Upper airway mechanics in chronic spinal cord injury during sleep

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Submitted 12 February 2014; accepted in final form 16 April 2014

Sankari A, Bascom AT, Badr MS. Upper airway mechanics in chronic spinal cord injury during sleep. J Appl Physiol 116: 1390–1395, 2014. First published April 17, 2014; doi:10.1152/japplphysiol.00139.2014.—Sleep-disordered breathing has been shown to be more prevalent in patients with spinal cord injury (SCI) than the general population. The pathogenesis of increased sleep-disordered breathing in individuals with chronic SCI is unknown. The purpose of this study is to determine whether SCI level affects upper airway (UA) collapsibility and neuromuscular compensatory responses to obstruction. Twenty-four participants (8 cervical SCI, 8 thoracic SCI, and 8 controls) were studied. The ventilation, timing, UA resistance, and pharyngeal collapsibility, defined by critical closing pressure, were determined during non-rapid eye movement sleep. Inspiratory duty cycle and minute ventilation were observed in response to increasing severity of UA obstruction. Compared with controls, both cervical and thoracic SCI participants demonstrated elevated passive critical closing pressure (0.5 ± 2.2 and 0.9 ± 2.7 vs. −2.5 ± 1.0 cmH2O, respectively; P = 0.01). No difference in UA resistance was observed between groups. Cervical and thoracic SCI individuals exhibited a similar degree of hypopnea and dose-dependent increase in inspiratory duty cycle in response to UA obstruction. Passive UA collapsibility is increased in both cervical and thoracic SCI compared with control. The neuromuscular compensatory responses to UA obstruction during sleep are preserved in chronic SCI and are independent of the level of injury.

SLEEP-DISORDERED BREATHING (SDB) is a very common condition after spinal cord injury (SCI), with estimated prevalence ranging between 27 and 93% (4, 8, 11–13, 16, 22, 23). The prevalence and type of SDB is dependent on the duration and level of injury (26–28). In a recent report, 93% of cervical and 55% of the thoracic chronic SCI had SDB defined by apnea-hypopnea index (AHI) ≥5 events/h, followed with 3% desaturations or arousals (22). Central SBW was predominant in cervical SCI participants, and obstructive SDB was predominant in thoracic SCI participants. However, despite this high prevalence of SDB in SCI, physiological mechanisms that explain the heterogeneity of the disease are not known.

Upper airway (UA) mechanics during sleep have been studied by a variety of measures, including UA resistance (RUA) (7, 14, 31), compliance, and collapsibility (18, 21, 24, 32). The dynamic behavior of the airway, including its propensity to collapse, and the neuromuscular responses can be better characterized by measuring the critical closing pressure (Pcrit) (17). UA collapsibility and the associated neuromuscular responses to loading play an important role in the pathogenesis of SDB in able-bodied individuals (18, 25). Nevertheless, the behavior of the UA collapsibility and the associated responses to UA mechanical loads in individuals with cervical and thoracic SCI remain unclear.

The purpose of the present study was to examine UA collapsibility and ventilatory responses to obstruction in SCI and normal individuals during sleep. Our hypotheses were as follows. 1) The UA Pcrit is higher in individuals with SCI relative to able-bodied control subjects. 2) UA obstruction in SCI triggers compensatory responses in the inspiratory duty cycle (Ti/Tt) that can mitigate hypoventilation. To this end, we measured passive Pcrit (a marker of UA collapsibility), Ti/Tt, and ventilation under different levels of UA flow-limitation during sleep.

METHODS

Subjects

The Human Investigation Committee of Wayne State University and the John D. Dingell Veterans Affairs Medical Center approved the experimental protocol. An informed, written consent was obtained, and participants had a screening polysomnography. We studied adults (>18 yr old) with chronic SCI and able-bodied participants, if they met the inclusion and exclusion criteria. All subjects were instructed not to have alcohol, caffeine products, or sedatives on the day of the study. Zolpidem was administered at standard doses (5–12.5 mg) one time orally 30 min before sleep to mitigate sleep disruption or difficulty sleeping with instrumentation.

