Published in final edited form as:

Respir Physiol Neurobiol. 2013 September 15; 188(3): 344–354. doi:10.1016/j.resp.2013.06.009.

The impact of spinal cord injury on breathing during sleep

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Abstract

The prevalence of sleep disordered breathing (SDB) following spinal cord injury (SCI) is considerably greater than in the general population. While the literature on this topic is still relatively small, and in some cases contradictory, a few general conclusions can be drawn. First, while both central and obstructive sleep apnea (OSA) has been reported after SCI, OSA appears to be more common. Second, SDB after SCI likely reflects a complex interplay between multiple factors including body mass, lung volume, autonomic function, sleep position, and respiratory neuroplasticity. It is not yet possible to pinpoint a “primary factor” which will predispose an individual with SCI to SDB, and the underlying mechanisms may change during progression from acute to chronic injury. Given the prevalence and potential health implications of SDB in the SCI population, we suggest that additional studies aimed at defining the underlying mechanisms are warranted.

Keywords

spinal cord injury; sleep disordered breathing; sleep apnea

1. Introduction

The focus of this review article is on sleep disordered breathing (SDB) following spinal cord injury (SCI). This topic has been reviewed recently (Biering-Sorensen et al., 2009), and our primary intent is to update the evidence indicating that the prevalence of SDB increases after SCI, and to provide a discussion of the underlying physiologic mechanisms. In particular we have focused on possible mechanisms leading to increases in obstructive sleep apnea (OSA) following SCI. We begin with an overview of how SCI impacts the respiratory neuromuscular system and then discuss the prevalence and mechanisms of SDB after SCI.

2. Impact of SCI on the respiratory system

The impact of SCI on pulmonary function has been the subject of several recent articles (Tollefsen and Fondenenes, 2012; Winslow and Rozovsky, 2003; Zimmer et al., 2008) and is briefly discussed here. Approximately half of all SCIs occur in the cervical region causing hypoventilation (Winslow and Rozovsky, 2003) and impaired ability to sigh and cough (Bolser et al., 2009). Pulmonary function studies reveal that the extent of SCI-induced deficits corresponds to the segmental level of the injury (i.e., more rostral lesions tend to produce greater functional impairments) (Tollefsen and Fondenenes, 2012). It should be emphasized, however, that injuries to the thoracic cord are also associated with respiratory-related impairments, with the most prominent feature being impaired ability to cough (DiMarco et al., 2009).

Impaired respiratory muscle control after SCI results from interruption of bulbospinal synaptic projections to spinal motoneurons and interneurons (i.e., white matter lesions; (Lane et al., 2009; Sandhu et al., 2009)) as well as direct gray matter damage (Lane et al., 2012; Reier et al., 2002). Cervical gray matter damage can result in loss of phrenic motoneurons (Lane et al., 2012; Nicaise et al., 2012), as well as propriospinal circuitry which may modulate respiratory motor output (Lane et al., 2009). Respiratory control deficits can be further exacerbated by atelectasis and chest wall muscle spasticity which reduce the compliance of the lung and chest wall (Winslow and Rozovsky, 2003). In addition, impairments in accessory inspiratory muscles contribute to “paradoxical” diaphragm contractions that are associated with inward movement of the rib cage during inspiration. Despite these complications, many individuals with incomplete cervical SCI can breathe independently but often with diminished tidal volume and elevated breathing frequency (Loveridge et al., 1992). However, even when adequate alveolar ventilation can be maintained without external support, SCI individuals remain at high risk for respiratory-related complications.

2.1. Plasticity in respiratory neurons and networks after SCI

It is well established that SCI induces neuroplastic changes in the neurons and networks that regulate breathing (reviewed by Goshgarian, 2009). Following SCI, time-dependent changes occur throughout the respiratory neuraxis including spinal respiratory motor neurons (Mantilla et al., 2012), propriospinal networks (Lane et al., 2009), and brainstem respiratory neurons (Golder et al., 2001; Zimmer and Goshgarian, 2007). Respiratory neuroplasticity has been characterized at the molecular level (e.g., increased expression of serotonin and glutamate receptors in the spinal cord (Mantilla et al., 2012)), the anatomical level (e.g., changes in the distribution of respiratory interneurons in the spinal cord (Lane et al., 2009) and the functional level (e.g., progressive increases in phrenic motor function (Goshgarian, 2009))). In general, it has been assumed that spontaneous respiratory neuroplasticity occurring over days - months post injury is beneficial to respiratory motor recovery, but the possibility that “maladaptive neuroplasticity” could impair the control of breathing should be considered. In particular, to our knowledge there have been no studies of the neural regulation of respiratory motoneurons during sleep following SCI in either animal models or

humans. Thus, the functional impact of SCI-induced respiratory neural plasticity on the control of breathing during sleep remains an open question.

2.2. Plasticity in respiratory muscles after SCI

The primary muscle of inspiration, the diaphragm, appears to be profoundly sensitive to periods of inactivity. For example, mechanical ventilation results in rapid diaphragm atrophy (i.e., within hours) and significant contractile dysfunction (Powers et al., 2009). Importantly, this finding has been demonstrated in both humans and animals, and has been confirmed by independent laboratories (reviewed by Jaber et al., 2011). In our opinion, the most likely reasons for diaphragm atrophy during inactivity are decreased protein synthesis along with a rapid increase in proteolysis (Powers et al., 2009). Thus, high cervical SCI – which is associated with diminished or absent respiratory muscle activity – is also likely to result in atrophy of the diaphragm with associated losses of contractile function. The overall extent of respiratory muscle atrophy is likely to be determined by the segmental level and functional completeness of the injury, both of which will impact the relative degree of preserved muscle activity. Studies in animal models have confirmed diaphragm atrophy following cervical SCI (Mantilla et al., 2013; Nicaise et al., 2012). Collectively the literature suggests that the function of respiratory “pump muscles” will be compromised following SCI – not only due to injury-induced paralysis, but also due to the subsequent muscle atrophy. Changes in pump muscle morphology and function could impact breathing during sleep both via alterations in pulmonary pressures and muscle afferent feedback. However, to our knowledge, the impact of SCI on upper airway muscle morphology and function, including the muscles of the tongue, has not been systematically evaluated. This is of considerable interest since the pharyngeal muscles are integral to maintaining airway patency.

