Tetraplegia is a risk factor for central sleep apnea

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Sankari A, Bascom AT, Chowdhuri S, Badr MS. Tetraplegia is a risk factor for central sleep apnea. J Appl Physiol 116: 345–353, 2014. First published October 10, 2013; doi:10.1152/japplphysiol.00731.2013.—Sleep-disordered breathing (SDB) is highly prevalent in patients with spinal cord injury (SCI); the exact mechanism(s) or the predictors of disease are unknown. We hypothesized that patients with cervical SCI (C-SCI) are more susceptible to central apnea than patients with thoracic SCI (T-SCI) or able-bodied controls. Sixteen patients with chronic SCI, level T6 or above (8 C-SCI; 8 T-SCI) age 42.5 ± 15.5 years; body mass index 25.9 ± 4.9 kg/m²) and 16 matched controls were studied. The hypocapnic apneic threshold and CO2 reserve were determined using noninvasive ventilation. For participants with spontaneous central apnea, CO2 was administered until central apnea was abolished, and CO2 reserve was measured as the difference in end-tidal CO2 (PETCO2) before and after. Steady-state plant gain (PG) was calculated from PEpetCO2 and VE ratio during stable sleep. Controller gain (CG) was defined as the ratio of change in V̇E between control and hypocapnia or apnea to the ΔPETCO2. Central SDB was more common in C-SCI than T-SCI (63% vs. 13%, respectively; P < 0.05). Mean CO2 reserve for all participants was significantly different. The CO2 reserve was an independent predictor of apnea-hypopnea index. In conclusion, C-SCI had higher rates of central SDB, indicating that tetraplegia is a risk factor for central sleep apnea. Sleep-related hyperventilation may play a significant role in the mechanism of SDB in higher SCI levels.

apnea; cervical; sleep; spinal; tetraplegia

Spinal cord injury (SCI) is prevalent worldwide, estimated at 15 to 40 cases per million population. It is estimated that in the United States there are 11,000 new cases of SCI each year (19), of which 10% are military veterans. Most SCIs occur during young adulthood, with life expectancy similar to the normal population (19). Sleep-disordered breathing (SDB) has been shown to be highly prevalent in subacute and chronic spinal cord injury patients (ranging between 27 and 62%) (5, 17, 23, 24, 27, 30, 42–44). Moreover, respiratory complications are major causes of morbidity and mortality in patients with SCI, particularly in patients with cervical SCI (32). A prospective, longitudinal study found that the prevalence of SDB in the Australian cohort of cervical SCI was 62% in the 4 wk immediately postinjury and remained at 60% after 1 yr follow up (5). However, despite this high prevalence of SDB in SCI patients, the underlying pathophysiology, consequences and treatment are unknown (17). Furthermore, there are insufficient and conflicting data on the type of SDB, the predictors of the increased prevalence of SDB, and the relationship between type of SDB and level of injury (16, 17). We recently found that more than 90% of cervical SCI patients demonstrated SDB, with the majority demonstrating central SDB not explained by daytime hyperventilation, cardiac dysfunction, or use of narcotics (39a, 39). Interestingly, central apnea was the predominant pattern in cervical (C-) SCI patients, whereas obstructive apnea was the predominant pattern in the thoracic (T-) SCI group. This unique observation may have significant implications regarding the mechanism of SDB in SCI patients. Most existing studies classify SDB in cervical SCI under the rubric “obstructive sleep apnea” (OSA), owing to the limitations of diagnostic tools available to SCI patients and the disparity in access to in-lab diagnostic sleep studies for patients with limited mobility. In fact, increased risk for central apnea in patients with cervical SCI was first reported by Severinghaus and Mitchell (41), who coined the term “On-dine’s curse” to describe sleep-related ventilatory failure after surgery to the upper cervical cord. Central apnea in patients with cervical SCI may be secondary to hypoventilation or increased posthyperventilation dis-facilitation. Many SCI studies have concentrated on respiratory changes in neural function caudal to injury; however, few have examined whether neural plasticity occurs in animal models rostral to SCI. Golder et al. (18) showed that supraspinal changes alter respiratory output after SCI. Furthermore, Zimmer et al. (51) showed that neural receptors change rostral to SCI in neonatal rats and alter motor output via supraspinal mechanisms. Therefore, neural changes rostral to cervical SCI levels may play an important role in the mechanism of sleep-disordered breathing and the increased susceptibility to central apnea in cervical SCI patients. The sleep state [specifically non-rapid eye movement (NREM) sleep] removes the wakefulness “drive to breathe,” rendering respiration critically dependent on CO2 and unmasking the hypocapnic apneic threshold. The CO2 reserve is the measure of the magnitude of hypocapnia that is required to induce central apnea. There are two ways in which the susceptibility to central apnea (i.e., CO2 reserve) may be altered. The first way is by changing the background drive to breathe, altering the effectiveness of the lung/respiratory system in lowering end-tidal CO2 in response to hyperventilation or “plant gain.” Accordingly, steady-state hyperventilation would increase the magnitude of hypocapnia for a given increase in minute ventilation (11). The second way is by changing the slope of the ventilatory response to induced hypocapnia or “controller gain.” The purpose of this study was to determine the suscep-
tibility to central apnea in patients with cervical and thoracic SCI compared with able-bodied control subjects and to ascer-
tain predictors of SDB in chronic SCI patients. To this end, we
measured the CO₂ reserve (a marker of susceptibility to central
apnea), plant gain and controller gain during non-REM sleep.
We hypothesized that CO₂ reserve is narrower in cervical SCI
compared with thoracic and able-bodied controls. Results of
this study were previously reported in the form of abstracts (39,
39a).