Inclusion criteria. Nonventilator-dependent participants with chronic SCI (>6 mo postinjury), spanned the spectrum from cervical (C4–C7) to thoracic levels (T1–T6). Able-bodied participants were recruited with similar demographics to the SCI group for age, body mass index (BMI), and sex.

Exclusion criteria. Participants were excluded from the study for any of the following: 1) <18 yr of age; 2) pregnant or lactating women; 3) currently ventilator dependent or with tracheostomy tube in place; 4) history of cardiac disease, including heart failure, peripheral vascular disease, or stroke; 5) history of head trauma resulting in neurological symptoms or loss of consciousness; 6) advanced lung, liver, or chronic kidney disease; 7) 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 8) other illness that would interfere with completion of the study in the investigators’ judgment.

Measurements

Every subject who agreed to enroll had a brief history and exam. All subjects had a baseline upright spirometry measurements followed by a night study using polysomnography recording in supine position. In addition to standard polysomnography, including electroencephalograph, electrooculogram, and chin electromyograph, nasal airflow was measured by a pneumotachometer (model 3700A, Hans Rudolph, Shawnee, KS) connected to a tight-fitting nasal mask. Tidal volume was obtained by integrating the pneumotachograph flow signal. Supraglottic pressure was measured with a pressure-tipped catheter (Millar Instruments, Houston, TX), positioned in the hypopharynx. Mask pressure was measured in all participants and used as the
Table 1. Participants characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>39.0 ± 13.8</td>
<td>38.5 ± 16.0</td>
<td>34.5 ± 13.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.0 ± 5.0</td>
<td>28.4 ± 5.1</td>
<td>26.9 ± 2.5</td>
</tr>
<tr>
<td>Sex (F/M)</td>
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<td>3/5</td>
<td>3/5</td>
</tr>
<tr>
<td>NC, cm</td>
<td>38.2 ± 3.2</td>
<td>40.6 ± 5.2</td>
<td>36.9 ± 3.6</td>
</tr>
<tr>
<td>Previous tracheostomy, no.</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Medications, no.</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Opiates</td>
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<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Baclofen</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. BMI, body mass index; NC, neck circumference; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PerCO₂, end-tidal CO₂; SaO₂, oxygen saturation; AHI, apnea-hypopnea index; CAI, central apnea index; *P < 0.05, control vs. spinal cord injury (SCI). †P < 0.05, cervical SCI vs. thoracic SCI.

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RESULTS

We studied 16 chronic SCI participants [including 8 cervical (C₄-C₇) and 8 thoracic (T₁-T₆) levels] and 8 noninjured controls with similar demographics. Table 1 summarizes the demographics and severity of SDB (AHI) in these participants. Compared with control participants and thoracic SCI, cervical SCI individuals had lower median ventilation and required the same Pn values to eliminate flow limitation during stable non-REM sleep (Table 2).

Figure 1 illustrates representative examples of maximal inspiratory airflow and Pn relationships for cervical SCI, thoracic SCI, and normal participants. Perit is higher in the SCI participants than the normal subjects. Figure 2 illustrates that both cervical and thoracic SCI participants demonstrated elevated passive Perit compared with control group.

Figure 3 illustrates the group values of calculated RUA at baseline during stable non-REM sleep. There is no significant difference in cervical and thoracic median (25th and 75th percentile ranges) RUA compared with control [6.1(3.4, 12.9) vs. 2.6 (1.7, 5.3) vs. 2.5 (1.7, 4.4) cmH₂O·l⁻¹·s⁻¹, respectively; P = 0.24]. Note that RUA was not included in one control and one thoracic SCI participant due to technical difficulties in pressure-flow measurements.

Figure 4 is a summary of data comparing the Ti/Tt at Pn in the cervical SCI, thoracic SCI, and control participants. Note the lower median (25th and 75th interquartile ranges) Ti/Tt.
during nonflow-limited breathing in cervical SCI compared with thoracic SCI and control participants \[0.36 (0.34, 0.46) \text{ vs. } 0.47 (0.43, 0.50) \text{ and } 0.49 (0.44, 0.58), \text{ respectively; } P < 0.001\]. Both cervical and thoracic SCI individuals, however, exhibited a similar degree of hypoventilation and dose-dependent increase in the TI/TT in response to UA loading (Fig. 5).