3. Sleep and SCI

3.1. Sleep quality after SCI

As reviewed by Biering-Sorensen et al. (2009), SCI individuals are highly likely to self-report sleeping difficulty. For example, increased difficulty falling asleep and increased reliance on sleep medications are common after SCI (Biering-Sorensen and Biering-Sorensen, 2001). In addition, when persons with SCI are interviewed regarding their sleep quality, they are much more likely to report an overall reduced quality (Norrbrink Budh et al., 2005). Snoring is common after SCI, as is daytime sleepiness (Jensen et al., 2009) and both of these features are hallmarks of SDB. However, sleep difficulties following SCI may be unrelated to SDB *per se*, and other factors such as pain, spasms, and postural influences must be considered (Norrbrink Budh et al., 2005; Scheer et al., 2006).

3.2. SDB after SCI

We were able to identify 29 published studies examining the impact of SCI on breathing during sleep (see Table 1). In addition, we found 13 related clinical case reports (Biering-Sorensen et al., 1995; Danielpour et al., 2007; Goh and Li, 2004; Graham et al., 2004; Heike et al., 2007; Howard et al., 1998; Kam et al., 2009; Kawaguchi et al., 2011; Miyano et al., 2009; Nagaoka et al., 2006; Russian et al., 2011; Star and Osterman, 1988; Vella et al., 1984). Collectively, this literature demonstrates unequivocally that the incidence of SDB

increases after SCI, with estimates ranging from 2–5 fold over the general population (Burns et al., 2000; Klefbeck et al., 1998b; Leduc et al., 2007; Stockhammer et al., 2002). There is evidence that sleep apnea is more likely to occur with higher neurologic level of injury (i.e., more rostral lesions) (Berlowitz et al., 2012; Burns et al., 2001), but this finding has not been consistent in all reports (Table 1). In addition, most studies have failed to find a relationship between the prevalence of sleep apnea and the extent of motor impairment as determined by the American Spinal Cord Injury Association (ASIA) impairment scale (Burns et al., 2005; Tran et al., 2010), although this has not been a universal finding (Berlowitz et al., 2012).

3.3. Classification of sleep apnea

Sleep apnea is common even in the general population, and is identified by prolonged periods in which inspiratory airflow is either absent or considerably reduced (i.e., hypopnea). Apneic and hypopneic events during sleep are associated with frequent oxygen desaturations and arousals. The patterns of respiratory muscle activity during periods of oxygen desaturation have resulted in three general classifications. Central apneas are associated with decreased or absent respiratory motor drive during sleep (i.e., a lack of “respiratory effort”). Centrally mediated apnea is a relatively rare condition in the absence of neurological disease or injury (De Backer, 1995). In contrast to central apneas, obstructive apneas are characterized by narrowing and/or collapse of the pharyngeal airways during inspiratory efforts (i.e., pharyngeal collapse while the respiratory pump muscles are contracting). Estimates are that approximately 2–7% of the general population experience OSA, and both gender and age related differences have been reported (Punjabi, 2008). Lastly, complex or “mixed” apneas represent a combination of central and obstructive events.

3.4. Central apneas after SCI

Several brain regions (e.g. raphe nuclei, locus coeruleus, hypothalamus) play an important role in state-dependent regulation of respiratory motoneuron activity. Synaptic inputs from these structures increase the excitability of respiratory motoneurons, and these inputs are gradually reduced when progressing from waking to sleep (Gestreau et al., 2008; Horner, 2000). Thus, sleep is associated with a “normal” reduction in respiratory motoneuron excitability and output, and would be predicted to be associated with hypoventilation when coupled with injury-induced impairments of bulbospinal synaptic inputs to respiratory motoneurons (Berlowitz et al., 2005). Indeed, neurologic injuries are associated with increases in respiratory disturbances during sleep (Dyken et al., 2012). Burns and colleagues (2000) studied 20 men with a range of SCI severity (including motor complete and incomplete), and found that 40% of subjects had sleep apnea, with 25% of the cases being a predominately centrally-mediated pattern. On the other hand, Tran et al. (2010) examined 16 subjects with SCI (SCI level of T12 and higher); and while greater than 70% of the subjects had sleep apnea, central apnea was not observed. In cases where central sleep apnea is detected after SCI, it seldom occurs alone. More often, this occurs in combination with upper airway obstruction as a mixed apnea (Biering-Sorensen et al., 1995; Burns et al., 2000; McEvoy et al., 1995; Short et al., 1992).

4. OSA and SCI

4.1. Mechanisms of OSA

Before addressing the prevalence of OSA in the SCI population (see 3.3.2), we briefly comment on the mechanisms underlying OSA in spinal intact individuals since this provides a framework for understanding how SCI exacerbates the problem. Cephalometric data indicate that OSA patients often have an enlarged soft palate, tongue and uvula (Cuccia et al., 2007). Excessive fat deposition around the pharynx can also cause upper airway narrowing, and is often present in OSA patients (Horner et al., 1989). Watanabe et al. (2002) reported that OSA patients tend to have smaller and receded mandibles, and an inferior shift of the hyoid bone has also been described (Tangugsorn et al., 1995). In addition to anatomic factors, the relative amount of upper airway muscle activity during sleep is particularly important. This is perhaps best illustrated by the observation that apnea/hypopnea during sleep coincides with decreases of upper airway muscle activity (Katz and White, 2004; Remmers et al., 1978). In addition, both animal and human studies demonstrate that electrically stimulating upper airway muscles or motor nerves can reduce airway collapse ability (Fuller et al., 1999; Schwartz et al., 2012a), and can also reduce obstructive events during sleep (Eastwood et al., 2011). Collectively, it is clear that OSA is caused by an increase in the collapsibility of the pharyngeal airway during sleep, with both anatomical and neural factors contributing to the disorder (Schwartz et al., 2011).