METHODS

Subjects

The Human Investigation Committee of the Wayne State Univer-
sity and the Detroit VA Medical Center approved the experimental
protocol. An informed written consent was obtained, and subjects had
a screening polysomnography.

We studied adults with chronic SCI (>18 yr old) if they met the
inclusion and exclusion criteria. Zolpidem 10 mg was administered
orally to all participants 30 min before sleep to minimize any arou-
sability or difficulty sleeping with instrumentation. Inclusion criteria
were as follows: non-ventilation-dependent subjects with chronic SCI
(more than 6 mo postinjury) and American Spinal Injury Association
grade A, B, C, or D spanning the spectrum from cervical (C5–C7) to
thoracic levels (T1–T6).

Exclusion criteria. Participants were excluded from the study if any
of the following applied: 1) <18 years of age; 2) pregnant or lactating
females; 3) history of cardiac disease including heart failure, periph-
eral vascular disease, or stroke; 4) history of head trauma that resulted
in neurological symptoms or loss of consciousness; 5) advanced lung,
liver, or chronic kidney disease; 6) extreme obesity, defined for this
protocol as BMI >38 kg/m² (to avoid the effect of morbid obesity on
pulmonary mechanics and ventilatory control); or 7) other illness that
would interfere with completion of the study in the investigators’
judgment.

The participants were recruited from local and regional spinal cord
injury care centers, including the Detroit VA Medical Center and the
Rehabilitation Institute of Michigan. Additionally, mailings were sent
to local electronic database of patients with ICD codes corresponding
to paraplegia or quadriplegia (344.0 or 344.1). Letters were sent to
area physicians soliciting referrals of appropriate patients. In addition,
SCI patients were contacted through publications on the internet and
by contacting SCI support groups. Control able-bodied subjects were
healthy adults (>18 yr old) with similar age, BMI, and gender.

Measurements

Every subject who agreed to enroll gave a brief history and
underwent a physical exam. In addition to standard baseline polysom-
nography in the supine position, airflow was measured by a pneu-
motachometer (Hans Rudolph, Model 3700A, Shawnee, KS) con-
nected to a tight-fitting nasal mask. Tidal volume (VT) was obtained
by integrating the pneumotachograph flow signal. End-tidal carbon
dioxide (PETCO₂) and O₂ (PETO₂) were measured with a CO₂ and O₂
gas analyzers (VacuMed, Model 17515 and Model 17518, Ventura,
CA, respectively). Supraglottic pressure was measured with a pressure
tipped catheter (Millar Instruments, Houston, TX), positioned in the
hypopharynx.

Apneic threshold measurement. NONINVASIVE VENTILATION PRO-
TOCUL: We used a portable noninvasive pressure-cycled ventilator
(Quantum PSV, Model 7703, Healthdyne Technologies, Andover,
MA) to induce hyperventilation using a 10 cmH₂O pressure support
for at least 3 min, resulting in a hypopnea or central apnea (Fig. 1).
Noninvasive ventilation (NIV) was terminated during expiration to
the baseline expiratory positive airway pressure (EPAP = 4.0
cmhH₂O) for a minimum of 3 min. The hyperventilation trials were
repeated at higher pressure support (1–2 cmH₂O) until central apnea
was obtained. If central apnea resulted from the NIV trial at a certain
pressure support, the trial was repeated at a lower pressure support
(1–2 cmH₂O) to identify the nearest PETCO₂ to the apneic threshold
(AT). AT was defined as the measured PETCO₂ at the end of the
hyperventilation trial at which the apnea occurred, as depicted in Fig. 1.

HYPERCAPNIA PROTOCOL. For subjects that had spontaneous cen-
tral apnea during sleep, 8% CO₂ was bled into a port on the face mask
at a low flow rate, beginning at 0.5 l/min for 1 min. If central apneas
were not abolished, CO₂ flow rate was increased by 0.5 l/min at 1-min
intervals until central apneas were absent. The hypercapnia trial was
repeated at least twice.

