype</th>
<th>Disease Duration, y</th>
<th>Unified Multiple System Atrophy Rating</th>
<th>Composite Autonomic Scoring Scale Subscore</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Scale Motor Impairment Score</td>
<td>Head-Up Till, mm Hg</td>
</tr>
<tr>
<td>1/M/69</td>
<td>Parkinsonism</td>
<td>0.92</td>
<td>9</td>
<td>−20</td>
</tr>
<tr>
<td>2/M/61</td>
<td>Parkinsonism</td>
<td>1.92</td>
<td>32</td>
<td>−56</td>
</tr>
<tr>
<td>3/M/77</td>
<td>Parkinsonism</td>
<td>1.00</td>
<td>24</td>
<td>−44</td>
</tr>
<tr>
<td>4/M/62</td>
<td>Parkinsonism</td>
<td>5.03</td>
<td>17</td>
<td>−91</td>
</tr>
<tr>
<td>5/M/50</td>
<td>Cerebellar</td>
<td>0.02</td>
<td>15</td>
<td>−31</td>
</tr>
<tr>
<td>6/F/56</td>
<td>Parkinsonism</td>
<td>0.17</td>
<td>19</td>
<td>−24</td>
</tr>
<tr>
<td>7/F/58</td>
<td>Parkinsonism</td>
<td>1.16</td>
<td>23</td>
<td>−4</td>
</tr>
<tr>
<td>8/M/77</td>
<td>Parkinsonism</td>
<td>1.16</td>
<td>25</td>
<td>−31</td>
</tr>
<tr>
<td>9/R/65</td>
<td>Parkinsonism</td>
<td>0.25</td>
<td>21</td>
<td>−35</td>
</tr>
<tr>
<td>10/M/51</td>
<td>Cerebellar</td>
<td>2.01</td>
<td>16</td>
<td>−52</td>
</tr>
<tr>
<td>11/M/74</td>
<td>Parkinsonism</td>
<td>1.25</td>
<td>18</td>
<td>−48</td>
</tr>
<tr>
<td>12/M/55</td>
<td>Parkinsonism</td>
<td>0.30</td>
<td>15</td>
<td>−60</td>
</tr>
<tr>
<td>13/M/56</td>
<td>Parkinsonism</td>
<td>1.33</td>
<td>4</td>
<td>−22</td>
</tr>
<tr>
<td>14/F/62</td>
<td>Cerebellar</td>
<td>0.33</td>
<td>10</td>
<td>−42</td>
</tr>
<tr>
<td>15/F/72</td>
<td>Cerebellar</td>
<td>1.42</td>
<td>28</td>
<td>−26</td>
</tr>
<tr>
<td>16/M/64</td>
<td>Cerebellar</td>
<td>0.02</td>
<td>23</td>
<td>−32</td>
</tr>
</tbody>
</table>

Abbreviation: ΔSBP, change in systolic blood pressure.

ª Period between the diagnosis of MSA (not symptom onset) and the study date.

by Weil and Zwillich.25 Subjects were breathing from a mouth-piece or mask connected to a nonrebreathing valve (Hans Rudolph, Inc) whose inspiratory port was linked to a pneumatic sliding valve (P0271, Hans Rudolph). While quietly breathing room air for at least 5 minutes, individual resting PCO2 was determined and kept constant (within 1 mm Hg) throughout the remaining study. Progressive normocapnic hypoxia was induced by switching the inspiratory port of the pneumatic sliding valve from room air to a gas reservoir (20-L balloon) containing a mixture of room air, nitrogen, and carbon dioxide. Partial pressure of nitrogen (PN2) of the inspired gas mixture was increased by a low-flow air blender (Tri-Anim, Sylmar, California) until the required SaO2 was achieved. Mean SaO2 levels of 90%, 87%, 84%, and 80% were maintained for 2 to 3 minutes. Normocapnic PCO2 was maintained by adding carbon dioxide into the inspired gas mixture. All ventilatory variables (VE, respiratory rate, PCO2, and PO2) were sampled at the mouth-piece on a breath-to-breath basis; the dependence of VE on SaO2 was digitized with 14-bit resolution and a sample frequency of 1000 Hz. All data were expressed as the mean (SEM). Cardiorespiratory responses to hypercapnia and hypoxia were compared between groups using unpaired t test (parametric data) or Mann-Whitney test (nonparametric data). Within-group comparisons (baseline vs hypercapnia and hypoxia) were performed using Wilcoxon matched-pair analysis. P < .05 was considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS

Clinical characteristics of cases and controls are summarized in Table 1 and Table 2. Among cases, 11 met criteria for parkinsonism subtype of MSA and 5 for cerebellar subtype of MSA.1 Autonomic function testing (combined cardiovagal, adrenergic, and sudomotor failure), scored using the CASS20 and the Autonomic Symptom Profile,21 revealed significant impairment in all cases (P < .001 for cases vs controls using the CASS, Mann-Whitney test). All cases had autonomic failure (neurogenic orthostatic hypotension, urinary incontinence, or both) (Table 2).

VENTILATORY EFFECTS OF HYPERCAPNIA AND HYPOXIA

Table 1 gives resting values for VE, PCO2, and SBP before hypercapnic and hypoxic stimulation in cases and in controls. During quiet rest, VE was significantly higher in cases (P = .03, t test), with no difference in resting PCO2 (P = .71, t test). Hypercapnic and hypoxic stimulation induced hyperventilation in cases and in controls (P < .001 for within-group change in VE, Wilcoxon matched-paired test), with no significant between-group differences in change in VE (P = .12 [t test] for hypercapnia and P = .52 [Mann-Whitney test] for hypoxia). When chemosensitivity was expressed as the slope of the regression line, relating VE to changes in PCO2, ventilatory responses to hypercapnia were significantly increased in
cases (P = .02 for hypercapnia and P = .55 for hypoxia, t test) (Figure 1 and Table 1). Ventilatory responses to hypoxia were similar in cases and in controls (Figure 1).

HEMODYNAMIC EFFECTS OF HYPERCAPNIA AND HYPOXIA

In controls, breathing a hypoxic gas mixture induced a significant increase in SBP of 15.0 (4.1) mm Hg (P < .001, Wilcoxon matched-pair test) (Table 1). In contrast, hypoxia in cases induced a decrease in SBP of −13.0 (4.8) mm Hg (P < .001, t test) (Table 1 and Figure 2). Progressive hypercapnia induced significant increases in SBP in cases (17.7 [3.3] mm Hg) and in controls (40.6 [3.7] mm Hg) but was more marked in controls (P < .001, t test) (Table 1 and Figure 2).

In controls, hypercapnia and hypoxia increased the heart rate by 7.8 (1.4) beats per minute (bpm) and 11.7 (1.2) bpm, respectively (Table 1). Compared with that in controls, hypoxia increased the heart rate in cases (8.3 [1.1] bpm; P = .048, t test), but hypercapnia did not (4.0 [1.3] bpm; P = .17, Mann-Whitney test).

RELATIONSHIP BETWEEN CHEMOREFLEX RESPONSES AND AUTONOMIC FAILURE

In cases, the abnormalities in chemoreflex-induced cardiovascular responses were directly related to the severity of adrenergic failure detected on autonomic testing.

The magnitude of SBP decrease induced by hypoxia correlated with the severity of orthostatic hypotension during head-up tilt (r = −0.67, P < .01). The pressor response to hypercapnia inversely correlated with the magnitude of SBP decrease during head-up tilt (r = −0.65, P < .01) and with the adrenergic impairment score on the CASS (r = −0.57, P = .02). Impaired chemosensitivity did not correlate with motor deficit or disease duration.

EFFECT OF MSA SUBTYPE

We found no differences in ventilatory or circulatory responses to hypercapnia or hypoxia with respect to MSA subtype (parkinsonism vs cerebellar) or sex. However, the small sample sizes prevented statistical comparisons.

COMMENT

The primary findings among patients with MSA in the present study are the following: (1) resting ventilation and ventilatory response to hypercapnia and hypoxia were preserved during wakefulness, despite evidence of se-
vere autonomic failure; (2) hypoxia elicited a decrease rather than the normal increase in arterial blood pressure; and (3) pressor responses to hypercapnia were blunted.