4.2. Prevalence of OSA following SCI

Initial reports indicated that OSA is considerably more prevalent following SCI when compared to the general population (Klefbeck et al., 1998b; McEvoy et al., 1995; Short et al., 1992; Stockhammer et al., 2002) (also see Table 1). One of the first comprehensive reports was provided by McEvoy and colleagues in 1995 who studied 40 quadriplegic patients with SCI at C8 or above. They observed that approximately 30% of their subjects had significant SDB that was primarily obstructive in nature. In 2000, Burns et al. evaluated the prevalence of sleep apnea in a randomly selected sample of 20 individuals with chronic (2–29 years post-injury) SCI. They observed a 40% prevalence of “moderate” sleep apnea with an average apnea index of 17 per hour. Apnea was more prevalent in tetraplegic compared to paraplegic subjects, and was common even with incomplete injury. Berlowitz et al. (2005) subsequently performed a longitudinal assessment of breathing during sleep during the first year following SCI. While none of the subjects in their study demonstrated SDB at 48 hours post injury, by two weeks post injury 60% had evidence for SDB, and this percentage was maintained over the course of the one-year study (Berlowitz et al., 2005). Leduc et al. (2007) evaluated the presence of OSA following SCI with rigid adherence to the diagnostic criteria recommended by the American Association of Sleep Medicine. From a sample of 41 individuals with incomplete and complete cervical injuries, 22 were diagnosed with OSA. Interestingly, they noted that the occurrence of obesity in their sample of SCI individuals was not greater than the prevalence in the general population. This observation has important implications for the mechanism(s) underlying OSA after SCI (see 3.4.1). Since the publication from Leduc and colleagues, several additional reports (Biering-Sorensen et al., 2009; Jensen et al., 2009; Tran et al., 2010) have all reached the same

fundamental conclusion: the prevalence of SDB following SCI greatly exceeds rates in the general population, and OSA is the predominant form of SDB.

4.3. Mechanisms of OSA after SCI

The physiologic mechanisms resulting in the increase in OSA in individuals with SCI are not clearly defined. At first glance, one would not necessarily predict increased airway collapsibility during sleep after SCI when compared to the spinal-intact condition. Specifically, the pharyngeal muscle activation, which makes a primary contribution to the regulation of upper airway patency, is typically not impaired after even high cervical SCI. However, a number of mechanisms can be plausibly suggested to contribute to the increased prevalence of OSA after SCI (see Table 2 for a summary). As is the case in the general population, it is our opinion that the considerable increase in the prevalence of OSA after SCI reflects the complex interplay between several different physiologic mechanisms.

4.3.1. Body mass and obesity—Obesity and neck circumference are primary risk factors for OSA in the general population (Cuccia et al., 2007). Following SCI, weight and body mass index (BMI) are often increased, and in the United States, 44–66% of the SCI population is considered overweight or obese (Chen et al., 2011; Gupta et al., 2006; Johnston et al., 2005; Tomey et al., 2005; Weaver et al., 2007). Indeed, BMI increases by approximately 1 kg/m² with each 10-year increase in age following SCI (de Groot et al., 2010). Given the same BMI, individuals with SCI also typically have a higher percentage of body fat than their non-disabled counterparts (Spungen et al., 2003; Spungen et al., 2000). Findings in the SCI population, however, are somewhat contradictory. Some studies suggest a robust and direct relationship between BMI and OSA (Burns et al., 2001; Flavell et al., 1992; Stockhammer et al., 2002), while others have failed to detect a relationship (Burns et al., 2000; Short et al., 1992; Tran et al., 2010). For example, Burns et al. (2001) used regression to assess the relationship between obesity and sleep apnea in tetraplegic patients. They found a statistically significant relationship between these two variables, and interestingly there was no relationship of apnea severity and the extent of motor deficits. Similarly, Stockhammer and colleagues (2002) reported that SDB was significantly correlated with BMI and neck circumference in tetraplegic patients ranging from 0.5–37 years post-SCI. In contrast, Tran et al. (2010) did not find a relationship between sleep apnea severity and BMI or neck circumference in a cohort of 16 SCI subjects. However, this study was conducted within the first six months of injury. This is significant since Berlowitz et al. (2005) noted that OSA was actually associated with a reduced BMI acutely following SCI. Accordingly, the mechanisms driving upper airway collapse during sleep after SCI may be dynamically changing as the individual transitions from the acute to chronic stage. For example, swelling of the neck in the acute injury phase could lead to OSA independent of the body mass index (Berlowitz et al., 2005). In our opinion, the literature collectively suggests that obesity and/or increases of neck circumference are likely to make a contribution to the increased prevalence of OSA following SCI, but this is probably not the primary mechanism in all cases, particularly during the acute phase after injury.

4.3.2. Loss of traction force associated with reduced lung volumes—SCI often results in reduced lung volumes (Schilero et al., 2009), and this could alter “traction forces”

(Schwartz et al., 2012b) which can impact airway patency. In other words, lung volume can influence upper airway airflow resistance via a mechanical influence on the geometry and collapsibility of the upper airways. Schwartz et al. (1996) have described a mechanical model by which increasing the volume of the lung reduces extraluminal upper airway tissue pressure and increases longitudinal tension in the upper airway as a result of caudal tracheal displacement. Indeed, caudal movement of the trachea can increase airflow rates, and decrease the critical pressure (i.e., P_{crit}) required for pharyngeal airway narrowing and/or collapse (Kairaitis et al., 2007; Kairaitis et al., 2012; Rowley et al., 1996). Accordingly, following SCI, chronic reductions in lung volume could lead to increases of pharyngeal airway collapsibility and thus contribute to the increased prevalence of OSA.

4.3.3. Increased time in supine position—Body position during sleep has a substantial impact on SDB (Berger et al., 1997). For example, many OSA patients experience > 50% increase in apneic events when sleep position is shifted from the side to prone (Oksenberg et al., 1997). Thus, increase in obstructive events following SCI could reflect increased or even exclusive sleeping in the supine position (McEvoy et al., 1995; Tran et al., 2010). McEvoy et al. (1995) reported that quadriplegics who slept in the supine position had a significantly greater number of apneic and hypopneic events per hour compared to those who slept in other positions. Another consideration, however, is that pulmonary function may be enhanced in the supine position after SCI (Baydur et al., 2001).