**DISCUSSION**

**Summary of Findings**

The major findings of our study are 1) the passive UA collapsibility is increased in both cervical and thoracic SCI compared with control noninjured individuals; and 2) the neuromuscular compensatory responses to UA obstruction during sleep are preserved in chronic SCI and are independent of the level of injury.

**Effect of SCI on UA Mechanics During Sleep**

Sleep is a physiological challenge rather than a rest period for the respiratory system; the removal of the “wakefulness drive to breathe” is associated with hypoventilation and impairment of immediate load compensation. While healthy humans are able to preserve stable sleep and alveolar ventilation, albeit at a higher arterial PCO2, individuals with abnormal respiratory function, such as neuromuscular disease, do not fare as well. Berlowitz et al. (4) found that SDB developed in the subacute phase following cervical SCI; interestingly, SDB severity correlated with increased neck size, which has been shown in able-bodied individuals and can increase UA surrounding pressure and collapsibility (24, 32).

The dissociation between RUA and Pcrit observed in this study corroborates findings demonstrated previously in able-bodied subjects (22). The increased Pcrit without significant change in RUA could be occurring because 1) these parameters are measuring different properties of the UA; 2) the two parameters are measuring the behavior of the UA at different locations; or 3) the methodologies utilized have different sensitivities to measure UA obstruction under reduced lung volumes vs. anatomical narrowing (21).

**Effect of UA Obstruction on Ventilatory Responses During Sleep**

The ventilatory control system compensates for increased mechanical impedance by increased neuromuscular output or by prolongation of inspiratory time, to preserve alveolar ventilation. In contrast, obstructive sleep apnea is associated with a reversible attenuation in immediate load compensation during wakefulness (1, 30). Conversely, immediate neuromuscular load compensation is abolished during sleep, perhaps to preserve sleep state stability (6).

Immediate load compensation could be accomplished by a change in respiratory cycle timing rather than an increase in respiratory drive. Evidence in the literature indicates that a prolongation of Ti or Ti/Ti may mitigate the effects of loading on Ve (25). The magnitude of the ensuing hypoventilation...
depends on the size of the UA lumen, UA structure, and the magnitude of the collapsing transmural pressure (19). We noted that the added UA load was associated with an immediate and dose-dependent prolongation of Ti/Tt. The degree of dose-response compensation was similar to a previous study in normal men and women during sleep independent of sex or BMI (26). Although patients in the cervical SCI group had shorter Ti/Tt at baseline, the prolongation of Ti/Tt was similar among the three groups, suggesting the vagal afferent mechanoreceptor inputs are preserved in patients with tetraplegia, who lack input from sympathetic afferents and afferent receptors from the respiratory muscles and chest wall joints. In summary, our findings suggest that SCI participants have a preserved ability to compensate for inspiratory resistive loading during sleep similar to able-bodied participants.

Mechanism of Increased UA Collapsibility in SCI

We noted that the SCI groups (cervical and thoracic) had higher Pcrit than the control group. This could be due to sleep onset-related decrease in lung volumes or increased UA surrounding pressure in the supine position. Vv and Ti/Tt were lower in cervical than in thoracic SCI and control groups during sleep, despite having similar Pcrit. Therefore, lower lung volume may explain the higher Pcrit in the cervical but not thoracic SCI group.

