Frontiers review

Pulmonary function and spinal cord injury

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ABSTRACT

Injury to the cervical and upper thoracic spinal cord disrupts function of inspiratory and expiratory muscles, as reflected by reduction in spirometric and lung volume parameters and static mouth pressures. In association, subjects with tetraplegia have decreased chest wall and lung compliance, increased abdominal wall compliance, and rib cage stiffness with paradoxical chest wall movements, all of which contribute to an increase in the work of breathing. Inspiratory muscle function is more compromised than expiratory muscle function among subjects with tetraplegia and high paraplegia, which can result in ineffective cough and propensity to mucus retention and atelectasis. Subjects with tetraplegia also demonstrate heightened vagal activity with reduction in baseline airway caliber, findings attributed to loss of sympathetic innervation to the lungs. Significant increase in airway caliber following inhalation of ipratropium bromide, an anticholinergic agent, suggests that reduction in airway caliber is not due to acquired airway fibrosis stemming from repeated infections or to abnormal hysteresis secondary to chronic inability of subjects to inhale to predicted total lung capacity. Reduced baseline airway caliber possibly explains why subjects with tetraplegia exhibit airway hyperresponsiveness to methacholine and ultrasonically nebulized distilled water. While it has been well demonstrated that bilateral phrenic nerve pacing or stimulation through intramuscular diaphragmatic electrodes improves inspiratory muscle function, it remains unclear if inspiratory muscle training improves pulmonary function. Recent findings suggest that expiratory muscle training, electrical stimulation of expiratory muscles and administration of a long-acting β2-agonist (salmeterol) improve physiological parameters and cough. It is unknown if baseline bronchoconstriction in tetraplegia contributes to respiratory symptoms, or if the chronic administration of a bronchodilator reduces the work of breathing and/or improves respiratory symptoms. Less is known regarding the benefits of treatment of obstructive sleep apnea, despite evidence indicating that the prevalence of this condition in persons with tetraplegia is far greater than that encountered in able-bodied individuals.

1. Introduction

The purpose of this review is to detail the mechanisms of pulmonary physiologic impairment in persons with spinal cord injury (SCI), and to discuss methods currently available to improve respiratory muscle strength and cough in this population. Possessing an understanding of these topics assumes great importance for clinicians involved in the care and rehabilitation of patients with SCI, as well as for researchers in the field, especially when armed with knowledge that pulmonary complications remain a major cause of morbidity and mortality in this population. Further, given recent findings that persons with tetraplegia have an unusually high prevalence of obstructive sleep apnea (OSA), and mounting evidence linking untreated OSA to increased cardiovascular disease risk in the general population, this review includes a discussion of what is currently known regarding OSA and its treatment in persons with SCI.

Injury to the cervical and upper thoracic cord disrupts function of the diaphragm, intercostal muscles, accessory respiratory muscles, and abdominal muscles (Fig. 1), thereby causing reduction in spirometric and lung volume parameters and static mouth pressures. As a result, subjects may have ineffective cough and difficulty clearing secretions which in turn predispose to mucus retention,
atelectasis and pulmonary infections, and ultimately to significant morbidity and mortality (Fishburn et al., 1990; DeVivo et al., 1993; Cotton et al., 2005). Although numerous studies have demonstrated restrictive ventilatory impairment, recent studies have also demonstrated the presence of baseline bronchoconstriction, which has been attributed to interruption of sympathetic innervation to the lungs. Recent studies have also focused upon factors that affect long-term pulmonary function in addition to level and completeness of injury, and upon methods for improving respiratory function in SCI.