4.3.4. Altered balance of parasympathetic and sympathetic tone—Autonomically driven changes in the upper airway vasculature and mucosal lining could directly impact airway resistance and lead to OSA (Berlowitz et al., 2005). In addition, autonomically mediated changes in lower airway caliber and/or regulation can influence overall pulmonary resistance, and this could also contribute to SDB. In regards to SCI and airway caliber, an important consideration is that injuries to the cord can create an “imbalance” between parasympathetic and sympathetic outflow. Thus, parasympathetic innervation of the lungs and airways is usually preserved after SCI, but sympathetic inputs can be profoundly disrupted (Radulovic et al., 2008). For example, autonomic dysreflexia following SCI is thought to result, at least in part, from impaired regulation of sympathetic motor outflow. In the case of the pulmonary system, after SCI there can be an unopposed cholinergic (parasympathetic) modulation of airway tone that triggers excessive bronchoconstriction. There are reports of reduced airway caliber after SCI (Schilero et al., 2005), and also airway hypersensitivity (Almenoff et al., 1995; Grimm et al., 1999; Schilero et al., 2005). Any reductions in airway caliber could contribute to changes in pulmonary resistance and thus increased prevalence of SDB.

4.3.5. Brainstem plasticity and/or alterations in chemosensitivity—There has been a limited amount of work in this area, but in our opinion, the literature supports the hypothesis that changes in brainstem respiratory neurons and networks are likely to occur after SCI (Johnson and Creighton, 2005). For example, Golder and colleagues showed that inspiratory motor drive to the tongue is altered following high cervical SCI in rats (Golder et al., 2001). Thus, medullary respiratory motor output can be influenced by injuries to the

cervical spinal cord. In addition, Zimmer and Goshgarian (2007) reported significant alterations in brainstem neurochemistry after a cervical SCI, albeit in a neonatal rat model.

Another consideration is that central chemosensitivity may be altered after SCI (Manning et al., 1992), and this has the potential to impact SDB. Simon et al. (1995) showed that individuals with high cervical SCI initiated inspiratory electromyogram (EMG) activity at a lower end-tidal CO₂ as compared to able-bodied controls (i.e., after SCI there was a lower CO₂ recruitment threshold). A similar finding has been reported in a rat model (Golder et al., 2011). A reduction in the CO₂ “apneic threshold” after SCI could reflect an increase in the CO₂ sensitivity of respiratory neurons and/or networks. However, other experiments indicate that the slope of the hypercapnic ventilatory response curve is actually blunted after SCI (Kelling et al., 1985; Manning et al., 1992). For example, Kelling et al. (1985) reported that able-bodied control subjects had a ventilatory response slope (i.e., l*min⁻¹*mmHg⁻¹) more than 2 fold greater than quadriplegic subjects. Manning et al. (1992) confirmed this finding. A blunted ability to increase inspiratory diaphragm EMG activity during hypercapnic respiratory challenge has also been reported following mid-cervical contusion injury in rats (Lane et al., 2012). On the other hand, Pokorski et al. reported that ventilatory chemoresponses were not altered in quadriplegics, although their ability to compensate for a resistive respiratory load was considerably impaired (Pokorski et al., 1990).

We suggest that the limited available data indicate that neuroplastic changes in the medullary respiratory control circuitry are likely after SCI, although functional impact is not certain. Changes in the overall chemosensitivity of respiratory motor output are possible after SCI, but the role of muscle afferent feedback in modulating chemoresponsiveness must be carefully considered (Simon et al., 1995). Clearly, the impact of SCI-induced respiratory neuroplasticity on breathing during sleep is an area requiring additional study.

4.3.6. Medications—Several authors have raised the possibility that use of medications could predispose SCI patients to SDB. For example, the GABA_B receptor agonist baclofen, which is commonly administered to treat spasticity following SCI, could trigger or exacerbate SDB (Bensmail et al., 2012). However, most studies have been unable to detect a strong relationship between baclofen use and the prevalence of SDB (Burns et al., 2001; Klefbeck et al., 1998b; Short et al., 1992). Benzodiazepines such as diazepam are also used as anti-spasticity drugs following SCI, and these compounds are capable of suppressing respiratory motor activity. These drugs may exacerbate SDB since Berlowitz et al. (2005) reported a strong tendency for a decrease in the AHI during sleep when benzodiazepine use was discontinued in tetraplegic patients. On the other hand, the same group was unable to find a correlation between benzodiazepine use and AHI in tetraplegics in a subsequent publication (Berlowitz et al., 2012). In addition, the use of cardiac medication to treat hypertension and arrhythmia is more frequent in tetraplegic patients with higher respiratory disturbance indices (Stockhammer et al., 2002). Overall, pharmacologically-induced changes in respiratory motor drive cannot be completely ruled out, and the medication status of the individual should obviously be considered when assessing SDB after SCI. However, the available data suggest that factors other than medications are likely making a considerably greater contribution to the increased prevalence of SDB after SCI (Table 1).

4.3.7. Gender—In the general population, age and body mass matched males have a greater prevalence of OSA when compared to pre-menopausal women (Young et al., 1993). To our knowledge, however, there have not yet been any studies specifically designed to evaluate the relationship between gender and SDB following SCI. Conclusions are difficult to draw from the literature, since the overall prevalence of SCI is substantially greater in males than females (National Spinal Cord Injury Statistical Center, 2013), and thus, the number of female subjects is generally smaller than male subjects in previous SCI studies (Table 1). In the general population, gender differences in OSA prevalence have been suggested to relate to obesity patterns (centripetal in males vs. peripheral in females) and also the influence of sex hormones. For example, the prevalence OSA increases in post-menopausal women, (Redline et al., 1994), and following menopause, hormone replacement therapy can lower the risk for OSA (Bixler (2001). Both obesity patterns and sex hormones could be influenced by SCI, and this could impact the relationship between gender and OSA. At the present time, however, it is not clear if gender differences in OSA persist after SCI, and future studies which specifically investigate this question are warranted.

