Tetraplegia is a Risk Factor for Central Sleep Apnea

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ABSTRACT

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 (C-SCI) are more susceptible to central apnea than patients with thoracic (T-SCI) or able-bodied controls. **Methods:** Sixteen patients with chronic SCI, level T6 or above, (8 C-SCI, 8 T-SCI) (age 42.5±15.5 years; BMI 25.9±4.9 kg/m²) and 16 matched controls were studied. The hypocapnic apneic threshold and CO₂ reserve were determined using non-invasive ventilation (NIV). 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 PETCO₂ and VE ratio during stable sleep. Controller gain (CG) was defined as the ratio of change in VE between control and hypopnea or apnea to the Δ PETCO₂. **Results:** 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 narrower in C-SCI than in T-SCI or control group (-0.4±2.9 vs. -2.9±3.3 vs. -3.0±1.2 L/min/mmHg, respectively; p<0.05). PG was higher in C-SCI than in T-SCI or control groups (10.5±2.4 vs. 5.9±2.4 vs. 6.3±1.6 mmHg/L/min, respectively; p<0.05) and CG was not significantly different. The CO₂ reserve was an independent predictor of AHI. **Conclusion:** C-SCI had higher rates of central SDB, indicating that tetraplegia is a risk factor for central sleep apnea. Sleep-related hypoventilation may play a significant role in the mechanism of SDB in higher SCI levels.
1. INTRODUCTION

Spinal cord injury (SCI) is prevalent worldwide, estimated at 15 to 40 cases per million populations. 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 sub-acute and chronic spinal cord injury patients (ranging between 27% and 62%) (5, 17, 23, 24, 27, 30, 42 43, 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 four weeks immediately post-injury and remained at 60% after one year 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 and 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 hypoventilation, cardiac dysfunction or use of narcotics (34, 39). Interestingly, central apnea was the predominant pattern in cervical (C-SCI) patients and obstructive apnea was the predominant pattern in the thoracic (T-SCI) group. This unique observation may have significant implication 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, who coined the term "Ondine’s curse" to describe sleep-related ventilatory failure following surgery to the upper cervical cord (41). Central apnea in patients with cervical SCI may be secondary to hypoventilation or increased post-hyperventilation 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. showed that supraspinal changes alter respiratory output after SCI (18). Furthermore, Zimmer et al. showed that neural receptors change rostral to SCI in neonatal rats and alter motor output via supraspinal mechanisms (51). 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-REM 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 hypoventilation 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 susceptibility to central apnea in patients with cervical and thoracic SCI compared to able-bodied control subjects, and to ascertain predictors of SDB in chronic SCI patients. To this end, we measured the CO$_2$ reserve (a marker of susceptibility to central apnea), plant gain and controller gain during non-REM sleep. We hypothesized that CO$_2$ reserve is narrower in cervical SCI compared to thoracic and able-bodied controls. Results of this study have previously been reported in the form of abstracts (34,39).

2. METHODS

2.1. Subjects

The Human Investigation Committee of the Wayne State University 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 years old) if they met the inclusion and exclusion criteria. Zolpidem 10 mg was administered orally to all participants 30 minutes before sleep to minimize any arousability or difficulty sleeping with instrumentation. Inclusion Criteria: non-ventilation dependent subjects with chronic SCI (more than 6 months post-injury), 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, peripheral 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 which 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 years old) with similar age, BMI and gender.

2.2. Measurements

Every subject who agreed to enroll had brief history and physical exam. In addition to standard baseline polysomnography in the supine position, airflow was measured by a pneumotachometer (Hans Rudolph, inc., Model 3700A, Shawnee, KS) connected 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®), positioned in the hypopharynx.
Apneic Threshold Measurement:

(1) Non-invasive Ventilation (NIV) Protocol: We used a portable non-invasive pressure-cycled ventilator (Quantum PSV, Model 7703, Healthdyne Technologies inc., Andover, MA) to induce hyperventilation using a 10 cmH₂O pressure support for at least 3 minutes resulting in a hypopnea or central apnea (Figure 1). NIV was terminated during expiration to the baseline expiratory positive airway pressure (EPAP=4.0 cmH₂O) for a minimum of 3 minutes. 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. Apneic threshold (AT) was defined as the measured PETCO₂ at the end of the hyperventilation trial at which the apnea occurred as depicted in Figure1.