2. Pulmonary function testing among subjects with spinal cord injury

2.1. Testing considerations

More than 80% of subjects with SCI are able to perform spirometry and provide acceptable results using standards developed for able-bodied individuals (Ashba et al., 1993; Standardization of Spirometry, 1995; Kelley et al., 2003; Miller et al., 2005). Some subjects, however, do not fulfill American Thoracic Society (ATS) standards because of excessive back-extrapolated volume and/or expiratory efforts lasting fewer than 6 s. Those failing to fulfill ATS test criteria generally have lower baseline forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), and frequently have neurologically complete cervical cord injury (Kelley et al., 2003). Overall, approximately 90% of subjects with chronic SCI are able to provide acceptable and reproducible spirometric results if ATS standards are modified to allow excessive back-extrapolated volume and expiratory efforts of less than 6 s duration if there has been a plateau of at least 0.5 s at residual volume (Kelley et al., 2003). Among those who fulfill ATS test criteria, however, there is greater variability in baseline FEV1 values compared to able-bodied individuals (Radulovic et al., 2008), which may be of significance in evaluating effects of bronchodilators. Maintenance of stable head position during FVC maneuvers reduces measurement variability (Amodie-Storey et al., 1996).

2.2. Spirometric and lung volume parameters

Historically, spirometric and lung volume studies in persons with tetraplegia and high levels of paraplegia have demonstrated restrictive dysfunction due to neuromuscular weakness characterized by significant reduction of vital capacity (VC), FEV1, maximal mid-expiratory flow (MMEF), peak expiratory flow (PEF), total lung capacity (TLC), maximum voluntary ventilation (MVV), expiratory reserve volume (ERV) and inspiratory capacity (IC), along with a significant increase in residual volume (RV), and little or no change in functional residual capacity (FRC) (Hemingway et al., 1958; Fugl-Meyer, 1971; Fugl-Meyer and Grimby, 1971a; Ohry et al., 1975; Kokkola et al., 1975; Forner, 1980; Bluehardt et al., 1992; Roth et al., 1995; Almenoff et al., 1995a; Linn et al., 2000, 2001). One major difference in tetraplegia compared to those with other neuromuscular diseases is greater preservation of inspiratory muscle function, principally of the diaphragm, relative to the compromise in expiratory muscle function resulting from paralysis of intercostal and abdominal musculature. This results in a disproportionate reduction in FVC, an expiratory maneuver, compared to TLC. Significant reduction in ERV is also reflective of the magnitude of expiratory muscle weakness. Following acute injury, vital capacity has been found to correlate well with FEV1, IC, ERV, TLC and the RV/TLC ratio, indicating that during this period VC can be used as a general measure of overall ventilatory status in SCI (Roth et al., 1995). Incomplete lesions appear to mitigate FVC loss in tetraplegia (Linn et al., 2000, 2001). The higher the level of injury, the more significantly pulmonary function parameters are reduced (Fig. 2). In addition to level of injury and severity of injury, other determinants of TLC, FVC, RV and ERV include body mass index (BMI), total pack-years of smoking, maximal inspiratory pressure (MIP), and physician-diagnosed chronic obstructive pulmonary disease (Stepp et al., 2008). Pulmonary function variables are also influenced by previous chest injury or operation, age, time since injury, obesity, and the presence of wheeze (Jain et al., 2006).
2.3. Gas exchange

Single breath nitrogen washout curves in tetraplegia have been reported to be slightly abnormal or normal, suggesting relatively even gas distribution (Forner, 1980). However, a xenon-133 study demonstrated decreased ventilation of basal regions in tetraplegia, which was attributed to “small airway disease” due to repeated infections, or possibly to increased basal small airway resistance (Bake et al., 1972). A subsequent radioisotope study demonstrated inhomogeneous ventilation in the upper and middle lung regions, which was attributed to changes in regional intrapleural pressure due to paradoxical movement of the thoracic cage (Hiraizumi et al., 1986).

2.4. Effects of smoking

Among subjects with low tetraplegia (C5–C8), high paraplegia (T1–T7), and low paraplegia (T8–L3), FEV1 and PEF were found to be significantly higher among ex-smokers and non-smokers compared to active smokers (Almenoff et al., 1995a). The absence of a smoking effect among subjects with high tetraplegia (C4 and above not requiring mechanical ventilation) was attributed to overriding injury-related functional loss. A cross-sectional evaluation of 440 subjects with SCI suggested that current smokers showed a significant excess decline in FEV1/FVC with increasing age, whereas never smokers showed no age-related decline beyond that expected in the general population (Linn et al., 2003). Whereas in one study of 57 subjects with tetraplegia followed for 20 years, no significant difference was found in mean VC between non-smokers and ex/current smokers (Tow et al., 2001), a recent longitudinal study demonstrated that cigarette smoking in SCI was associated with an accelerated rate of decline of FVC and FEV1 (Stolzmann et al., 2008).