Data Analysis

Standard polysomnography (PSG) was performed according to
American Academy of Sleep Medicine (AASM) standards, using the
Comet Polysomnography System (Grass Technologies, Warwick, RI).
Respiratory events were scored by the 2012 AASM recommended
scoring criteria (6). In addition, supraglottic pressure was used to
differentiate central from obstructive apneas. Baseline wake and
non-REM sleep ventilation were monitored in each subject. Periods of
10 breaths from wakefulness and stable non-REM sleep, with no
apneas preceding it for 2 min, were measured to assess baseline
ventilation (VE, V̇ T, RR, TP, Ṫ E, PETCO₂, and O₂Sat) using the
PowerLab acquisition system (AD Instruments, Model 16SP, Color-
ado Springs, CO). The coefficient of variation (CV) of baseline VE
was measured similar to previous studies as a marker for breathing
instability and periodic breathing (47).

SDB was identified if the calculated apnea-hypopnea index (AHI)
was greater than or equal to 5 events/h of sleep. Central SDB was
defined as AHI greater than or equal to 5 events/h of non-REM sleep
and a central apnea index (CAI) greater than or equal to 5 central
events/h of sleep. Cheyne-Stokes respiration was defined as at least
three consecutive cycles of cyclical crescendo and decrescendo
change in breathing amplitude and at least one of the following:
1) five or more episodes of central apnea or hypopnea per hour of
sleep; 2) the cyclical crescendo and decrescendo changes in breathing
lasted for at least 10 consecutive min (6). Periodic breathing (PB) was
defined as cyclical increases in the rate and depth of breathing
(hyperpnea) alternating with either a reduction by 50% (hypopnea)
or complete cessation (apnea) of nasal air flow and respiratory effort
lasting at least 10 s (8, 37).

All able-bodied control subjects (n = 16) and SCI patients (without
central apnea) underwent apneic threshold measurement using NIV
method (as described above). After stable non-REM sleep was
achieved, in each hyperventilation trial (Fig. 1) the control period
was represented by the average of five breaths immediately preceding
the onset of mechanical ventilation. The hyperventilation data were
the calculated averages of the last five NIV breaths prior to the ventilator
being turned back to the baseline EPAP. The change in PETCO₂
(ΔPETCO₂) was calculated as the difference between the control period
and the last five NIV breaths. AT was defined as the measured PETCO₂
at which the apnea closest to the last hypopnea occurred. The CO₂
reserve was defined as ΔPETCO₂ between control and central apnea.
Steady-state plant gain (PG) was calculated in each participant from
baseline PETCO₂ – V̇ E ratio during stable non-REM sleep as de-
scribed recently (14). Hypocapnic chemoreflex sensitivity or control-
ler gain (CG) was defined as the ratio of change in V̇ E between control
and hypopnea or apnea to the corresponding change in PETCO₂.

Spinal cord injury participants who had central sleep apnea (n = 5)
were given CO₂ (8%) until central apnea was eliminated. After stable
non-REM sleep was achieved, CO₂ was decreased until central apnea
recurred. The trial was repeated at least twice and the CO₂ reserve was
defined as ΔPETCO₂ between the control period (stable non-REM sleep
after central apnea is eliminated) and the last five breaths before
central apnea.
**Statistical Analysis**

All data were assessed for normal distribution. An unpaired t-test was used to compare group means for all demographic parameters. Analysis of variance (ANOVA) was used to compare group values for each ventilatory variable in cervical SCI, thoracic SCI, and controls between wake and non-REM sleep (VE, VT, RR, Ti, Te, PETCO₂, CV, and O₂Sat) and the mean values of chemoresponsiveness parameters (PETCO₂, PETCO₂-AT, CO₂ reserve, PG, and CG) for each group (C-SCI vs. T-SCI vs. control). To assess the relationship between CO₂ reserve and putative risk factors for central apnea (age, AHI, BMI, and eupnic PETCO₂) in all groups (C-SCI, T-SCI, and control), a Spearman correlation analysis was used. Multiple linear regression models were used to identify independent predictors of AHI across groups.

**RESULTS**

We studied 16 chronic SCI patients, including 8 cervical (C4–C7) and 8 thoracic (T2–T6) levels and 16 able-bodied matched controls with similar demographics. Table 1 summarizes the demographics, time since injury, use of narcotics, daytime sleepiness and severity of sleep-disordered breathing (AHI) in these participants.

