Title

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Journal

Chest Journal, 155(2)

Authors

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Publication Date

2019-02-01

DOI

10.1016/j.chest.2018.10.002

Peer reviewed

CHEST

Sleep-Disordered Breathing and Spinal Cord Injury

A State-of-the-Art Review

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Individuals living with spinal cord injury or disease (SCI/D) are at increased risk for sleep-disordered breathing (SDB), with a prevalence that is three- to fourfold higher than the general population. The main features of SDB, including intermittent hypoxemia and sleep fragmentation, have been linked to adverse cardiovascular outcomes including nocturnal hypertension in patients with SCI/D. The relationship between SDB and SCI/D may be multifactorial in nature given that level and completeness of injury can affect central control of respiration and upper airway collapsibility differently, promoting central and/or obstructive types of SDB. Despite the strong association between SDB and SCI/D, access to diagnosis and management remains limited. This review explores the role of SCI/D in the pathogenesis of SDB, poor sleep quality, the barriers in diagnosing and managing SDB in SCI/D, and the alternative approaches and future directions in the treatment of SDB, such as novel pharmacologic and nonpharmacologic treatments.

CHEST 2019; 155(2):438-445

KEY WORDS: central sleep apnea; continuous positive airway pressure; multiple sclerosis; OSA; sleep apnea; sleep-disordered breathing; spinal cord injury; tetraplegia

Sleep disturbances, including sleep-disordered breathing (SDB), are common albeit underrecognized in individuals with spinal cord injury or disease (SCI/D).[1,2] This review explores the relationship between SCI/D and SDB, discusses the pathogenesis of SDB after acute and chronic SCI/D, outlines a diagnostic and management approach, and identifies barriers to optimal management of this condition.

Epidemiology of SDB in Patients With SCI/D

Improved acute care after traumatic injury has resulted in increased survival for patients with SCI/D and increased likelihood of experiencing chronic diseases common in

ABBREVIATIONS: CSA = central sleep apnea; HSAT = home sleep apnea testing; PAP = positive airway pressure; Pcrit = critical closing pressure; SCI = spinal cord injury; SCI/D = spinal cord injury or disease; SDB = sleep-disordered breathing

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FUNDING/SUPPORT: Dr Sankari is supported by Career Development Award No. 1IK2CX000547 from VA Office of Research and Development from the (U.S.) Department of Veterans Affairs and the National Heart, Lung, and Blood Institute Award No. R21HL140447. Dr Badr is supported by the VA Office of Research and Development, Department of Veterans Affairs No. 1I01RX002116, the National Heart, Lung, and Blood Institute Award No. R01HL130552 and the Department of Defense No. SC150201.

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DOI: https://doi.org/10.1016/j.chest.2018.10.002

middle-aged and older adults. Several studies, mostly single-site case series, have found a high prevalence of SDB in patients with subacute and chronic spinal cord injury (SCI) (range, 27%-82%).[3-6] The variability in estimated prevalence is related to multiple factors, including different diagnostic methods, (ie, polysomnography, home sleep apnea testing [HSAT], nocturnal oximetry), different definitions of respiratory events, and different thresholds for defining SDB (Table 1).[7-16] Therefore, it is difficult to make definitive statements about actual prevalence.

Several factors may influence the prevalence and type of SDB in patients with SCI/D, such as level of injury, type of injury, and associated comorbidities. First, the level of spinal injury affects the occurrence and manifestations of SDB, and patients with tetraplegia are more likely to have SDB than those patients with paraplegia.[3] In a study by Berlowitz et al,[4] the prevalence of SDB in a cohort of cervical SCI was 62% in the 4 weeks immediately postinjury and remained 60% after 1 year of follow-up. Our data also reveal a higher prevalence of SDB in patients with cervical relative to thoracic SCI (93% vs 55%, respectively).[3] Patients with cervical SCI suffer from the full continuum of derangements that impair the ability of the ventilatory system to compensate for physiologic challenges, including neuromuscular weakness, decreased lung volumes, abnormal chest wall mechanics, frequent use of CNS suppressants, and an unopposed parasympathetic system promoting airway narrowing. Second, although most studies address traumatic SCI, SDB rates are also higher in spinal cord disorders such as spinal muscular atrophy, myelomeningocele, multiple sclerosis, rheumatoid arthritis, tumors, or infections.[17-19]