2.5. Effects of body position

Pulmonary function parameters differ based upon the body position at which they are measured. Among subjects with SCI, in contrast to able-bodied individuals, FVC and FEV1 are significantly higher in the supine position compared to the sitting position (Estenne and De Troyer, 1987; Chen et al., 1990; Ali and Oi, 1995; Baydur et al., 2001). Expiratory reserve volume is almost uniformly less throughout all injury levels compared to able-bodied individuals (Baydur et al., 2001). The increase in VC in SCI during recumbency has been attributed to a reduction in RV due to the effect of gravity on abdominal contents rather than due to an increase in intrathoracic blood volume (Estenne and De Troyer, 1987); elevation of the diaphragm results in greater downward excursion of the contracting diaphragm because muscle fibers are operating at a more favorable portion of their length-tension curve (Fugl-Meyer, 1971; Estenne and De Troyer, 1987; Baydur et al., 2001). In support of a more favorable diaphragmatic length–tension relationship, VC, IC, and TLC improve among subjects with tetraplegia with abdominal binders (Maloney, 1979; Goldman et al., 1986; McCool et al., 1986; Hart et al., 2005) and those immersed in isothermal water to shoulder level (Thomaz et al., 2005).

2.6. Temporal changes in pulmonary function following traumatic SCI

Vital capacity and expiratory flow rates are low in the first week following cervical cord injury; individuals with an FVC of less than 25% of predicted are likely to develop respiratory failure requiring ventilator support. During the first 12 months following injury, VC, IC, TLC and inspiratory and expiratory flow rates increase and FRC decreases, after which time changes in VC and FRC are more gradual while TLC and ventilatory indices remain unchanged (Ledsome and Sharp, 1981; Haas et al., 1985; Anke et al., 1993; Mueller et al., 2008). Initial improvement has been attributed to return of functional respiratory muscles coincident with resolution of inflammation and edema above the injury level (Haas et al., 1985). Later increases have been attributed to improvement in diaphragm function (McMichan et al., 1980; Axen et al., 1985; Oo et al., 1999; Brown et al., 2006), increased performance of accessory respiratory muscles (Frisbie and Brown, 1994) and chest wall changes including increased rib cage stability (McMichan et al., 1980; Haas et al., 1985). The improvement in VC has been attributed to an increase in IC resulting from a decrease in FRC (Haas et al., 1985). In general, the time course of recovery of pulmonary function is variable following SCI and can only be weakly predicted by knowledge of the initial pulmonary function test values and the level of lesion (Bluechardt et al., 1992). Significant determinants of longitudinal decline in FVC and FEV1 include age, current smoking, increase in BMI, wheeze, and respiratory muscle strength (Stolzmann et al., 2008).

2.7. Breathing pattern and sighs

With regard to the ability of persons with SCI to take maximally deep breaths or sighs, which may be of help in preventing airway collapse, assessment of breathing pattern parameters and sigh frequency has yielded variable findings (Table 1), presumably due to methodology. Loveridge and Dubo (1980) used rubber strain gauges that were attached around the rib cage and the abdomen, Spungen et al. (unpublished data) used a portable magnetometer with electromagnetic coils secured to the rib cage and abdomen, and Bodin et al. (2003) used a body plethysmograph while subjects were breathing though a mouthpiece. Despite the different methodologies employed, findings from the 3 studies demonstrate that tidal volume (VT), minute ventilation (VE) and mean inspiratory flow (tidal volume/inspiratory time: VT/Ti) were reduced in subjects with tetraplegia. Assessment of mean inspiratory flow (VT/Ti), however, a widely employed measure of respiratory drive (Tobin, 1992), may not be applicable to subjects with tetraplegia because of underestimation of respiratory drive in the presence of marked abnormalities in respiratory system mechanics (Tobin, 1992). Loveridge and Dubo (1990) found sighs (defined as 2× mean VT) to be normal in tetraplegia, although 8 of 14 subjects with tetraplegia had no breaths greater than 2× mean VT. Using different criteria, Spungen et al. (unpublished data) found sighs (defined as mean VT +500 mL) to be significantly reduced among those with tetraplegia compared to gender-, age-, and height-matched controls.