Table 2 summarizes the characteristics of sleep and polysomnography data. There were similar sleep stages in both C-SCI and T-SCI groups. However, the sleep efficiency was lower in C-SCI than in T-SCI. It is of note that 6 of 8 (75%) C-SCI patients had moderate SDB (defined as AHI >15 event/h) vs. 2 of 8 (25%) of the T-SCI (P < 0.05). It was noted also that 5 of 8 (63%) of the C-SCI patients had primarily central sleep apnea (defined by central apnea index >5 event/h and AHI >5 event/h) and 88% had periodic breathing (PB). Although only 1 of 8 (13%) T-SCI patients had primarily central sleep apnea, 38% had PB (P = 0.04). Baseline ventilation, timing, and PETCO₂ were similar between C-SCI and T-SCI patients during wake (Table 3) and non-REM sleep (Table 4). Minute ventilation coefficient of variation, however,

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Fig. 1. A representative polygraph from one spinal cord injured (SCI) patient during non-rapid eye movement (REM) sleep depicting the noninvasive ventilation (NIV) protocol to induce central apnea. Left: baseline ventilation preceding NIV trial. NIV is performed for 3 min; termination of NIV resulted in central apnea. Pscg, supraglottic pressure; PETCO2, end-tidal CO2; Pmask, mask pressure.
was highest in cervical SCI compared with thoracic and control subjects during both wake and sleep.

Figure 1 illustrates a representative example of induced central apnea using NIV in SCI subjects without spontaneous central apnea at baseline. An example of spontaneous central apnea is shown in Fig. 2. C-SCI patients demonstrated higher steady-state plant gain (10.5 ± 2.9 mmHg·l⁻¹·min⁻¹) compared with T-SCI (5.9 ± 2.4 mmHg·l⁻¹·min⁻¹, P < 0.05) and able-bodied control subjects (6.3 ± 1.6 mmHg·l⁻¹·min⁻¹, P < 0.05; Fig. 3). There was no significant difference in the hypocapnic chemoreflex sensitivity (CG) among the three groups (C-SCI 0.93 ± 0.38 l·min⁻¹·mmHg⁻¹, T-SCI 1.25 ± 1.1 l·min⁻¹·mmHg⁻¹, and control 1.68 ± 0.7 l·min⁻¹·mmHg⁻¹; P = NS). The net effect was narrower CO2 reserve in C-SCI than in T-SCI or control group (−0.4 ± 2.9 vs. −2.9 ± 3.3 vs. −3.0 ± 1.2 mmHg, respectively; P < 0.05). After removing all subjects who had hypercapnia protocol (3 patients with C-SCI and 2 patients with T-SCI) and recalculating the mean CO2 reserve in the subgroups that required noninvasive ventilation to induce central apnea, the cervical SCI group continued to have narrower CO2 reserve than the thoracic SCI group (−2.4 ± 0.9 vs. −4.6 ± 1.5 mmHg, respectively; P < 0.05; Fig. 4).

Table 2. Characteristics of sleep and polysomnography data

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
<th>P Value</th>
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<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>TST, min</td>
<td>148.38 ± 40.2</td>
<td>180.5 ± 53.6</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N1, %</td>
<td>26.6 ± 24.1</td>
<td>16.8 ± 18.9</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N2, %</td>
<td>47.1 ± 19.3</td>
<td>48.1 ± 14.1</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N3, %</td>
<td>19.8 ± 19.5</td>
<td>28.2 ± 18.1</td>
<td>NS</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>2.5 ± 3.8</td>
<td>7.0 ± 11.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>59.0 ± 14.0</td>
<td>83.5 ± 15.7</td>
<td>&lt;0.05</td>
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<tr>
<td>Mean AHI, event/h</td>
<td>32.9 ± 22.7</td>
<td>15.3 ± 22.1</td>
<td>NS</td>
</tr>
<tr>
<td>AHI, &gt; 5 events/h</td>
<td>90.0</td>
<td>50.0</td>
<td>NS</td>
</tr>
<tr>
<td>AHI, &gt; 15 events/h</td>
<td>75.0*</td>
<td>25.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ODI, &gt; 5 events/h</td>
<td>13.6</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>CAI, &gt; 5 events/h</td>
<td>63.0*</td>
<td>13.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OAI, &gt; 5 events/h</td>
<td>0.9</td>
<td>6.9</td>
<td>NS</td>
</tr>
<tr>
<td>CSR, %</td>
<td>4.0</td>
<td>10.0</td>
<td>NS</td>
</tr>
<tr>
<td>PB, %</td>
<td>88.0*</td>
<td>38.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR, beat/min</td>
<td>64.6 ± 9.7</td>
<td>74.0 ± 6.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>95.9 ± 1.1</td>
<td>97.0 ± 1.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data are means ± SD. TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen-desaturation index; ARI, respiratory-related arousal index; CAS, central apnea index; OAI, obstructive apnea index; CSR, Cheyne-Stokes respiration; PB, periodic breathing; HR, heart rate; SaO₂, oxygen saturation. *P < 0.05 cervical vs. thoracic.

Figure 5 depicts the PETCO₂ changes from eupnea to central apnea (apneic threshold) in control, C-SCI, and T-SCI subjects. There was no difference in PETCO₂-AT among the three groups (C-SCI 40.8 ± 6.0 mmHg, T-SCI 36.6 ± 3.0 mmHg, and able-bodied control 38.0 ± 4.1 mmHg, P = NS).