5. SCI and SDB: current therapeutic approaches

Therapeutic approaches for SDB in the general population include both surgical and non-surgical options (Goodday, 2011). The most widely used non-surgical treatment is continuous positive airway pressure (CPAP). CPAP acts as a “pneumatic splint” to hold the upper airway open, and has been shown to improve oxygen saturation and sleep architecture in SCI patients (Biering-Sorensen et al., 1995; Burns et al., 2000; Stockhammer et al., 2002). Berlowitz and colleagues (2009) have demonstrated the feasibility of “auto-titrating” CPAP in patients with acute tetraplegia. The auto-titration CPAP device can automatically adjust the amount of positive airway pressure to ensure airflow. Of 19 subjects in their study, 14 had OSA, and 7 were able to successfully adhere to the CPAP therapy. CPAP effectively maintained ventilation during sleep, and patients reported reduced daytime sleepiness. LeGuen et al. (2012) recently compared the CPAP requirements and effectiveness between a sample of 219 able-bodied and 25 tetraplegic patients. While CPAP was effective in both groups, the authors found that the able-bodied subjects actually required a significantly greater level of CPAP to effectively manage OSA. This is an extremely important observation as it may suggest that tetraplegic OSA patients have a less collapsible pharyngeal airway as compared to spinal intact individuals with OSA. If this can be validated through studies of pharyngeal Pcrit (Schwartz et al., 1996)), it would indicate that neurologic changes in regulation of the upper airway may be a primary factor leading to OSA after SCI.

Unfortunately, in both the general and SCI population, adherence to CPAP therapy tends to be poor. Interference with sleep and/or mask discomfort have been reported by SCI patients as reasons for discontinuing CPAP use (Burns et al., 2001; Burns et al., 2000). Furthermore, many individuals with SCI may be reliant on assistance from caregivers due to limited hand function, thereby compounding difficulties with mask placement and adjustment. Berlowitz et al. (2009) found that if tetraplegic patients received “intensive clinical support” during initial CPAP trials, those patients who were able to tolerate a minimum of four hours during initial treatments were more likely to continue using the therapy. In addition, the authors

commented that patients who were older, “sleepier”, and had more severe OSA were more likely to maintain the use of CPAP. Castriotta and Murthy (2009) have suggested that some relatively newer devices (e.g. averaged volume assured pressure support and adaptive servo-ventilators) used to treat OSA in the general population should be applied to SCI patients.

6. Conclusions

SDB is a significant complication of SCI, and as suggested by Tran et al., screening for SDB in the SCI population should be considered (Tran et al., 2010). In the general population, SDB is associated with cardiovascular disease, cognitive impairments, daytime sleepiness, and reduced quality of life. Thus, following SCI, SDB will likely exacerbate an already medically, physically, and emotionally challenging condition. For example, Sajkov et al. reported that cognitive impairments in tetraplegic patients were significantly correlated with the severity of hypoxic episodes during sleep (Sajkov et al., 1998). The authors noted that deficits in the ability to concentrate, memory function, and learning also correlated with the severity of oxygen desaturation during sleep. Berlowitz et al. (2012) studied a large sample of tetraplegic individuals, and convincingly demonstrated a relationship between the self-reported quality of life and health scores and the severity of SDB. Specifically, as the nocturnal apnea-hypopnea index increased, the overall quality of life scores decreased. The authors concluded that in the tetraplegic population, OSA makes a considerable contribution to the decrease in overall health status.

It appears that obstructive apnea is more common than central apnea following SCI (Table 1). While mechanisms leading to increased OSA prevalence after SCI are not yet clearly defined, the increase in pharyngeal airway collapsibility during sleep is likely to reflect a complex interaction between multiple variables (Table 2). These variables include body mass, lung volume, sleeping position, autonomic function, and respiratory neuroplasticity. In addition, the mechanisms driving OSA may be dynamically changing as an individual progresses from acute to chronic SCI. Lastly, it is conceivable that individuals with OSA are more likely to have a SCI (i.e., in some cases OSA might be a pre-existing condition) (Tran et al., 2010). For example, in the general population OSA is associated with more frequent automobile accidents (George et al., 1987). Further study of this problem and delineation of the mechanisms causing OSA after SCI should lead to improved therapeutic approaches for this condition. In particular, we feel that studies of the neural regulation of the pharyngeal muscles during sleep following both acute and chronic SCI are needed.

Acknowledgments

DDF was supported by R01NS080180-01A1. NJT was supported by the VA RR&D Service (B7182W and F2182C). KZL was supported by National Science Council (NSC) NSC100-2320-B-110-003-MY2, National Health Research Institutes (NHRI-EX102-10223NC) and NSYSU-KMU Joint research Project (2013-I006).

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Table 1

Studies examining the impact of SCI on breathing during sleep.

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
Braun et al., 1982	M: 10 & F: 1 Age: 17 – 57 yrs	Cervical: 7 Thoracic: 4	Complete	Unknown	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> 9.1% (1/11) had $SpO_2 < 85\%$ 18.2% (2/11) had $SpO_2 < 90\%$ Age, but not lesion level or % predicted ERV, significantly correlated with desaturation amount
Wang et al., 1987	M: 13 & F: 13 Age: 4 mos – 6 yrs	n=9, upper cervical spinal cord compression	Achondroplasia (congenital dwarfism) leading to spinal cord compression	N/A	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Sleep apnea cited as predominant clinical concern
Bonekat et al., 1990	M: 4 Age: 38–70 yrs	Cervical: 3 Thoracic: 1	Unknown	2–26 yrs	<ul style="list-style-type: none"> Apneic event: apnea (4 10 s) associated with % O_2 desaturation. Sleep apnea: 5 apneas/hr or 30 apneic events during night sleep 	<ul style="list-style-type: none"> 100% (4/4) had OSA
Gilgoff et al., 1992	M: 17 & F: 2 Age: Birth – 19 yrs	C2–C5	Complete—requiring portable, positive pressure ventilators	Unknown	<ul style="list-style-type: none"> Adequate ventilation: $SpO_2 > 96\%$ Apnea: interval > 12 sec between recorded breaths with recorded V_T less than 25% of resting V_T 	<ul style="list-style-type: none"> Upper airway mechanics differ between sleep and wakefulness and may affect air leak around tracheostomies 82% (9/11) children on volume controlled systems were found to be inadequately ventilated during sleep; while substitution with cuffed tracheostomies allowed adequate ventilation during wakefulness and sleep Pressure controlled ventilation improves adequacy of gas exchange during sleep and wakefulness
Flavell et al., 1992	M: 10 Age: 17 – 55 yrs	C4 – C6	Frankel grade A or B	5 mos – 29 yrs	<ul style="list-style-type: none"> Severe O_2 desaturations: < 90% for 10% of night 	<ul style="list-style-type: none"> 30% (3/10) showed severe desaturations (SpO_2 minimums at 38–56%)