2.8. Maximal inspiratory and expiratory pressures

Maximal mouth static respiratory pressures, which are considered surrogate measures of global inspiratory and expiratory muscle strength, are reduced among those with tetraplegia, and in contrast to normal subjects, MIP is higher than maximal expiratory pressure (MEP) due to greater compromise of expiratory muscle function (Fugl-Meyer and Grimby, 1971a,b; Gounden, 1997). Among 30 subjects with complete lesions between C5 and C8 of greater than 6 months duration, mean MEP in the sitting position was 48 cm H2O and mean MIP was −64 cm H2O (Gounden, 1997). Static mouth pressures have been found to correlate with level of injury among subjects with complete motor lesions, but not among those with incomplete lesions (Mateus et al., 2007). Static pressure values are dependent upon lung volumes at which they are measured and the type of mouthpiece used in the assessment; therefore, interpretation is problematic in this population. Although a flange-type mouthpiece is generally used, a study of 50 subjects with tetraplegia demonstrated that MEP values obtained by use of a tube-style
mouthpiece were significantly greater than those obtained by use of an intra-oral flange-style mouthpiece due to perioral air leaks with the flange-style device (Tully et al., 1997). Similarly, among able-bodied individuals and subjects with muscle weakness, it has been determined that measurements of MEP were best performed using a large-bore circular mouthpiece or a scuba-diving mouthpiece with the cheeks supported (Koulouris et al., 1988; Rubinstein et al., 1988). When compared with cough gastric pressure, MEP was found to be falsely low in 42% of 171 subjects with neuromuscular disease (4 with SCI) (Man et al., 2003). However, it is doubtful that the measurement of cough gastric pressure is of value in assessing expiratory muscle strength in SCI, because cough gastric pressure is low due to abdominal muscle weakness (Siebens et al., 1964).

Sniff nasal inspiratory pressure (SNIP) has also been used to assess inspiratory muscle strength. Sniff nasal inspiratory pressures are obtained using a tight-fitting intranasal device during a short, sharp maximal inspiratory effort, with the contralateral nostril plugged or unplugged. Among able-bodied individuals and those with neuromuscular or skeletal disorders (none with SCI), SNIP correlated significantly with sniff maximum esophageal pressure (sniff Pes) and with MEP (Koulouris et al., 1989; Heritier et al., 1994; Stefanutti et al., 2000). However, among 61 patients undergoing assessment of global inspiratory muscle strength, 11 subjects with low MEP had normal sniff Pes and transdiaphragmatic pressure, indicating that MEP was falsely low, possibly because of difficulties with the measurement technique (Laroche et al., 1988). A study of 9 subjects with tetraplegia revealed significant correlation of MEP with SNIP ($r = 0.8, p < 0.003$) (Radulovic et al., unpublished data). Ultimately the usefulness of SNIP and MEP as measurements of inspiratory muscle strength in SCI will require comparison of these parameters with those of sniff Pes in a research protocol.

3. Cough

Cough effectiveness is reduced among subjects with tetraplegia and high paraplegia due to loss of function of the major muscles of expiration including the muscles of the anterolateral wall of the abdomen, the expiratory intercostals, and the triangularis sterni (De Troyer and Estenne, 1991; Fujiwara et al., 1999). Apparent residual expiratory function, as reflected by ERV, has been attributed to activity of the clavicular portion of the pectoralis major muscle, which is innervated by nerve fibers originating in the fifth, sixth, and seventh cervical segments (De Troyer et al., 1986a), and the latisimus dorsi muscles (Fujiwara et al., 1999). Cough modulated by the clavicular portion of the pectoralis major muscle is an active, rather than passive process (Estenne and De Troyer, 1990), and muscle contraction causes dynamic airway compression during expiratory efforts in a substantial proportion of subjects with tetraplegia (Estenne et al., 1994). Cough-induced paradoxical expansion of the abdomen is due to contraction of the pectoralis major and not due to diaphragmatic activity (Estenne and Gorini, 1992).