Type of SDB: Obstructive vs Central SDB

The level of SCI/D influences the type of SDB. Specifically, tetraplegia may represent a risk factor for central sleep apnea (CSA) in particular. In a recent study, 60% of patients with cervical SCI demonstrated central SDB, manifesting as CSA, periodic breathing pattern, or high propensity to develop CSA despite normal breathing during wakefulness.[20] Increased risk for CSA in patients with cervical SCI was first reported by Severinghaus and Mitchell,[21] who coined the term Ondine's curse to describe sleep-related ventilatory failure after surgery to the upper cervical cord. A recent systematic review confirmed increased prevalence of CSA in patients with tetraplegia.[22] Medication use may also contribute to increased central apnea risk. However, the use of opiate analgesics did not predict CSA in patients with SCI.[3] Conversely, another study found that baclofen use correlated with increased CSA prevalence.[6]

Obstructive SDB is the most predominant type reported at all levels of SCI (Table 1). However, based on the criteria used to score respiratory events (ie, hypopnea), many events (estimated 20%) were reported to be central in nature.[6] There are limited data on the prevalence of mixed apnea in this population. For example, McEvoy et al[9] found that $>$ 80% of apneas were obstructive or mixed. Conversely, Bauman et al[6] found that a higher obstructive apnea-hypopnea index was associated with CSA, suggesting that some CSA events were responses to preceding obstructive events.

Although adverse consequences of SDB in the general population are widely accepted, SDB in patients with SCI/D has received little attention, despite its high frequency and adverse consequences,[1,6,17] including higher mortality.[6,23-26,28-31] Cardiovascular conditions have surpassed respiratory causes of mortality in patients with cervical SCI/D,[26,31] and SDB may contribute to increased cardiovascular mortality. In a retrospective study of BP in patients with SCI/D, those with cervical injuries were found to have more reversed dipping (ie, higher BP at night rather than during the day) and nocturnal hypertension than those with thoracic injuries.[23] Accordingly, SDB may represent a modifiable cardiovascular disease risk factor for patients with SCI/D. However, long-term outcome data on the effect of untreated SDB in individuals with SCI/D are lacking.

Mechanisms of SDB in Patients With Chronic SCI

SDB in Patients With SCI: Common Mechanisms

Sleep is a physiologic challenge rather than relief for the respiratory system. Sleep-related changes lead to pharyngeal narrowing, increased upper airway collapsibility, unmasking of the apneic threshold, and impaired load compensation as depicted in Figure 1.

Respiration during non-rapid eye movement sleep is critically dependent on P_{CO_2}; therefore, central apnea occurs if P_{CO_2} decreases below the hypocapnic apneic threshold. Central apnea rarely occurs as a single event; instead, it occurs in cycles of apnea or hypopnea, alternating with hyperpnea, reflecting the negative feedback closed-loop cycle that characterizes ventilatory