(2) Hypercapnia protocol: For subjects that have spontaneous central 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 minute. If central apneas were not abolished; CO₂ flow rate was increased by 0.5L/min at one minute intervals until central apneas were absent. The hypercapnia trial was repeated at least twice.

2.3. Data Analysis

Standard polysomnography (PSG) was performed according to American Academy of Sleep Medicine (AASM) standards, using the Comet PSG 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 ten breaths from wakefulness and
stable non-REM sleep, with no apneas preceding it for two minutes, were measured to
assess baseline ventilation \(({V_E, V_T, RR, T_i, T_e, P_{ETCO_2}, \text{and } O_2Sat})\) using the PowerLab
acquisition system (AD Instruments, inc. Model 16SP, Colorado Springs, CO). The
coefficient of variation (CV) of baseline \(V_E\) was measured similar to previous studies as
a marker for the breathing instability and periodic breathing \(^{(47)}\).

SDB was identified if the calculated AHI was greater than or equal to 5 events
per hour of sleep. Central SDB was defined as AHI greater than or equal to 5 events per
hour of non-REM sleep and a central apnea index (CAI) greater than or equal to 5
central events per hour of sleep. Cheyne-Stokes respiration (CSR) was defined as at
least 3 consecutive cycles of cyclical crescendo and decrescendo change in breathing
amplitude and at least one of the following: 1) five or more central apnea or hypopnea
per hour of sleep; 2) the cyclical crescendo and decrescendo changes in breathing
lasted for at least 10 consecutive minutes \(^{(6)}\). 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 seconds \(^{(8,37)}\).

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 (Figure 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 $P_{ET}CO_2$ ($\Delta P_{ET}CO_2$) was calculated as the difference
between the control period and the last 5 NIV breaths. Apneic threshold (AT) was
defined as the measured $P_{ET}CO_2$ at which the apnea closest to the last hypopnea
occurred. The CO$_2$ reserve was defined as $\Delta P_{ET}CO_2$ between control and central
apnea. Steady-state plant gain (PG) was calculated in each participant from baseline
$P_{ET}CO_2$ -$V_E$ ratio during stable non-REM sleep as described recently (14). Hypocapnic
chemoreflex sensitivity or controller gain (CG) was defined as the ratio of change in $V_E$
between control and hypopnea or apnea to the corresponding change in $P_{ET}CO_2$.

Spinal cord injury participants who had central sleep apnea (n=5) were given
CO$_2$ (8%) until central apnea was eliminated. After stable non-REM sleep was
achieved, CO$_2$ was decreased until central apnea recurred. The trial was repeated at
least twice and the CO$_2$ reserve was defined as $\Delta P_{ET}CO_2$ between the control period
(stable non-REM sleep after central apnea is eliminated) and the last 5 breaths before
central apnea.

2.5. 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 ($V_E$, $V_T$, RR, $T_i$, $T_E$, $P_{ET}CO_2$, CV, and
O₂Sat), and the mean values of chemoresponsiveness parameters (P_{ET}CO₂, P_{ET}CO₂-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 P_{ET}CO₂) 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.