Reduced expiratory pressures with ineffective cough are frequently associated with mucus plugging and atelectasis, two major causes of morbidity and mortality in SCI (Slonimski and Aguilera, 2001). Problems may be amplified in the immediate post-injury period, during which time excessive and tenacious mucus is produced, possibly due to amplified or uninhibited parasympathetic activity (Bhaskar et al., 1991).

Using a capsaicin challenge technique, it was determined that cough reflex sensitivity was normal in tetraplegia, but may be suppressed among those receiving baclofen (Dicpinigaitis et al., 1999, 2000). In another study, cough thresholds following administration of citric acid aerosol were found to be lower among subjects with SCI compared with able-bodied individuals (Lin et al., 1999).

4. Rib cage, compliance, work of breathing and response to resistive loading

Among subjects with high tetraplegia, synchronous contraction of neck muscles including the sternocleidomastoids, trapezius, platysma, mylohyoid and sternohyoid, acts to pull the sternum cranially and to expand the upper rib cage, but results in paradoxical inward displacement of the lateral walls of the lower rib cage (Danon et al., 1979; De Troyer et al., 1986b). Conversely, isolated diaphragmatic contraction is generally associated with expansion of the lower rib cage and collapse of the upper rib cage (Moutlon and Silver, 1970; Fugl-Meyer and Grimby, 1971b; Mead et al., 1984; Estenne and De Troyer, 1985; McCool et al., 1986; Urmy et al., 1986; Scanlon et al., 1989). Collectively, these findings demonstrate that diaphragm/upper rib cage coupling is abnormal in tetraplegia, presumably because of loss of intercostal muscle activity and increased compliance of the abdominal wall (Moutlon and Silver, 1970; Goldman and Mead, 1973; De Troyer and Heilporn, 1980; Estenne and De Troyer, 1985). Rib cage paradox decreases with time after injury (Scanlon et al., 1989), possibly due to the development of bony rib cage stiffness, increased strength of cervical accessory muscles, and improved coupling of the various rib cage elements (Estenne and De Troyer, 1986). Increase in rib cage stiffness has been attributed to anklyosis of joints due to chronic inability of subjects to inhale deeply and to an increase in intercostal spasticity (Estenne and De Troyer, 1986), as has been observed among patients with chronic respiratory muscle weakness due to processes other than spinal cord injury (Estenne et al., 1983). In association, chest wall, lung, and rib cage compliance are reduced in tetraplegia, and diaphragm–abdomen compliance is increased (Stone and Keltz, 1963; Fugl-Meyer and Grimby, 1971a; Forner, 1980; Scanlon et al., 1989; Estenne and De Troyer, 1986). The decrease in lung compliance occurs within 1 month after injury, and has been.

<table>
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<tr>
<th>Table 1</th>
<th>Breathing pattern parameters among subjects with tetraplegia.</th>
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<tr>
<td></td>
<td>Loveridge and Dubo (1990)</td>
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<tr>
<td></td>
<td>Bodin et al. (2003)</td>
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<td></td>
<td>Spungen et al. (unpublished data)</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>Tetra</td>
</tr>
<tr>
<td>Respiratory rate (RR)</td>
<td>20′</td>
</tr>
<tr>
<td>Tidal volume (Vt, ml)</td>
<td>305′</td>
</tr>
<tr>
<td>Minute ventilation (Ve, L/min)</td>
<td>5.8</td>
</tr>
<tr>
<td>Inspiratory time (Ti, s)</td>
<td>1.3</td>
</tr>
<tr>
<td>Expiratory time (Te, s)</td>
<td>1.9′</td>
</tr>
<tr>
<td>Mean inspiratory flow (Vt/Ti)</td>
<td>0.24′</td>
</tr>
<tr>
<td>Ti/Tot</td>
<td>0.44′</td>
</tr>
<tr>
<td>Sighs (h)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported; tetra = tetraplegia.