The finding that during wakefulness cases had preserved or exaggerated responses to hypercapnia and preserved responses to hypoxia seems inconsistent with the neuropathologic evidence of neurodegeneration in putative chemosensitive areas in MSA.13 However, there are several possible explanations for this apparent clinicopathologic dissociation. There is widespread distribution of central chemosensitive neurons.10 Therefore, in most awake patients with MSA, ventilatory responses to hypercapnia and hypoxia may be preserved until late disease stages and may become evident only after there is loss of a critical number of chemosensitive neurons, as detected in a postmortem study.13 This is supported by results in experimental animals.20 Furthermore, the higher resting ventilation and response to hypercapnia in some cases than in controls could reflect impaired descending or segmental modulation of the brainstem network for automatic ventilation in these patients. Our finding of preserved ventilatory responses to hypoxia differs from the results reported by Tsuda et al15 among patients with cerebellar subtype of MSA. This may be explained in part by the variability of ventilatory responses to hypoxia, which occurs in healthy subjects, as well as by methodologic differences in assessing hypoxic ventilatory drive, as acute ventilatory responses to hypoxia differ according to the stimulus.27 In our study, hypoxia was induced by stepwise decreases in PO2, so the ventilatory response appeared as a linear rise in VE as a function of SaO2. In contrast, Tsuda et al used a rebreathing technique in which linear decreases in PO2 resulted in a curvilinear ventilatory response. This rebreathing technique elicits a significantly lower ventilatory response than the method used in our study.27 The preserved responses to hypoxia in MSA could also reflect relative sparing of structures involved in the peripheral chemoreflex. However, a systematic neuropathologic exploration of these areas has not been performed, to our knowledge. Finally, it is likely that in most patients with MSA, impaired automatic ventilation in response to hypercapnia and hypoxia would initially be detectable during sleep. We are recruiting patients to address this issue.

The abnormal cardiovascular responses to hypercapnia and hypoxia may have important clinical implications in MSA. In humans, the direct vasomotor effect of acute hypoxia is vasodilation within the skeletal muscle bed. This is compensated for by a reflex increase in sympathetic vasoconstrictor activity and norepinephrine spillover, which allows maintenance or a slight elevation of the mean arterial pressure in this condition.17,28,29 In the present study, cases not only failed to have increased blood pressure but rather had a hypotensive response to hypoxia, likely reflecting impaired baroreflex-triggered sympathetic vasoconstriction. Loss of sympathoexcitatory neurons in the rostroventrolateral medulla, including the C1 area,30 which are critical not only for baroreflex but also for chemoreflex vasoconstrictor responses, may also explain the blunted pressor response to hypercapnia in MSA. There are antagonistic interactions between the chemoreflexes and the baroreflexes31,32 that may contribute to the preservation of hypercapnic and hypoxic ventilatory responses, as well as orthostatic hypotension and supine hypertension in MSA.33 The depressor responses to hypoxia may contribute to death during sleep in MSA, primarily among patients with underlying cardiovascular conditions such as coronary heart disease. Hypercapnia-induced and hypoxia-induced sympathoexcitation may cause a sympathovagal imbalance that may predispose patients with MSA to cardiac arrhythmias during sleep, particularly in the setting of baroreflex and cardiovascular failure.

Our study has several limitations. First, the number of cases was small; we might have missed cases in whom impaired ventilatory chemosensitivity is an early manifestation of MSA. Second, our cases were studied in the waking state, so we could have underestimated the presence of impaired ventilatory chemosensitivity during sleep. Third, the cardiorespiratory effects observed in our study were induced by acute chemoreflex activation. Chronic hypercapnia, hypoxia, or both could have induced considerably different ventilatory or cardiovascular effects. For example, initial hyperventilation in adults decays during sustained hypoxia (hypoxic ventilatory depression).34

In summary, the present study demonstrates possible preservation of ventilatory responses to hypercapnia or hypoxia during wakefulness, despite the presence of severe autonomic failure and blunted cardiovascular responses to these stimuli in patients with MSA. Our results suggest that (1) a critical number of chemosensitive neurons may need to be lost before impaired automatic ventilation may be detected during wakefulness in MSA and (2) the central drive from the forebrain can maintain normal ventilation during wakefulness, despite impairment of the chemoreflex. Therefore, our findings emphasize the importance of polysomnography in patients with MSA to exclude alveolar hypoventilation or sleep apnea during sleep, as the primary drive for ventilation during sleep is provided by the chemoreflexes, triggered by changes in carbon dioxide or oxygen levels. Loss of sympathoexcitatory neurons in the rostroventrolateral medulla may occur earlier than loss of chemosensitive neurons in the ventromedullary surface, which could explain the presence of orthostatic hypotension and the blunted cardiovascular responses to hypercapnia and hypoxia in this disorder.

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