TABLE 1] Literature Review of SDB Prevalence in Patients With Spinal Cord Injury

Study/Year	No. of Patients	Level	SDB Prevalence	Method of Testing	Criteria of SDB Diagnosis
Short et al[7]/1992	22 (20 men)	T10-above	25% (10% central)	In laboratory PSG	> 5 events/h with Sao_2 dip rate > 4%
Flavell et al[8]/1992	10 (10 men)	Cervical	30%	Continuous pulse oximetry recording	> 10% of Sao_2 levels < 90%
McEvoy et al[9]/1995	40 (37 men)	Cervical	27.5% (> 80% of apneas were obstructive or mixed)	HSAT with nasal airflow plus EEG, EOG, submental EMG	RDI ≥ 15 events/h with nadir Sao_2 ranging from 49% to 95%
Klefbeck et al[10]/1998	33 (28 men)	Cervical	15%	Combined oximetry and respiratory movement monitoring	ODI > 4%/h and > 45% of the total sleeping time had PB
Burns et al[11]/2000	20 (20 men)	L1-above	40%	HSAT with nasal airflow	RDI > 5 events/h
Stockhammer et al[12]/2002	50 (40 men)	Cervical	62%	Portable monitoring in-hospital with the nasal thermistor, SPo_2, and chest wall motion	RDI ≥ 15 and an apnea index ≥ 5 events/h
Berlowitz et al[4]/2005	30 (25 men)	Cervical	62%	HSAT plus EEG	AHI[a] >10 events/h
Leduc et al[13]/2007	41 (41 men)	Cervical	53%	HSAT plus EEG	AHI[b] > 5 events/h
Sankari et al[3]/2014	26 (16 men)	T6-above	77%	In laboratory PSG plus pneumotach and epiglottic pressure catheter	AHI[c] > 5 events/h
Bauman et al[6]/2015	81 (75 men)	T6-above	81%	HSAT plus $Tcco_2$	AHI[c] > 5 events/h

AHI = apnea-hypopnea index; EMG = electromyogram; EOG = electrooculgram; HSAT = home sleep apnea testing; ODI = oxygen desaturation index; PB = periodic breathing; PSG = polysomnography; RDI = respiratory disturbance index; Sao_2 = oxygen saturation; SPo_2 = pulse oxymetery; $Tcco_2$ = transcutaneous carbon dioxide.
[a]Respiratory events are scored based on the American Academy of Sleep Medicine Task Force 1999 criteria.[14]
[b]Respiratory events are scored based on the American Sleep Disorders Association criteria.[15]
[c]Respiratory events are scored based on the 2012 American Academy of Sleep Medicine recommended criteria.[16]