*p ≤ 0.05 compared with control.
attributed more to lung volume loss than to intrinsic changes in the mechanical properties of the lungs (De Troyer and Heilporn, 1980; Scanlon et al., 1989). The increase in abdominal wall compliance causes abnormal distribution of ventilation by reducing appositional forces during inspiration that act to expand the lower rib cage (Estenne and De Troyer, 1985, 1987; Goldman et al., 1986, 1988). Alterations in chest wall, lung and abdominal compliance in tetraplegia are associated with an increase in the work of breathing, although overall resting oxygen uptake is lower (Silver, 1963; Stone and Keltz, 1963; Bergofsky, 1964a; Bergofsky, 1964b; Haas et al., 1965), and may contribute to respiratory muscle fatigue (Brown et al., 2006). Less rib cage distortion and higher pulmonary function parameters occur among subjects with residual electromyographic activity of intercostal and scalene muscles (Guttman and Silver, 1965; De Troyer and Heilporn, 1980; Estenne and De Troyer, 1985).

Several studies have demonstrated that subjects with chronic tetraplegia have a blunted ventilatory and occlusion response to hypercapnia (Kelling et al., 1985; McCool et al., 1988; Manning et al., 1992a; Lin et al., 1998). Findings of a normal response in tetraplegia by Pokorski et al. (1990) may have been due to the study of subjects with better preserved lung function than those evaluated in other studies (Manning et al., 1992a). It has been suggested that the blunted response cannot be attributed solely to respiratory muscle weakness or functioning length of the diaphragm, but may be due to reduced ventilatory drive (McCool et al., 1988; Manning et al., 1992a). Among subjects with paraplegia the response to hypercapnia is preserved through rapid and shallow breathing (Gorini et al., 2000). In contrast to the response to hypercapnia, breath holding times and the response to inspiratory and expiratory resistive loading is preserved in tetraplegia (Frankel et al., 1971; Kelling et al., 1985; Im Hof et al., 1986; O’Donnell et al., 1993), although the sensation of loading may be blunted (Gottfried et al., 1984). However, the oxygen cost of breathing with inspiratory resistive loading is greater among subjects with tetraplegia, which may be related to the elastic work of chest wall distortion, shorter mean operational diaphragm length and possible differences in the mechanical advantage of available inspiratory muscles (Manning et al., 1992b).

### 5. Airway obstruction

Historically, spirometric studies of subjects with tetraplegia have consistently demonstrated ventilatory restrictive impairment without apparent air-flow obstruction (Hemingway et al., 1958; Forner, 1980). Of note, in 1965 Haas et al., suggested that differences in time constants among subjects with acute and post-acute tetraplegia compared to those with chronic injury was possibly due to an increase in pulmonary resistance. In 1993, it was found that administration of the β2 agonist metaproterenol sulfate to 34 subjects with chronic tetraplegia resulted in a significant increase in FEV1 (≥12% and 200 mL) in 14 of the subjects (41%) (Spungen et al., 1993). The findings demonstrated that subjects with tetraplegia have unsuspected airway obstruction not previously appreciated because of normal FEV1/FVC ratios. It was postulated that heightened responsiveness was due to interruption of sympathetic innervation to the lung, thereby resulting in parasympathetic (bronchoconstrictive) predominance. Support came from a study which demonstrated that 12 of 25 (46%) of subjects with tetraplegia had a significant increase in FEV1 following inhalation of the anticholinergic agent ipratropium bromide (IB) (Almenoff et al., 1995b). Significant insight was obtained from a body plethysmographic study, which revealed that baseline specific airway conductance (sGaw) was significantly lower in tetraplegia (0.16 ± 0.05 cm H2O−1 s−1) compared to subjects with paraplegia (0.26 ± 0.05 cm H2O−1 s−1) and control subjects (0.27 ± 0.05 cm H2O−1 s−1) (Schilero et al., 2005), and that subjects with tetraplegia had a significantly greater increase in sGaw following inhalation of IB (Table 2).