Across the three groups, AHI correlated positively with daytime sleepiness ESS, NC, age, PG and CO2 reserve (r = 0.63, 0.43, 0.52, 0.42, and 0.51, respectively; P < 0.05) but not with BMI, baseline CO2, or PETCO₂-AT (P = NS). Using multiple linear regression model to predict AHI in all participants from the ESS, NC, age, PG, and CO2 reserve, CO2 reserve was the only independent predictor of AHI (Table 5).

Table 3. Ventilatory parameters during wake

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>Vₐ, l/min</td>
<td>6.3 ± 2.1</td>
<td>6.7 ± 1.4</td>
<td>7.6 ± 1.2</td>
</tr>
<tr>
<td>Vₑ, liters</td>
<td>0.44 ± 0.20</td>
<td>0.40 ± 0.6</td>
<td>0.53 ± 0.11</td>
</tr>
<tr>
<td>RR, breath/min</td>
<td>15.3 ± 3.8</td>
<td>16.9 ± 3.0</td>
<td>14.7 ± 2.3</td>
</tr>
<tr>
<td>Tₑ, s</td>
<td>1.8 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>Tₛ, s</td>
<td>2.5 ± 0.8</td>
<td>2.1 ± 0.5</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>T/Tₑₛ, s</td>
<td>0.43 ± 0.04</td>
<td>0.43 ± 0.03</td>
<td>0.47 ± 0.05</td>
</tr>
<tr>
<td>PETCO₂, mmHg</td>
<td>40.6 ± 4.8</td>
<td>37.5 ± 4.6</td>
<td>40.5 ± 3.3</td>
</tr>
<tr>
<td>Vₑ -CV, %</td>
<td>23.3 ± 14.7</td>
<td>11.6 ± 4.0</td>
<td>10.2 ± 4.1</td>
</tr>
</tbody>
</table>

Data are means ± SD. Ve, minute ventilation; Vt, tidal volume; RR, breathing frequency; Ti, inspiratory time; Te, expiratory time; CV, coefficient of variation.

**DISCUSSION**

**Summary of Findings**

The major findings of our study are 1) the majority of chronic cervical SCI patients had SDB, predominantly central, compared with thoracic SCI; 2) the CO2 reserve was narrower in patients with C-SCI, relative to T-SCI or able-bodied control subjects. This was associated with increased steady-state plant gain but no difference in hypocapnic chemoreflex sensitivity; 3) the CO2 reserve was a predictor of SDB in patients with SCI.

**Effect of SCI Level on the Susceptibility to Central Apnea during Sleep**

Sleep is a physiologic challenge, rather than a rest period for the respiratory system. The removal of the “wakefulness drive to breathe” is associated with hypoventilation and unmasking of the hypocapnic apneic threshold. Patients with impaired respiratory function, such as those with neuromuscular disease or “sleep apnea” is associated with hypoventilation and unmasking of the hypocapnic apneic threshold. Patients with impaired respiratory function, such as those with neuromuscular disease, exhibit marked breathing disturbances during sleep. Several studies have demonstrated high prevalence of SDB in subacute...
and chronic SCI patients (5, 23, 24, 27, 30, 41–43). Berlowitz et al. (5) found that SDB developed in the subacute phase after cervical SCI; interestingly, SDB was not apparent until 2 wk postinjury, peaked at 3 mo after the injury, and declined to an estimated prevalence of 60% 1 yr after injury, representing a two- to fourfold increase relative to the general population. We recently showed high central SDB in a consecutive sample of SCI patients (39). Thus cervical SCI contributes to the development of SDB and may be an independent risk factor for the development of central apnea.

**Mechanism of Central Sleep Apnea in Cervical SCI**

We noted that patients with cervical SCI had narrower CO2 reserve than thoracic SCI patients or the control group. This can be a marker of propensity to breathing instability because central apneas rarely occur as isolated events, but instead as cycles of apnea or hypopnea alternating with hyperpnea. Perpetuating instability reflects the negative feedback closed-loop cycle that characterizes ventilatory control. This is often described using the engineering concept of “loop gain,” which represents the net ventilatory change for a given perturbation. Loop gain combines two types of gain: plant gain (PG) and controller gain (CG) (11, 21). The propensity to central apnea during non-REM sleep is determined by an interaction between the response of the brain and chemoreceptors to changing P_{ETCO2}, representing the controller, and the effectiveness of the lung/respiratory system in lowering P_{ETCO2} in response to hyperventilation (the plant). The controller gain (chemoreflex sensitivity) however, represents the response of the ventilatory system to changing P_{ETCO2}, and the plant gain represents the effectiveness of the lung/respiratory system in lowering P_{ETCO2} in response to hyperventilation (14). Changes in chemoreflex sensitivity (slope of the changes in alveolar volume vs. changes in end-tidal P_{CO2} below eupnea) or plant gain (change in background drive to breathe) without slope changes would alter the requisite hypocapnia to reach central apnea (the CO2 reserve) (11). For instance, hypoventilation and reduced ventilatory drive make the individual highly susceptible to central apnea, requiring small changes in ventilation and end-tidal CO2 below eupnea to cross the apneic threshold (as shown in Fig. 6). In contrast, steady-state hyperventilation, under constant isometabolic state, protects against ventilatory instability and central apnea by requiring larger hyperventilation to reach the apneic threshold.