### 3. 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 out of 8 (75%) C-SCI patients had moderate SDB (defined as AHI >15 event/hour) versus 2 out of 8 (25%) of the T-SCI (p<0.05). It was noted also that 5 out of 8 (63%) of the C-SCI patients had primarily central sleep apnea (defined by CAI >5 event/hour and AHI >5 event/hour) and 88% had periodic breathing (PB). While only 1 out of 8 (13%) of T-SCI patients had primarily central sleep apnea and 38% had PB (p=0.04). Baseline ventilation, timing, and P_{ET}CO₂ 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, was highest in cervical SCI compared to 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 Figure 2. C-SCI patients demonstrated higher steady-state plant gain (10.5±2.4 mmHg/L/min) compared to T-SCI (5.9±2.4 mmHg/L/min; p <0.05) and able-bodied control subjects (6.3±1.6 mmHg/L/min; p <0.05) (Figure 3). There was no significant difference in the hypocapnic chemoreflex sensitivity (CG) among the three groups (C-SCI 0.93±0.38 L/min/mmHg, T-SCI 1.25±1.1 L/min/mmHg and control 1.68±0.7 L/min/mmHg; 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 with spontaneous central apnea (3 patients with C-SCI and 2 patients with T-SCI) and recalculating the mean CO₂ reserve in the sub-groups that required non-invasive 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) (Figure 4).

Figure 5 depicts the P_{ET}CO₂ changes from eupnea to central apnea (apneic threshold) in control, C-SCI and T-SCI subjects. There was no difference in P_{ET}CO₂-AT among the three groups (C-SCI 40.8±2.9 mmHg, T-SCI 36.6±3.0 mmHg and able-bodied control 41.1±4.2 mmHg, p=NS).
Across the three groups, AHI correlated positively with day-time 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 P_{ETCO₂-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).

4. DISCUSSION

Summary of Findings:

The major findings of our study are: (1) The majority of chronic cervical SCI patients had SDB, predominantly central, as compared to 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 and 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, exhibit marked breathing disturbances during sleep. Several studies have demonstrated high
prevalence of SDB in sub-acute and chronic SCI patients\(^{5, 23, 24, 27, 30, 41, 42, 43}\). Berlowitz et al. \(^{5}\) found that SDB developed in the sub-acute phase following cervical SCI; interestingly, SDB was not apparent until 2 weeks post-injury, peaked at 3 months following the injury and declined to an estimated prevalence of 60% one year after injury, representing a 2-4 fold increase relative to the general population. We have recently shown 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 patients had narrower CO\(_2\) reserve than thoracic SCI patients or the control group. This can be a marker of propensity to breathing instability as 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\(_{ET\text{CO}_2}\), representing the controller, and the effectiveness of the lung/respiratory system in lowering P\(_{ET\text{CO}_2}\) in response to hyperventilation (the plant). The controller gain (chemoreflex sensitivity) however, represents the response of
the ventilatory system to changing $P_{ETCO_2}$, and the plant gain represents the effectiveness of the lung/respiratory system in lowering $P_{ETCO_2}$ in response to hyperventilation \(^{(14)}\). Changes in chemoreflex sensitivity (slope of the changes in alveolar volume vs. changes in end-tidal PCO\(_2\) below eupnea) or plant gain (change in background drive to breathe) without slope changes would alter the requisite hypocapnia to reach central apnea (the CO\(_2\) 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 CO\(_2\) below eupnea to cross the apneic threshold (as shown in Figure 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 CO\(_2\) reserve. Our findings in SCI patients differ from other conditions that alter CO\(_2\) reserve such as congestive heart failure (CHF) or OSA. For example, data from our laboratory demonstrated narrower CO\(_2\) 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 versus 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 versus peripheral chemoreflex sensitivity following 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. (2001) investigated respiratory plasticity in anesthetized, paralyzed and ventilated rats, 2 months after a C2 hemisection\(^{(18)}\). Decreased hypoglossal motor output noted by Golder et al. (2001) supported the notion that supraspinal respiratory plasticity was associated with rostral “progression” of the neurologic deficit\(^{(18)}\). 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 CO\(_2\) reserve in patients with cervical SCI was associated with increased steady-state plant gain. Plant factors, expressed by the
relationship between ventilation and alveolar PCO$_2$ are critical determinants of susceptibility to central apnea (15). Steady-state plant gain affects the effectiveness of the respiratory system to eliminate CO$_2$ for a given alveolar ventilation level. Hence, high steady-state plant gain can occur when a small change in ventilation results in a large change in PCO$_2$. 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 PCO$_2$ 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 CO$_2$ reserve, independent of changes in chemoreflex sensitivity. Nakayama, et al. (33) demonstrated an inverse relationship between background ventilatory drive and the susceptibility to post-hyperventilation apnea; as metabolic acidosis was associated with increased CO$_2$ reserve and metabolic alkalosis was associated with narrowing of the CO$_2$. Similarly, Chenuel et al. (7) found that specific carotid chemoreceptor inhibition with dopamine increased was associated with narrowing the CO$_2$ 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 brainstem 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 examined medullary slices following acute injury (2 days) in neonate rat tissue; the main finding was a reduction in proteins involved in excitatory neurotransmission and an increase in proteins involved in inhibitory neurotransmission \(^{(51)}\). 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 by 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 are 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. Such intervention can stabilize ventilation by lowering plant gain by shifting the eupneic PCO₂ to the steeper portion of the metabolic hyperbola, as illustrated in Figure 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.