To the extent that sGaw represents the number, length and patency of the conducting airways (Butler et al., 1960), body plethysmography findings demonstrate that baseline airway caliber is reduced among subjects with tetraplegia (Schilero et al., 2005). The significant increase in sGaw in tetraplegia following IB meets the established criteria for significant bronchodilator responsiveness (Van Noord et al., 1994), and demonstrates that reduced baseline caliber in tetraplegia is due to heightened vagal tone. Other investigators have also found low baseline sGaw among subjects with tetraplegia that increased significantly following inhalation of IB (Mateus et al., 2006). Of note, sGaw has been measured in subjects with chronic muscle weakness due to processes other than cervical cord injury (Inkley et al., 1974; Gibson et al., 1977; Demedts et al., 1982). Although many of the subjects had reduced static lung compliance, comparable to that found among subjects with tetraplegia (De Troyer and Heilporn, 1980; Forner, 1980), sGaw ranged from normal to high. Therefore, findings of reduced baseline sGaw in tetraplegia suggest a major difference in factors governing airway caliber compared with those who have general muscle weakness.

### 6. Autonomic nervous system and airway tone

Activity carried within parasympathetic nerves represents the major bronchoconstrictive system in all animal species (Barnes, 1986). Centrally generated efferent vagal output remains intact with cervical cord injury. Effenter coded action potentials are carried in the vagus nerve to autonomic ganglia located in airway walls, and then widely distributed throughout the lungs through post-ganglionic fibers. Synaptic transmission in autonomic ganglia and at the level of airway smooth muscle is influenced by autacoids, tachykinins, bradykinin, nitric oxide, and catecholamines (Racke and Matthiesen, 2004). Release of norepinephrine from adrenergic

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**Table 2**

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<th>Tetraplegia (n = 6)</th>
<th>Paraplegia (n = 6)</th>
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<tr>
<td></td>
<td>Mean ± S.D.</td>
<td>% ch</td>
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<tr>
<td>FEV1 (L)</td>
<td>2.11 ± 0.57</td>
<td>(12 ± 6)*</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>75 ± 4</td>
<td>(5 ± 7)</td>
</tr>
<tr>
<td>ERV (L)</td>
<td>0.63 ± 0.56</td>
<td>(57 ± 63)*</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>2.67 ± 1.02</td>
<td>(0 ± 10)</td>
</tr>
<tr>
<td>sGaw (cm H2O−1 s−1)</td>
<td>0.13 ± 0.05</td>
<td>(135 ± 47)*</td>
</tr>
</tbody>
</table>

FEV1 = forced expired volume in one second; FEV1/FVC = the ratio of the FEV1 to the forced vital capacity; ERV = expiratory reserve volume; FRC = functional residual capacity; sGaw = specific airway conductance. Values in parentheses represent percentage change from baseline following ipratropium bromide. The data is adapted from Schilero et al. (2005).

*p < 0.05 represents significant change following ipratropium bromide.
nerves may influence bronchomotor tone indirectly by modulating cholinergic neurotransmission at the level of autonomic ganglia by inhibiting activity of acetylcholine (Barnes, 1986; Davis and Kannan, 1987).

In contrast to parasympathetic innervation, sympathetic innervation of the lungs arising in the upper 6 thoracic segments of the spinal cord is interrupted with cervical cord injury. Postganglionic nerve fibers synapse in the middle and inferior cervical ganglia and in the upper four thoracic ganglia to enter the hilum to intermingle with cholinergic nerves to form a dense plexus round airways and vessels (Barnes, 1986). Although early studies indicated that adrenergic (sympathetic) nerves were not present at the level of airway smooth muscle (Richardson and Ferguson, 1979; Doig and Satchell, 1982), additional studies, however, demonstrated that sympathetic fibers innervate the smooth muscle layer of the human bronchial tree, with a few fibers reaching the level of secondary bronchi and terminal bronchioles (Partanen et al., 1982; Laitinen et al., 1985). Even sparse innervation may have physiologic significance in the regulation of bronchial smooth muscle tone in humans because muscle cells are electrically coupled, indicating that every cell need not be innervated to contract (Partanen et al., 1982).