We found that hypocapnic chemoreflex sensitivity was similar in the three groups despite differences in the CO2 reserve. Our findings in SCI patients differ from other conditions that alter CO2 reserve such as congestive heart failure (CHF) or OSA. For example, data from our laboratory demonstrated narrower CO2 reserve and increased chemoreflex sensitivity in patients with OSA relative to normal subjects (38). Thus the mechanism underlying central apnea is different in SCI patients vs. patients with OSA.

Chemoreflex sensitivity includes an interaction between peripheral and central chemoreflex sensitivity. Our findings do not permit a delineation of the relative contribution of central
vs. peripheral chemoreflex sensitivity after NIV. In fact, it is probable that opposing changes in central and peripheral chemosensitivity contributed to the lack of difference in chemoreflex sensitivity among the three groups. Evidence in the literature suggests blunted central chemoresponsiveness in tetraplegic animals and humans (26, 28). Golder et al. (18) investigated respiratory plasticity in anesthetized, paralyzed and ventilated rats, 2 mo after a C2 hemisection. Decreased hypoglossal motor output noted by Golder et al. (18) supported the notion that supraspinal respiratory plasticity was associated with rostral “progression” of the neurologic deficit. The mechanisms and pathways leading to rostral progression remain unknown.

Patients with chronic SCI are predisposed to frequent chronic intermittent hypoxia (CIH) during sleep due to poor cough, impaired secretion clearance, atelectasis, and sleep-disordered breathing. CIH can induce plasticity in the cervical spinal cord, resulting in enhanced inspiratory phrenic motor output (33), sensitization of the carotid body and a long-lasting increase in baseline peripheral chemoreceptor activity (sensory long-term facilitation or LTF) (35). The latter may result in augmented response to hypoxia and increased likelihood of developing unstable breathing. In summary, the similarity of the chemoreflex sensitivity under hypocapnia among the three groups may be due to the additive effect of two opposing changes: decreased central chemoreflex sensitivity and increased peripheral chemoreflex sensitivity; if proven, this may be a markedly destabilizing combination. This interpretation remains a speculation awaiting experimental proof.

We found that narrowed CO₂ reserve in patients with cervical SCI was associated with increased steady-state plant gain. Plant factors, expressed by the relationship between ventilation and alveolar PCO₂ are critical determinants of susceptibility to central apnea (15). Steady-state plant gain affects the effectiveness of the respiratory system to eliminate CO₂ for a given

![Graph showing CO₂ reserve and Plant Gain comparisons](image_url)

Fig. 3. A summary of data to compare the controller gain (top), steady-state plant gain (middle) and CO₂ reserve (bottom) in the cervical, thoracic and able-bodied control groups. Data are expressed as mean ± SE. *P < 0.05 for cervical vs. control; +P < 0.05 for cervical (C)-SCI vs. thoracic (T)-SCI. Note that the steady-state plant gain and controller gain analysis included only NIV protocol to induce central apnea (5 C-SCI and 6 T-SCI).

![Graph showing CO₂ reserve comparisons](image_url)

Fig. 4. A summary data to compare the CO₂ reserve in the cervical (n = 5) and thoracic (n = 6) subgroups that underwent NIV protocol to induce central apnea. Data are expressed as mean ± SE. *P < 0.05 for cervical vs. thoracic.

![Graph showing eupneic and hypocapnic PCO₂ comparisons](image_url)

Fig. 5. A plot box represents the summary data to compare the eupneic PCO₂ and hypocapnic apneic threshold (dotted lines) in the cervical, thoracic and able-bodied control groups. CO₂ reserve is indicated by parentheses for cervical (A), control (B), and thoracic (C), respectively. Data are expressed as mean ± SE for SCI and as means for control group.

Patients with chronic SCI are predisposed to frequent chronic intermittent hypoxia (CIH) during sleep due to poor cough, impaired secretion clearance, atelectasis, and sleep-disordered breathing. CIH can induce plasticity in the cervical spinal cord, resulting in enhanced inspiratory phrenic motor output (33), sensitization of the carotid body and a long-lasting increase in baseline peripheral chemoreceptor activity (sensory long-term facilitation or LTF) (35). The latter may result in augmented response to hypoxia and increased likelihood of developing unstable breathing. In summary, the similarity of the chemoreflex sensitivity under hypocapnia among the three groups may be due to the additive effect of two opposing changes: decreased central chemoreflex sensitivity and increased peripheral chemoreflex sensitivity; if proven, this may be a markedly destabilizing combination. This interpretation remains a speculation awaiting experimental proof.