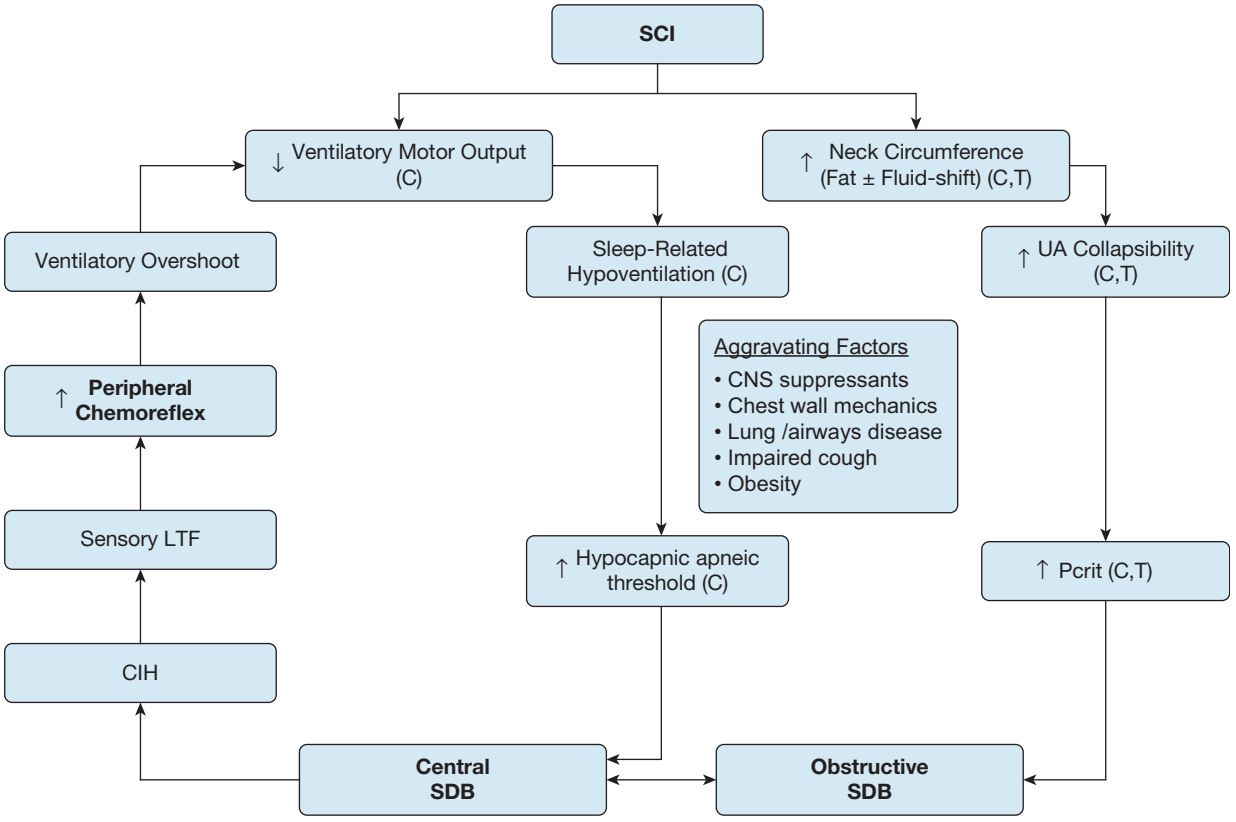

Figure 1 – *A diagram to illustrate the mechanism(s) for sleep-disordered breathing because of spinal cord injury. C = cervical; CIH = chronic intermittent hypoxia; LTF = long-term facilitation; Pcrit = critical collapsing pressure; SCI = spinal cord injury; T = thoracic; UA = upper airway.*

control. This is often described using the engineering concept of loop gain, which combines the response of the ventilatory system to changing P_{CO_2} (the controller or chemoreflex sensitivity) and the effectiveness of the lung/respiratory system in lowering P_{CO_2} in response to hyperventilation (the plant). Changes in either parameter would change the requisite magnitude of hypocapnia to reach central apnea (carbon dioxide reserve). Chemoreflex sensitivity is often invoked as a determinant of central apnea. However, plant factors, expressed by the relationship between ventilation and P_{CO_2}, also influence the propensity to develop central apnea. Specifically, high P_{CO_2}, for a given metabolic rate, promotes respiratory instability by increasing the effectiveness of the respiratory system in lowering P_{CO_2} in response to hyperventilation. Therefore, exaggerated sleep-related hypoventilation promotes hypocapnic central apnea by increasing plant gain via increased effectiveness of carbon dioxide elimination.

Central apnea may also influence the development of OSA because pharyngeal obstruction or narrowing develop when ventilatory drive reaches a nadir during central apnea or hypopnea. Pharyngeal collapse, combined with mucosal and gravitational factors, may impede pharyngeal opening and necessitate a substantial increase in a drive that perpetuates breathing instability.

SCI/D-Specific Pathophysiologic Factors

Established SDB risk factors, including obesity and male sex, are more common among patients with SCI/D than in the general population.[24] In addition, patients with cervical SCI/D experience multiple derangements that impair the ability of the ventilatory system to compensate for physiologic challenges of sleep, including neuromuscular weakness, small lung volume, abnormal chest wall mechanics, frequent use of central nervous system suppressants, and an unopposed parasympathetic system promoting airway narrowing.[6,25] Additional physiologic derangements in patients with SCI/D may contribute to increased risk of central or obstructive apnea in this population.