Methodological Considerations

Our laboratory has used NIV to induce hypocapnic central apnea in humans during sleep in multiple studies. 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. 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. Therefore, it is unlikely that zolpidem affected the CO₂ reserve or the apneic threshold in our study. Even if an effect was 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 opioids users for pain). When we remove opioid users from the analysis and keep only non-opioid 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 that the difference in the CO2 reserve between the two groups persisted when we reanalyzed the data to include only NIV protocol and removing all subjects with spontaneous central apnea that required CO2 administration (Figure 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. 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 have found that chronic C-SCI is associated with increased propensity to post-hyperventilation 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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Figures legends:

Figure 1: A representative polygraph from one SCI patient during non-REM sleep depicting the NIV protocol to induce central apnea. Left panel is baseline ventilation preceding NIV trial. NIV is performed for 3 minutes; termination of NIV resulted in central apnea. Abbreviations: P_{SG}, supraglottic pressure; P_{ETCO2}, end-tidal CO_2; P_{mask}, mask pressure.

Figure 2: A representative polygraph from one cervical SCI patient who had spontaneous central apnea and breathing instability associated with fluctuations in end-tidal CO_2 (P_{ETCO2}) and O_2 saturation during sleep. Abbreviations: P_{SG}, supraglottic pressure; P_{ETCO2}, end-tidal CO_2; P_{mask}, mask pressure; F_{I,O2}, fractional inspired O_2.

Figure 3: A summary data to compare the controller gain (top panel), steady-state plant gain (middle panel) and CO_2 reserve (bottom panel) in the cervical, thoracic and able-bodied control groups. Data is expressed as mean ± SE. (*) indicates p < 0.05 for cervical vs. control and (+) indicates p < 0.05 for C-SCI vs. 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).

Figure 4: A summary data to compare the CO_2 reserve in the cervical (n=5) and thoracic (n=6) sub-groups that underwent NIV protocol to induce central apnea. Data is expressed as mean ± SE. (*) indicates p < 0.05 for cervical vs. thoracic.

Figure 5: A plot box represents the summary data to compare the eupneic PCO_2 and hypocapnic apneic threshold (dotted lines) in the cervical, thoracic and able-bodied
control groups'. CO2 reserve was indicated by parentheses for cervical (A), control (B), and thoracic (C), respectively. Data is expressed as mean ± SE for SCI and as means for control group.

**Figure 6:** A schematic diagram depicting the ventilatory responsiveness to CO2 below eupnea in cervical (C-SCI) and thoracic (T-SCI) patients for a given isometabolic hyperbolae. This illustration depicts two 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 hyperbolae than C-SCI example (X) despite similar chemoreflex sensitivity. Slopes indicate the 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).
References


   [http://dx.doi.org/10.1016/j.resp.2013.06.009](http://dx.doi.org/10.1016/j.resp.2013.06.009)