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
					<ul style="list-style-type: none"> Mild-moderate O₂ desaturations: < 90% for < 10% of night 	<ul style="list-style-type: none"> 30% (3/10) had mild-moderate desaturations (SpO₂ minimums ranging from 62 – 80%) Direct relationship between BMI and time spent below 90% SpO₂ Weight, level of injury, and extent of respiratory muscle weakness correlated with mean overnight SpO₂
Short et al., 1992	M: 20 & F: 2 Age: 40–77 yrs	Cervical: 15 Thoracic: 7	Frankel grade A, B, or C	0.3–46 yrs	<ul style="list-style-type: none"> Hypoxic dips: 4 % O₂ desaturation Obstructive apnoea: absence and/or decrease in oronasal airflow with continuing ribcage and/or abdominal effort Central events: absence or reduction in oronasal airflow, continuing ribcage effort, and abdominal effort Apnoea index: number of oronasal airflow cessations in excess of 10 s per hr Abnormal respiration: hypoxic dips > 15/hr 	<ul style="list-style-type: none"> 45.5% (10/22) had > 5 hypoxic dips/hr— cause was obstructive apneas in most cases 27.3% (6/22) had abnormal respiration No correlation between degree of hypoxic dipping and age, level or duration of injury, obesity index, neck circumference, or lung function
Cahan et al., 1993	M: 16 Age: 23–78 yrs	Cervical: 12 Thoracic: 4 (C4-T5)	Unknown	0.5–32 yrs	<ul style="list-style-type: none"> Apnea: absence of airflow 10 s 	<ul style="list-style-type: none"> 37.5% (6/16) showed > 4 % reduction of SpO₂ (SpO₂ values lower than normative values during 70% of recorded time) 42.9% (3/7) undergoing polysomnography had sleep apnea (AHI = 12, 53, and 54) consisting of both obstructive and central events
Bach and Wang, 1994	M: 9 & F: 1 Age: 34 – 77 yrs	C4 – C7	Complete Motor	6 mos – 19 yrs	<ul style="list-style-type: none"> Abnormal SpO₂: < 94% 	<ul style="list-style-type: none"> 60% (6/10) had SpO₂ < 90% at 0.5 yrs post-injury At 5 yr follow-up, 50% (5/10) had increased number of transient O₂ desaturations

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
						<ul style="list-style-type: none"> Over 5 yr period, detected a general decrease in nocturnal SpO₂ (80% had SpO₂ < 90%) and significant increase in nocturnal ETCO₂
McEvoy et al., 1995	M: 37 & F: 3 Age: 19–60 yrs	Cervical	Frankel grade A, B, or C	> 0.5 yrs	Unknown	<ul style="list-style-type: none"> 27.5% (11/40) had RDI 15 with SpO₂ from 49–95% 30% (12/40) had AI 5 75% (9/12) had obstructive sleep apneas 25% (3/12) of these had central or mixed sleep apnea SDB was associated with increased neck circumference
Sajkov et al., 1998	M: 34 & F: 3 Age: 19–60 yrs	Cervical	Frankel grade A, B, or C	> 0.5 yrs	<ul style="list-style-type: none"> SDB: AHI > 15/hr 	<ul style="list-style-type: none"> 29.7% (11/37) had SDB, with most apnoeas obstructive in type 18.9% (7/37) showed SpO₂ < 80 % Major associations between sleep apnoea-related hypoxia and cognitive function
Kliefbeck et al., 1998a	M: 8 & F: 1 Age: 22–42 yrs	Cervical (C5–C6)	Frankel grade A: 4 Frankel grade B: 5	2–25 yrs	<p>ODI = average number of desaturations 4% per hour</p>	<ul style="list-style-type: none"> 0% (0/9) had OSA 18.9% (1/9) patients had ODI = 8 44.4% (4/9) had SpO₂ < 90 % due to central hypoventilation
Kliefbeck et al., 1998b	M: 28 & F: 5 Age: 22–59 yrs	C4 - T1	Complete: 17 Incomplete: 16	1–33 yrs	<p>ODI: number of O₂ desaturations 4% per sleeping hour</p> <p>OSA: ODI 6 and > 45% periodic respiration time out of the total estimated sleeping time</p> <p>OSAS: OSA criteria above, plus reports of sleep disturbances, excessive</p>	<ul style="list-style-type: none"> 15% (5/33) had OSA, with additional 18% (6/33) cases considered borderline 9% (3/33) had OSAS Inverse correlation between O₂ desaturation index and ASIA motor score in subjects with complete injury, but no such correlation in entire study group No significant correlations between ODI or periodic