Hypoventilation: Patients with cervical SCI/D experience exaggerated sleep-related hypoventilation, manifesting by decreased minute ventilation and

increased end tidal P_{CO_2}, compared with thoracic SCI. Hypoventilation is noted starting at sleep onset and is independent of respiratory mechanics.[26] Furthermore, medullary respiratory motor output may be affected by injuries to the cervical spinal cord. Golder et al[27] demonstrated reduced inspiratory motor drive to the tongue in anesthetized, paralyzed, and ventilated rats, 2 months after a C2 hemisection. Likewise, Zimmer and Goshgarian[25] identified significant alterations in brainstem neurochemistry after a cervical SCI in rats, with a reduction in proteins involved in excitatory neurotransmission and an increase in proteins involved in inhibitory neurotransmission. These medullary changes may account for the exquisite sensitivity to hypoventilation at sleep onset in patients with cervical SCI. Sleep-related hypoventilation in patients with chronic cervical SCI/D leads to increased plant gain and increased propensity to central apnea, relative to patients with thoracic SCI/D or able-bodied control subjects.

Upper Airway Collapsibility: Increased critical closing pressure (Pcrit) is a marker of upper airway collapsibility. Patients with SCI have higher Pcrit independent of the level of injury, neck circumference, BMI, or upper airway resistance.[28] Contributing factors include higher nasal resistance in individuals with cervical SCI[29] and supine rostral fluid shift in patients with SCI at all levels[30] because of paralysis-induced fluid stasis in the lower extremities.[4] The role of fluid shift per se has not yet been tested in individuals with SCI/D.

Peripheral Ventilatory Chemoresponsiveness: Elevated peripheral chemoreflex sensitivity promotes respiratory instability via ventilatory overshoot after a transient ventilatory perturbation. Furthermore, peripheral chemoreceptors may influence the respiratory sensitivity of central chemoreceptors to carbon dioxide.[31,32] The underlying mechanism of enhanced peripheral chemoresponsiveness in patients with SCI is unclear but could be because of exposure to chronic intermittent hypoxia.[33] Specifically, individuals living with SCI may experience chronic intermittent hypoxia because of decreased lung volume, impaired chest wall mechanics, retained secretions, and impaired cough. Accordingly, alleviating SDB may decrease peripheral chemoreflex sensitivity and overall chemoresponsiveness and decrease the propensity to central apnea.

Arousal Threshold: Arousal threshold is one of the physiologic traits that contributes to the pathogenesis of SDB.[24] A recent study found that arousal threshold is significantly reduced in individuals with SCI, indicating increased arousal propensity,[34] which may contribute also to the mechanism of sleep disturbances in SCI.

In summary, the combination of sleep-related hypoventilation and increased peripheral chemoresponsiveness may explain why patients with cervical SCI demonstrate increased propensity for central apnea. However, elevated Pcrit provides a physiologic explanation for increased risk of OSA in patients with cervical and thoracic SCI. Understanding the unique pathophysiologic mechanisms may inform the development of targeted therapies in this population.

Clinical Presentation and Management

Individuals living with disabilities, especially those with limited mobility, experience significant disparities in health-care services. Individuals living with SCI/D may suffer inequity in treatment of SDB as well.

Clinical Evaluation of Patients With SCI/D With Suspected SDB

Poor sleep quality, hypersomnolence, and daytime fatigue are common complaints in individuals with SCI/D.[35] SDB should be considered a potential underlying contributory factor for these symptoms. Recent data in individuals with acute cervical SCI reported that increased SDB severity was associated with worse attention, information processing, and short-term memory.[36]

Despite this high rate of abnormal sleep and daytime symptoms, SDB remains underdiagnosed and undertreated in these patients.[37] Furthermore, commonly used questionnaires (eg, Berlin Questionnaire Sleep Apnea, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale) are limited in their ability to identify patients with SCI/D likely to suffer from SDB.[38] The relevance of select items on these measures is questionable for patients with limited mobility because of SCI/D. Extremely high rates of overall poor sleep quality may limit the clinical utility of screening questionnaires for SDB.