High thoracic and cervical SCI is associated with significant dysfunction of the sympathetic nervous system (10). The peripheral blood vessels receive only sympathetic innervation, except in the pelvic organs. Specifically, blood vessels in the upper portion of the body receive sympathetic innervation from the upper thoracic spinal sympathetic preganglionic neurons. Following cervical and high thoracic SCI, parasympathetic (vagal) control remains intact, while the spinal sympathetic circuits lose their tonic supraspinal autonomic control. There is evidence that the loss of sympathetic modulation of adrenergic outflow to the peripheral blood vessels results in vasodilatation in individuals with SCI. Conversely, several changes that occur after SCI can mitigate the severity of vasodilatation, including the recovery of peripheral sympathetic reflexes, the development of spasticity and increased muscle tone, and changes in the renin-angiotensin system (29). While these changes have the potential to reduce the severity of vasodilatation, the reality is that it remains a significant problem for the majority of the SCI population. Damage to the pathways from the lower brain stem to sympathetic preganglionic neurons has a central role in abnormal cardiovascular control observed in individuals with cervical or high thoracic SCI. During sleep, the remaining sympathetic activity is at its lowest level of function, which can lead to vasodilatation of the blood vessels in the upper body (such as the neck region surrounding the UA) and contribute to the increased UA surrounding pressure and collapsibility in supine position.

Finally, potential influences that should be considered include decreased ventilatory motor output in a subset of SCI individuals, particularly those with cervical SCI. Ventilatory motor output is an important determinant of UA patency during sleep. Periodic breathing or central apnea are associated with UA narrowing and even closure (2, 7), which can explain, in part, the increased UA collapsibility in participants with SCI.

Methodological Considerations

Our laboratory has measured Pcrit in humans during sleep previously (21). Nevertheless, several considerations may influence the interpretation of the findings. First, changes in sleep state might have caused a misinterpretation of the data. However, we performed the Pcrit protocol only during periods of stage 2 sleep and analyzed the breath-by-breath data only when sleep was in stable stage 2 or 3 non-REM sleep, with no evidence of arousal. Thus the data reported here were from periods where there was no change in sleep state.

Second, our participants were studied during sleep after the administration of Zolpidem to prevent awakening due to heavy instrumentation. Although the majority of participants from all three groups received Zolpidem at standard dose (10 mg
immediate-release orally) 30 min before sleep study, a few subjects received different dosage or did not take the medication due to the following reasons: 1 subject from the control group took 5 mg of Zolpidem immediate release (per FDA 2013 recommendations); 2 cervical SCI subjects did not take 10 mg dose (1 refused and 1 female subject received 6.25 mg dose of extended-release Zolpidem due to difficulty maintaining sleep more than 2 h); 2 thoracic subjects did not take Zolpidem (1 refused and 1 was on Trazadone); 1 female subject received 5.5 mg dose (per FDA 2013 recommendations); 2 young male thoracic subjects received 12.5 mg dose of extended-release Zolpidem (due to difficulty maintaining sleep more than 2 h). Zolpidem is less likely to affect our findings, given that all three groups were treated similarly and previous studies found minimal effect on UA collapsibility, ventilation, or sleep parameters with Zolpidem (3, 15, 20).

Third, we assessed passive Perit after eliminating flow limitation using a standard protocol that does not allow us to compare the UA neuromuscular contribution from active to passive state. Future studies are needed to assess the role of UA muscles and their function in the pathogenesis of sleep apnea in SCI.

In summary, we have shown that UA collapsibility under passive conditions is increased in cervical and high thoracic SCI and can contribute to the pathogenesis of SDB in chronic SCI. The compensatory responses to UA obstruction during sleep are preserved in chronic SCI, independent of the level of injury. Reduced baseline lung volume, increased cervical vascular volume, combined with reduced ventilatory motor output, may play important role in the mechanism of UA obstruction in cervical SCI.

ACKNOWLEDGMENTS

The authors thank Nicole Nickert, Sukanya Pranathageswaran, and Oluwafunmide Adekanmbi for the technical assistance. The authors thank Roespironics for providing the Perit research machine.

GRANTS

This work was supported by the Department of Veterans Affairs. A. Sankari is a recipient of a Career Development Award from the VA Office of Research and Development. The study was funded by the US Department of Veterans Affairs (award no. 10BX07080 from the Biomedical Laboratory Research & Development Service of the VA Office of Research and Development).

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.T.B. analyzed data; A.S. and M.S.B. interpreted results of experiments; A.S. prepared figures; A.S. and M.S.B. approved final version of manuscript; A.T.B. performed experiments; A.T.B. performed experiments.

REFERENCES


J Appl Physiol • doi:10.1152/japplphysiol.00139.2014 • www.jappl.org