**TABLE 1: PATIENTS CHARACTERISTICS**

<table>
<thead>
<tr>
<th></th>
<th>CERVICAL</th>
<th>THORACIC</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td><strong>AGE (YEAR)</strong></td>
<td>50.1±19.0</td>
<td>38.1±16.0</td>
<td>42.7±18.6</td>
</tr>
<tr>
<td><strong>BMI (Kg/m²)</strong></td>
<td>25.6±4.6</td>
<td>28.6±5.1</td>
<td>25.6±2.9</td>
</tr>
<tr>
<td><strong>GENDER (F/M)</strong></td>
<td>3/5</td>
<td>4/4</td>
<td>7/9</td>
</tr>
<tr>
<td><strong>NC (CM)</strong></td>
<td>37.9±3.8</td>
<td>39.9±5.3</td>
<td>37.4±1.9</td>
</tr>
<tr>
<td><strong>TIME SINCE INJURY (YEAR)</strong></td>
<td>10.9±5.5</td>
<td>12.0±7.4</td>
<td>-</td>
</tr>
<tr>
<td><strong>USE OF NARCOTICS (%)</strong></td>
<td>37.5</td>
<td>25.0</td>
<td>-</td>
</tr>
<tr>
<td><strong>ESS (POINTS)</strong></td>
<td>11.0±4.4</td>
<td>10.3±4.0</td>
<td>4.7±2.7**</td>
</tr>
<tr>
<td><strong>AHI (EVENT/HR)</strong></td>
<td>32.9±22.7</td>
<td>15.3±22.1</td>
<td>1.6±2.3*</td>
</tr>
</tbody>
</table>

All data mean±SD

*NC, neck circumference; BMI, body mass index; ESS, Epworth Sleepiness Scale (0-24). (*) P value is <0.01 CERVICAL vs. CONTROL. (+) P value is <0.01 THORACIC vs. CONTROL.*
### Table 2: Characteristics of Sleep and Polysomnography Data

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>TST (Minutes)</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>
</tr>
<tr>
<td>Mean AHI (event/hr)</td>
<td>32.9±22.7</td>
<td>15.3±22.1</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (%&gt;5 events/hr)</td>
<td>90.0</td>
<td>50.0</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (%&gt;15 events/hr)</td>
<td>75.0*</td>
<td>25.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ODI (%&gt;5 events/hr)</td>
<td>13.6</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>CAI (%&gt;5 events/hr)</td>
<td>63.0*</td>
<td>13.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OAI (%&gt;5 events/hr)</td>
<td>0.9</td>
<td>6.9</td>
<td>NS</td>
</tr>
<tr>
<td>CSR (%)</td>
<td>40.0</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/Minute)</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 Mean±SD**

TST, Total Sleep Time; AHI, Apnea-Hypopnea Index; ODI, Oxygen-Desaturation Index; ARI, Respiratory Related Arousal Index; CAI, Central Apnea Index; OAI, Obstructive Apnea Index; CSR, Chyne-Stokes Respiration; PB, Periodic Breathing; HR, Heart Rate; SaO2, Oxygen Saturation. (*) P value <0.05 Cervical vs. Thoracic.
**TABLE 3: VENTILATORY PARAMETERS DURING WAKE**

<table>
<thead>
<tr>
<th></th>
<th>CERVICAL</th>
<th>THORACIC</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_E$ (L/min)</td>
<td>6.3±2.1</td>
<td>6.7±1.4</td>
<td>7.6±1.2</td>
</tr>
<tr>
<td>$V_T$ (L)</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>$T_I$ (SEC)</td>
<td>1.8±0.4</td>
<td>1.6±0.2</td>
<td>2.0±0.4</td>
</tr>
<tr>
<td>$T_E$ (SEC)</td>
<td>2.5±0.8</td>
<td>2.1±0.5</td>
<td>2.4±0.6</td>
</tr>
<tr>
<td>$T_I/T_{TOT}$ (SEC)</td>
<td>0.43±0.04</td>
<td>0.43±0.03</td>
<td>0.47±0.05</td>
</tr>
<tr>
<td>$P_{ETCO_2}$ (MMHg)</td>
<td>40.6±4.8</td>
<td>37.5±4.6</td>
<td>40.5±3.3</td>
</tr>
<tr>
<td>$V_E$ CV (%)</td>
<td>23.3±14.7</td>
<td>11.6±4.0</td>
<td>10.2±4.1</td>
</tr>
</tbody>
</table>