Diagnostic Testing for SDB

Patients living with SCI/D face numerous hurdles to accessing high-quality care for sleep disorders, including inadequate recognition, erroneous attribution of daytime symptoms, limited access to sleep diagnostic services, and difficulties using ventilatory support or positive airway pressure (PAP) therapy.[38] In addition, most clinical sleep laboratories are not equipped to address the needs of patients with SCI/D. Figure 2

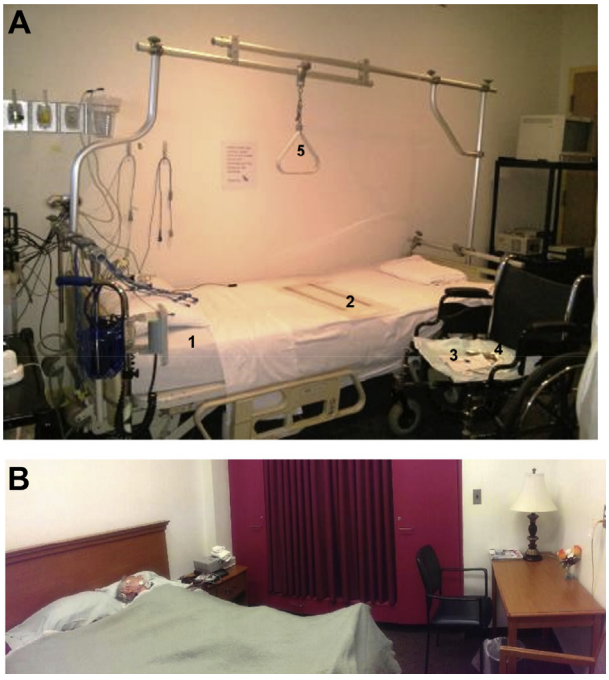

Figure 2 – *A, B, Comparison between a specially equipped room for studying patients with spinal cord injury or disease (A) and a standard room in a clinical sleep laboratory (B). Number 1 shows a hospital bed with specially designed mattress, 2 shows a transfer board, 3 shows a urinary catheter, 4 shows a wheelchair, and 5 shows a lift.*

provides a comparison between a standard sleep laboratory room in a clinical sleep laboratory and a specially equipped room that we use for conducting polysomnography in patients with SCI/D. Some of these requirements may be required for patients with limited mobility for a number of comorbid conditions. Specifically, patients with SCI/D who need polysomnography should be referred to sleep centers that have the necessary expertise and resources to care for these patients, such as wheelchair access, availability of a lift, a special wound care bed, and adequate training of staff. Hospital-based sleep centers could serve as a referral center for patients with limited mobility.

HSAT is an attractive option, especially if combined with transcutaneous carbon dioxide monitoring to identify sleep-related hypoventilation[6]; however, HSAT devices await sufficient empirical evidence of validity and reliability of event detection without the benefit of EEG in patients with SCI/D. Alterations in the pathophysiology of SDB itself in these patients, including high rates of CSA, may limit the utility of HSAT for diagnostic purposes.

Management of SDB in Patients With SCI/D

It is estimated that two-thirds of patients with SCI/D do not require ventilatory support after recovery from the acute injury and < 10% may require long-term ventilation.[39,40] However, there is increased risk of pulmonary complications, including delayed apnea in patients with high cervical SCI and more complete injuries.[41,42] Therefore, it may be prudent to consider early tracheostomy and ventilation in acute high cervical SCI (complete SCI above the level of C5) and noninvasive ventilation and assisted coughing techniques in lower cervical and thoracic level injuries.[43] For patients with SCI below C4 who do not require continuous mechanical ventilation but have evidence of hypoventilation, bilevel PAP with volume-assured pressure support has been recently used and reported an improvement of nocturnal hypercapnia in 77% of patients.[44] However, there are no studies comparing PAP and bilevel PAP in patients with SCI who have SDB and nocturnal hypoventilation.