We found that narrowed CO₂ reserve in patients with cervical SCI was associated with increased steady-state plant gain. Plant factors, expressed by the relationship between ventilation and alveolar PCO₂ are critical determinants of susceptibility to central apnea (15). Steady-state plant gain affects the effectiveness of the respiratory system to eliminate CO₂ for a given

![Graph showing CO₂ reserve and Plant Gain comparisons](image_url)

Fig. 3. A summary of data to compare the controller gain (top), steady-state plant gain (middle) and CO₂ reserve (bottom) in the cervical, thoracic and able-bodied control groups. Data are expressed as mean ± SE. *P < 0.05 for cervical vs. control; +P < 0.05 for cervical (C)-SCI vs. thoracic (T)-SCI. Note that the steady-state plant gain and controller gain analysis included only NIV protocol to induce central apnea (5 C-SCI and 6 T-SCI).

![Graph showing CO₂ reserve comparisons](image_url)

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alveolar ventilation level. Hence, high steady-state plant gain can occur when a small change in ventilation results in a large change in PCO₂. Increased plant gain is seen in individuals with low metabolic rate, low cardiac output, small functional residual capacity, or waking hypercapnia (49). High plant gain can also be found in ventilatory control disorders (central alveolar hypoventilation) or neuromuscular disease, which manifests as high baseline PCO₂ and can lead to central apneas upon transition to non-REM sleep when breathing is mainly dependent on chemoreceptor activity (31). Our findings corroborate previous studies demonstrating that differences in plant gain alter the CO₂ reserve, independent of changes in chemoreflex sensitivity. Nakayama et al. (33) demonstrated an inverse relationship between background ventilatory drive and the susceptibility to posthyperventilation apnea; as metabolic acidosis was associated with increased CO₂ reserve and metabolic alkalosis was associated with narrowing of the CO₂. Similarly, Chenuel et al. (7) found that specific carotid chemoreceptor inhibition with dopamine increased was associated with narrowing of the CO₂ reserve due solely to increased plant gain without change in chemoreflex sensitivity. Thus non-REM sleep induced hypoventilation in patients with cervical SCI is associated with increased plant gain and enhanced propensity to central apnea.

What is the etiology of sleep-related hypoventilation in patients with cervical SCI who have normal gas exchange during wakefulness? Originally, central sleep apnea and nocturnal ventilatory failure were noted in the aftermath of upper cervical cordotomy for intractable pain and was referred to as the “Ondine’s curse” (45, 46), which was attributed to the disruption of the ascending reticular fibers of the higher cervical spinal cord and the ensuing effects on the brain stem respiratory centers (44). Studies in animal models support the possibility of time-dependent decrease in ventilatory motor output rostral to the level of injury. For example, Zimmer and Goshgarian (51) examined medullary slices after acute injury (2 days) in neonatal rat tissue; the main finding was a reduction in proteins involved in excitatory neurotransmission and an increase in proteins involved in inhibitory neurotransmission. These changes could potentially be involved in the alteration of the descending command of autonomic function. This may explain the exquisite sensitivity of cervical SCI patients to sleep, manifesting as hypoventilation, increased plant gain and promotion of breathing instability.

**Clinical Implications**

Our findings may have significant implications regarding pathogenesis and management of SDB. The occurrence of central apnea initiates a cascade of events that may perpetuate breathing instability. The associated hypoxia and transient arousals lead to ventilatory overshoot, hypocapnia and subsequent ventilatory undershoot. Furthermore, the decreased ventilatory motor output or central apnea is associated with upper airway narrowing and even closure (27). The net effect is prolongation of apnea and perpetuation of breathing instability.

Another implication is the destabilizing effect of steady-state hypoventilation by increasing plant gain. Thus measures to decrease plant gain may stabilize respiration and have therapeutic value. Examples of such measures include mechanical means such as positive airway pressure, which reduce plant gain by unloading the upper airway and increasing lung volume, or increasing ventilatory motor output with pharmacological agents, such as acetazolamide (20). Such intervention can stabilize ventilation by lowering plant gain by shifting the eugenic PCO₂ to the steeper portion of the metabolic hyperbola as illustrated in Fig. 6. Thus treatment approaches that decrease plant gain may be an effective treatment of sleep-disordered breathing in patients with cervical SCI who suffer from central apnea.