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
Burns et al., 2000	M: 20 Age: 24–73 yrs	Cervical: 12 Thoracic or Lumbar: 8	ASIA A or B: 14 ASIA C or D: 6	2–29 yrs	<ul style="list-style-type: none"> Apnea: pause of chest movement or oronasal airflow > 10 s Hypopneas: > 50 % decreases in airflow > 10 seconds with a 3% O₂ desaturation SAS: elevated AI, in conjunction with daytime somnolence 	<ul style="list-style-type: none"> 40% (8/20) patients had sleep apnea 25% (2/8)-central sleep apnea 50% (4/8)-OSA 25 % (2/8)-mixed sleep apnea Trend toward greater prevalence of sleep apnea with tetraplegia (58%–7/12) compared to paraplegia (12.5%–1/8) No associations with age or BMI 75% (6/8) with sleep apnea were unable to tolerate CPAP. Of the 2 that tolerated it, apneic episodes decreased.
Lu et al., 2000	M: 29 & F: 7 Age: 19 – 77 yrs Delayed catastrophic apnea in n=8; others (n=28) recruited as controls with SCI, but no apnea	C4–C8	Frankel grade A: 30 Frankel grade B: 6	Unknown	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Sleep was the most common associated event when apnea developed (with delayed onset), occurring in 62.5% (5/8)
Burns et al., 2001	M: 584	Cervical: 42 Thoracic: 9 Lumbar: 2 (Injury level information is from patients who had sleep apnea)	ASIA A: 17 ASIA B: 9 ASIA C: 7 ASIA D: 9	Unknown	<ul style="list-style-type: none"> Unknown: (retrospective review of medical chart diagnosis) 	<ul style="list-style-type: none"> 9.1% (53/584) diagnosed with sleep apnea 14.9% (42/282) tetraplegics had sleep apnea 3.7% (11/302) paraplegics had sleep apnea Sleep apnea associated with obesity and higher neurologic level, but not ASIA Medical co-morbidities more frequent, and treatment acceptance was poor with higher level motor-complete injuries

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
Tow et al., 2001	M: 41 & F: 16 Age at injury: 23.2 ± 9.1 yrs	Cervical: 57	Frankel grade A: 38 Frankel grade B & C: 17 Frankel grade C: 2	10 & 20 yrs	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> 5.3% (3/57) had sleep apnea
Ayas et al., 2001	M & F: 197 Age: 51.2 ± 14.8 yrs				<ul style="list-style-type: none"> Snoring 	<ul style="list-style-type: none"> 42.6% (84/197) were habitual snorers Use of antispasmodic medications with BMI > 25.3 kg/m² significantly increased risk for snoring Neurological motor completeness, injury level, age, and duration post-injury were unrelated to snoring
Wang et al., 2002	M: 12 & F: 2 Age: 19–56 yrs	Cervical	Complete	> 6 mos	<ul style="list-style-type: none"> SpO₂ and ET/CO₂ 	<ul style="list-style-type: none"> Resistive inspiratory muscle strength training can ameliorate SDB
Stockhammer et al., 2002	M: 40 & F: 10 Age: 20–81 yrs	C3–C8	ASIA A or B: 40 ASIA C or D: 10	0.5–37 yrs	<ul style="list-style-type: none"> SDB: RDI 15 Sleep apnea: RDI 15 & AI 5 Hypopnea: a reduction in airflow of 50–90 % from the baseline value, lasting 10 s Apnea: a reduction in airflow of 90–100% from the baseline value, lasting 10 s 	<ul style="list-style-type: none"> 62% (31/50) had SDB 48% (24/50) had sleep apnea No correlations between RDI and lesion level, ASIA, or spirometric values Significant correlations between RDI and age, BMI, neck circumference, time post-injury, gender, and cardiac medications
Berlowitz et al., 2005	M: 25 & F: 5 Age: 14–70 yrs (13 completed 12 mos follow-up)	Cervical	ASIA A: 17 ASIA B: 7 ASIA C: 3 ASIA D: 3	2 days–1yr	<ul style="list-style-type: none"> SDB: AHI 10 Apnea: complete cessation of airflow Hypopnea: > 50 % reduction in respiration signal or < 50 % reduction in respiration associated with either > 3 % O₂ desaturation or cortical arousal. 	<ul style="list-style-type: none"> 0% (0/30) had SDB at 2 days post-injury > 60 % patients had SDB from 2 to 52 wks post-injury 60% at 2 wks post-injury 62% at 4 wks post-injury 83% at 13 wks post-injury 68% at 26 wks post-injury 62% at 52 wks post-injury

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
Burns et al., 2005	M: 40 ¹ Age: 60.1 ± 11.0 yrs ² Age: 55.6 ± 10.3 yrs ¹ Treatment ² No treatment	Cervical: 37 Non-cervical: 3	All participants with SCI and diagnosed with SAS	¹ 22.0 ± 18.5 yrs ² 15.3 ± 12.4 yrs	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> CPAP tried by 80%, but only 63% continued to use, suggesting treatment was beneficial compared to side effects for many, but not those that chose to discontinue treatment
Scheer et al., 2006	M: 5 Age: 27–42 yrs	Cervical: 3 Thoracic: 2	Frankel grade A	4.7–18.5 yrs	<ul style="list-style-type: none"> Respiratory events scored using the American Academy of Sleep Medicine Task Force criteria(1999) 	<ul style="list-style-type: none"> 40% (2/5, 1 cervical and 1 thoracic) had mild sleep apnea (AHI between 10–20/hr)
Leduc et al., 2007	M: 34 & F: 7	Cervical	ASIA A: 21 ASIA B: 7 ASIA C: 6 ASIA D: 7	0.5 – 38 yrs	<ul style="list-style-type: none"> Apnea: complete oronasal airflow interruption Hypopnea: 50% reduction of airflow or < 50 % reduction of airflow associated with > 3% O₂ desaturation or arousal Mild OSAHS: AHI = 5–14 Moderate OSAHS: AHI = 15–30 Severe OSAHS: AHI > 30 	<ul style="list-style-type: none"> 53% (22/41) had AHI 5 59.1% (13/22) had mild OSAHS 4.5 % (1/22) had moderate OSAHS 36.4% (8/22) had severe OSAHS
Berlowitz et al., 2009	M: 17 & F: 2 Age: 20 – 70 yrs	C3 – C7	ASIA A: 12 ASIA B: 3 ASIA C: 3 ASIA D: 1	Acute	<ul style="list-style-type: none"> OSA: AHI > 10 	<ul style="list-style-type: none"> 73.7% (14/19) had OSA 50% (7/14) adhered to CPAP for 3 mos and had improved sleepiness
Shoda et al., 2009	M: 3 & F: 26 Age: 28–81 yrs	Cervical	Rheumatoid arthritis patients planning on undergoing surgery for occipitocervical lesions due to progressive myelopathy	Unknown	<ul style="list-style-type: none"> Sleep apnea: AHI > 5 	<ul style="list-style-type: none"> 79.3% (23/29) diagnosed with sleep apnea (all obstructive) Gender, age, BMI, and radiographic parameters were significantly associated with the presence of sleep apnea
Tran et al., 2010	M: 11 & F: 5 Age: 34.1 ± 12.3 yrs	Cervical: 8 Thoracic: 8	ASIA A: 11 ASIA B: 5	6–8 wk post-SCI & repeat evaluation at	<ul style="list-style-type: none"> SDB: AHI > 5 Mild SDB: AHI = 5–15 	<ul style="list-style-type: none"> 68.8% (11/16) had SDB at 6–8 wks post-injury