PAP therapy is the treatment of choice for patients with SCI/D with SDB. In fact, the use of PAP for SDB treatment in SCI is now recognized and recommended as a key component in standardized SCI reporting.[45] There are limited data on the acceptance of PAP treatment for patients with SCI and SDB. One study which used phone interviews found that PAP therapy was initiated in 60% of individuals with SDB.[38] Another study found that most individuals (> 90%) agreed to initiate PAP therapy.[44] Nevertheless, adherence to PAP therapy in patients with SCI/D remains a challenge despite education, follow-up, and support.[46,47] Some factors that lead to discontinuation of therapy are related to weakness and mobility impairment to the upper extremities, mask claustrophobia, increased awakenings, nasal congestion, lack of education, and inconvenience. Many of these can be mitigated through the better nasal interface and through PAP education.

Future Directions

Increasing interest in understating the mechanism(s) of SCI/D-related sleep and respiratory disorders has identified several gaps that require further investigation. These opportunities include the pathophysiology, diagnosis, and management of SDB in this population.

- Etiology of SDB: The mechanisms underlying sleep-related hypoventilation and increased CSA risk in patients with tetraplegia require further investigation, including the mechanisms of increased chemoreflex sensitivity. Understanding these mechanisms may inform treatment of central SDB of multiple etiologies.

- What is the optimal PAP modality or titration approach for patients with SCI? How does limited upper extremity mobility in patients with tetraplegia, who may not be able to remove the mask in the case of discomfort or device malfunction, influence the selection of a PAP modality or interface?
- The limitations of PAP acceptance and adherence mandate investigation of alternative approaches to enhancing PAP usability, acceptance, and adherence. In addition, it is important to assess the effect of PAP therapy on sleep quality and quality of life and to determine the minimum severity requiring PAP therapy in this population.
- The targeted and personalized therapies aiming to stabilize ventilatory motor output is sorely needed in patients with central apnea who may not respond to or tolerate PAP therapy. Nevertheless, none of these interventions have been tested systematically in patients with SCI/D and SDB. Potential approaches include decreasing peripheral chemoreflex sensitivity with supplemental oxygen therapy, decreasing loop gain with acetazolamide, or elevating the arousal threshold with trazodone or hypnotics.
- Is there a role for interventions focusing on upper airway dilating muscle activity? Targeted therapies for the laryngeal and oropharyngeal muscles, such as hypoglossal nerve stimulation or oropharyngeal muscle training, may be beneficial particularly in patients with obstructive SDB. Opportunities for further investigation include interventions that promote ventilatory recovery or long-term facilitation,[48-50] such as the use of daily administration of intermittent hypoxia or pharmacologic agents, which capitalizes on the intrinsic plasticity of the respiratory system to enhance ventilatory motor output and restore respiratory function via serotonin and brain derivative neutrophilic factor-dependent mechanisms.[51,52]

Conclusions

SDB is common among individuals with SCI/D, particularly among those with cervical injuries. The mechanism(s) for the increased prevalence of SDB after surviving SCI are not clear yet, but evidence points toward complex pathways that include hypoventilation, upper airway collapsibility, and neuromuscular weakness. Other types of spinal cord disorders such as multiple sclerosis and other degenerative disorders that cause paralysis are important to study and assess in a large epidemiologic fashion. The current diagnostic approach of SDB in patients with SCI/D may be challenging for patients with limited mobility and high care needs. Therefore, enhancing the current diagnostic approach may be required to ensure optimal access and care quality for SDB in patients with SCI/D. Finally, PAP acceptance and adherence remain suboptimal and require additional equipment modification, provider training, or patient education. This also supports the need to develop and evaluate alternative therapies.

Acknowledgments

Financial/nonfinancial disclosures: A. S. is supported by Career Development Award # 1IK2CX000547 from VA Office of Research and Development from the (U.S.) Department of Veterans Affairs and the National Heart, Lung, and Blood Institute Award # R21HL140447. M. S. B. is supported by the VA Office of Research and Development, Department of Veterans Affairs #1I01RX002116, the National Heart, Lung, and Blood Institute Award # R01HL130552 and the Department of defense # SC150201. None declared (S. V., A. B., J. L. M.).

Other contributions: The opinions expressed in this article reflect those of the authors and do not necessarily represent official views of the US government (VA, NIH or the Department of Deference).

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