**Table 5. Multivariable regression analysis showing the contribution of each variable to predict AHI**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-38.20</td>
<td>37.95</td>
<td>0.33</td>
</tr>
<tr>
<td>ESS</td>
<td>0.76</td>
<td>0.76</td>
<td>0.33</td>
</tr>
<tr>
<td>NC</td>
<td>1.08</td>
<td>0.83</td>
<td>0.21</td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>0.18</td>
<td>0.53</td>
</tr>
<tr>
<td>PG</td>
<td>1.48</td>
<td>1.15</td>
<td>0.22</td>
</tr>
<tr>
<td>CO₂ reserve</td>
<td>4.41</td>
<td>1.37</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

PG, plant gain.

Fig. 6. A schematic diagram depicting the ventilatory responsiveness to CO₂ below eupnea in C-SCI and T-SCI patients for a given isometabolic hyperbole. This illustration depicts 2 examples of C-SCI and T-SCI with similar chemoreflex sensitivity slopes (solid and dotted lines; respectively). Note that in C-SCI example (solid lines) a smaller change in PETCO₂ (from 42.8 mmHg at baseline to 40.8 mmHg) in response to hyperventilation is required to cross the apneic threshold (A) and results in an apnea. In T-SCI case (dotted lines), however, a larger change in PETCO₂ (from 40.0 mmHg at baseline to 36.6 mmHg) in response to hyperventilation is required to cross the apneic threshold (B) and develop an apnea. Note that the T-SCI example is at higher point (Y) on the isometabolic hyperbole than C-SCI example (X) despite similar chemoreflex sensitivity. Slopes indicate similar chemoreflex sensitivity below eupnea in the thoracic and cervical groups. The solid line and arrow in T-SCI example indicate the estimated change in PETCO₂ (from 40.0 mmHg at baseline to 38.5 mmHg) for the same change in ventilation, which is noted in C-SCI example in response to hyperventilation reaching (C) point without crossing the apneic threshold (B).

**Methodological Considerations**

Our laboratory has used NIV to induce hypocapnic central apnea in humans during sleep in multiple studies (37, 46). Nevertheless, several considerations may influence the interpretation of the findings. First, we asked participants to have partial sleep deprivation one night before the study to maximize the likelihood of stable sleep during the experiments; however, partial sleep deprivation has not been shown to affect
ventilatory response to CO2 or apneic threshold (37). Second, our subjects were studied during sleep after the administration of zolpidem to prevent awakening due to heavy instrumentation. Zolpidem is less likely to affect our findings given all three groups were treated similarly and previous studies found that this medication at a dosage of 10 mg has no effect on respiration in terms of occlusion pressure, ventilation, Pco2, SaO2, ventilatory response to CO2, or respiratory disturbance index (4, 28, 35, 52). Therefore, it is unlikely that zolpidem affected the CO2 reserve or the apneic threshold in our study. Even if an effect were present, it would be present in all groups and thus would not alter our conclusions. Third, medications such as opioids, muscle relaxants, or nicotine use can influence breathing in SCI patients during sleep. Opioids in particular can affect breathing patterns and precipitate central sleep apnea. However, opioid users were similar between the two groups (3 patients with C-SCI and 2 with T-SCI were opioid users for pain). When we remove opioid users from the analysis and keep only nonopioid users, central sleep apnea remained more common in C-SCI [3/5 (60%)] vs. T-SCI [0/6 (0%)]. We also asked all participants to abstain from any narcotics or sedatives on the day of the study. Likewise C-SCI and T-SCI patients had similar rates of nicotine use/tobacco smoking (38% in both groups). Fourth, we used two protocols to measure the CO2 reserve based on the presence or absence of spontaneous central apnea at baseline in the cervical and thoracic SCI groups. The differences in the techniques, however, were unlikely to alter the conclusion that tetraplegia is associated with central sleep apnea, especially because the difference in the CO2 reserve between the two groups persisted when we reanalyzed the data to include only NIV protocol and removed all subjects with spontaneous central apnea that required CO2 administration (Fig. 4). Finally, repetitive arousals and sleep stage shifts may contribute to the breathing instability and periodic breathing in tetraplegic patients who may have increased occurrences of spasticity, pain and periodic leg movements (44). In our study, both C-SCI and T-SCI individuals had similar arousal indices and respiratory-related arousals; however, subtle autonomic arousals, without EEG changes, may potentially contribute to unstable breathing.

In summary, we found that chronic C-SCI is associated with increased propensity to posthyperventilation central apnea relative to T-SCI or able-bodied controls. This is likely due to increased plant gain secondary to sleep-induced hypoventilation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: A.S. and M.S.B. conception and design of research; A.S. and A.B. performed experiments; A.S. and A.B. analyzed data; A.S., S.C., and M.S.B. interpreted results of experiments; A.S. prepared figures; A.S. drafted manuscript; A.S. and M.S.B. edited and revised manuscript; A.S. and M.S.B. approved final version of manuscript.

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Tetraplegia is a Risk Factor for Central Sleep Apnea • Sankari A et al.