Author	Subjects	Injury level	Injury Classification/ Diagnosis	Duration post-injury	Criteria of SDB	Major findings
				6 mos post-SCI 6 mos post-SCI for n=12	Moderate SDB: AHI = 15–30 Severe SDB: AHI > 30	<ul style="list-style-type: none"> 54.5% (6/11) had mild SDB 45.5% (5/11) had moderate/severe SDB 75% (9/12) had SDB on repeat polysomnography at 6 mos post-injury 25% (3/12) were moderate-severe All obstructive, and no central apneas No associations between severity of sleep apnea and ASIA, level of injury, or gender AHI did not correlate with BMI, neck circumferences, or SpO₂
Bensmail et al., 2012	SCI: 6 M: 4 & F: 2 Other neurological disorder: 5	T4–T11	Unknown	Unknown	<ul style="list-style-type: none"> Mild SAS: RDI = 5–15 Moderate SAS: RDI = 16–29 Severe SAS: RDI = 30 	<ul style="list-style-type: none"> Increases in RDI, obstructive apneas, mixed apneas, and central apneas were observed following bolus intrathecal baclofen. Values decreased, but still remained above baseline (pre-treatment) following continuous administration of intrathecal baclofen.
Berlowitz et al., 2012	M: 59 & F: 19 Age: 18 – 70 yrs	C1 – T1	Complete: 35 Incomplete: 43	Unknown	<ul style="list-style-type: none"> OSA: AHI > 10 	<ul style="list-style-type: none"> 91% with complete injuries had OSAHS 55.8% with incomplete injuries had OSAHS
Le Guen et al., 2012	M: 20 & F: 5 Age: 46.9 ± 14.2	Tetraplegia (Cervical)	Complete: 11 Incomplete: 14	Acute: 15 Chronic: 10	<ul style="list-style-type: none"> Respiratory event scored according to the American Academy of Sleep Medicine criteria(1999) 	<ul style="list-style-type: none"> No significant difference in AHI between complete versus incomplete groups No significant difference in CPAP between acute and chronic groups No significant correlation between AHI and effective CPAP or between AHI and BMI Significant correlation between effective CPAP and BMI

Abbreviations:

AHI: Apnea/Hypopnea Index (number of apneas and/or hypopneas per hour of sleep)
 AI: Apnea Index
 ASIA: American Spinal Injury Association scale of motor and sensory impairment
 BiPAP: Bilevel Positive Airway Pressure
 BMI: Body Mass Index
 C: Cervical
 CPAP: Continuous Positive Airway Pressure
 d(s): day(s)
 ETCO₂: end-tidal partial pressure of carbon dioxide
 M: male
 F: female
 hr: hour
 IPPV: Intermittent Positive Pressure Ventilation
 L: Lumbar
 N/A: Not Applicable
 OA: Obstructive Apnea
 ODI: Oxygen Desaturation Index
 OSA: Obstructive Sleep Apnea
 OSAHS: Obstructive Sleep Apnea Hypopnea Syndrome
 ODI: O₂ Desaturation Index (the average number of > 4% O₂ desaturations/hr of sleep)
 RDI: Respiratory Disturbance Index (respiratory events per hr of sleep)
 REM: Rapid Eye Movement
 SA: Sleep Apnea
 SAS: Sleep Apnea Syndrome
 SCI: Spinal Cord Injury
 SDB: Sleep Disordered Breathing
 sec/s: second
 SpO₂: saturation of peripheral oxygen
 T: Thoracic
 VT: tidal volume
 wk(s): week(s)
 yr(s): year(s)

Table 2
An overview of the mechanisms potentially contributing to the increased incidence of SDB after SCI

Changes in breathing during sleep following SCI, and in particular the increased incidence of OSA, are likely to occur due to a complex interaction between multiple variables. In addition, the mechanisms driving SDB may be dynamically changing during the progression from acute to chronic SCI. While it is not yet possible to draw definitive conclusions regarding underlying physiological mechanisms, each of these variables listed in the left hand column can be altered by SCI and could theoretically contribute to an increase in upper airway narrowing or collapse during sleep. Please see the text for a more detailed discussion of each variable, and how it is changed following SCI.

Variable	Potential Change after SCI	Potential Physiological Impact
Neck circumference	Increase	Increased parapharyngeal tissue pressure
Body mass / obesity	Increase	Increased parapharyngeal tissue pressure
Waist size	Increase	Reduction of caudal traction of the upper airway
Lung volume	Decrease	Reduction of caudal traction of the upper airway
Time in supine sleep position	Increase	Increase upper airway collapsing force
Parasympathetic and/or Sympathetic tone	*Altered	Bronchoconstriction; Changes in upper airway vasculature and/or mucosal lining
Brainstem activity	*Altered	Unclear
Central chemosensitivity	*Altered	Unclear
Medication	Increased	Reduced respiratory motor activity

* in some cases, we elected to list the variable as “altered” since the changes are likely to be extremely complex and difficult to classify as “increased vs. decreased”.