*Mean ± SD*

VE, MINUTE VENTILATION; VT, TIDAL VOLUME; RR, BREATHING FREQUENCY; TI, INSPIRATORY TIME; TE, EXPIRATORY TIME; PETCO2, END-TIDAL CO2; CV, COEFFICIENT OF VARIATION.
TABLE 4: VENTILATORY PARAMETERS DURING SLEEP

<table>
<thead>
<tr>
<th></th>
<th>CERVICAL</th>
<th>THORACIC</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (L/Min)</td>
<td>5.0±1.3*</td>
<td>6.4±1.6</td>
<td>6.2±1.9</td>
</tr>
<tr>
<td>VT (L)</td>
<td>0.36±0.13</td>
<td>0.41±0.11</td>
<td>0.38±0.12</td>
</tr>
<tr>
<td>RR (BREAT/Min)</td>
<td>14.3±2.1</td>
<td>16.1±3.0</td>
<td>16.7±3.1</td>
</tr>
<tr>
<td>T1 (sec)</td>
<td>1.9±0.4</td>
<td>1.7±0.4</td>
<td>1.7±0.4</td>
</tr>
<tr>
<td>TE (sec)</td>
<td>2.6±0.7</td>
<td>2.2±0.6</td>
<td>2.1±0.6</td>
</tr>
<tr>
<td>T1/T Tot (sec)</td>
<td>0.42±0.08</td>
<td>0.45±0.10</td>
<td>0.45±0.08</td>
</tr>
<tr>
<td>PETCO2 (mmHg)</td>
<td>41.4±5.3</td>
<td>39.2±5.5</td>
<td>38.3±5.0</td>
</tr>
<tr>
<td>VE -CV (%)</td>
<td>37.5±20.4*</td>
<td>13.0±7.5</td>
<td>10.8±16.7</td>
</tr>
</tbody>
</table>

(MEAN ±SD)

VE, MINUTE VENTILATION; VT, TIDAL VOLUME; RR, BREATHING FREQUENCY; T1, INSPIRATORY TIME; TE, EXPIRATORY TIME; PETCO2, END-TIDAL CO2; CV, COEFFICIENT OF VARIATION. (*) P VALUE <0.05 CERVICAL VS. THORACIC. (+) P VALUE <0.01 CERVICAL VS. CONTROL.
**TABLE 5:** MULTIVARIABLE REGRESSION ANALYSIS SHOWING THE CONTRIBUTION OF EACH VARIABLE TO PREDICT AHI.

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Std. Error</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>

ESS, EPWORTH SLEEPINESS SCALE; NC, NECK CIRCUMFERENCE; PG, PLANT GAIN.
Figure 1:

Baseline Ventilation

NIV Followed by Apnea

- Flow (l/sec)
- Volume (ml)
- $P_{SO_2}$ (cm H$_2$O)
- $P_{\text{mask}}$ (cm H$_2$O)
- $P_{\text{mask}}^{\text{CO}_2}$ (%)
- $SaO_2$ (%)
- $FiO_2$ (%)
- $CO_2$ Reserve

Time stamps:
- Baseline Ventilation: 2:36:20 AM, 2:36:25 AM, 2:36:30 AM
Figure 2:
Figure 3:

- **Controller Gain (L/min/mmHg):**
  - Cervical
  - Thoracic
  - Control

- **Plant Gain (mmHg/L/min):**
  - Cervical
  - Thoracic
  - Control

- **CO₂ Reserve (mmHg):**
  - Cervical
  - Thoracic
  - Control
Figure 4:

- CO₂ Reserve (mmHg)
Figure 5:
Figure 6:

Isometabolic hyperbolae

T-SCI

CO₂ reserve

C-SCI

CO₂ reserve

Vᵢ (L/min)

PₑTₐCO₂ (mmHg)