However, associated pharmacological manipulation studies using electrical field stimulation of excised human tracheal and lung tissue failed to demonstrate functional sympathetic innervation of human airways (Doig and Satchell, 1982; Davis et al., 1982), but demonstrated the presence of nonadrenergic, noncholinergic bronchodilator innervation (Lammers et al., 1988), thereby leading to the current belief that there is no functional sympathetic innervation of human airway smooth muscle, and that relaxation of airway smooth muscle is due to inhibitory nonadrenergic, noncholinergic nerves (Barnes, 1986; Canning and Fischer, 2001). However, recent findings among subjects with high paraplegia (T3 to T6) that baseline airway caliber was comparable to that found in low paraplegia, whereas epinephrine levels were low in high paraplegia and tetraplegia in comparison with low paraplegia (Schmid et al., 1998), provides circumstantial evidence that sympathetic innervation to the lungs is of functional significance in the maintenance of airway tone (Radulovic et al., 2008) (Table 3).

Support for the suggestion that human lung contains functional sympathetic innervation comes from studies of patients who have undergone bilateral video-assisted sympathectomy at levels T2 and T3 for cure of essential hyperhidrosis (Noppen and Vincken, 1996; Tseng and Tseng, 2001; Vigil et al., 2005). These studies demonstrated that FEV1, FEV1/FVC and forced expiratory flow between 25% and 75% of vital capacity (FEF25–75) were significantly lower under baseline airway caliber in SCI (Radulovic et al., 2008), suggest that subjects with tetraplegia have reduced baseline airway caliber comes from additional observations that IB pretreatment blocked ultrasonically nebulized distilled water-induced bronchoconstriction (Grimm et al., 1999), that the y-aminobutyric acid (GABA)-agonist (baclofen), and oxybutynin chloride, both with anticholinergic activity, inhibited hyperresponsiveness to methacholine (Dicpinigaitis et al., 1994b; Singas et al., 1999) and that pretreatment with aerosolized metaproterenol sulfate markedly attenuated methacholine- and histamine-induced hyperresponsiveness (DeLuca et al., 1999). Attenuation with metaproterenol does not specifically demonstrate abnormal sympathetic responsiveness because beta-2 agonists cause functional airway relaxation regardless of the underlying cause of bronchoconstriction (Barnes, 1986).

Further observations, however, suggest that factors in addition to reduced baseline airway caliber may contribute to histamine-induced airway hyperresponsiveness among those with tetraplegia. These include findings that pretreatment with aerosolized IB did not attenuate histamine-induced hyperreactivity (Fein et al., 1998), and that subjects receiving baclofen or oxybutynin chloride did not demonstrate reduced responsiveness to histamine (Singas et al., 1999; Grimm et al., 1997).

Several additional mechanisms may cause or contribute to reduced airway caliber in tetraplegia. Airway narrowing in asthma has also been attributed to airway remodeling caused by chronic inflammation (Cockcroft and Davis, 2006). The contribution of inflammation, if any, to airway hyperreactivity in SCI has not been investigated. Exaggerated bronchoconstriction and reduced baseline airway caliber may also be explained by the inability of subjects with tetraplegia to breathe to their predicted total lung capacity (Fugl-Meyer, 1971; Kokkola et al., 1975; Ohry et al., 1975). Deep inspiration dilates the airways by exerting an increase in the airway transmural pressure (Moore et al., 1997). Normal subjects develop exaggerated airway narrowing if deep breathing is voluntarily suppressed prior to methacholine challenge (Skoob et al., 1995), therein suggesting that bronchoconstriction in diseases such as asthma and chronic obstructive pulmonary disease may be due to a failure of deep inspiration to reverse airway narrowing rather than an exaggerated capacity of the airways to narrow (Fish et al., 1981; Pellegrino et al., 1998). However, observations that subjects with tetraplegia demonstrate a dramatic increase in sGaw following inhalation of IB suggest that their inability to inhale to predicted TLC does not explain reduced baseline airway caliber (Schilero et al., 2005). Likewise, because of rapid increase in sGaw following IB, it is unlikely that reduced baseline airway caliber in tetraplegia is due to processes decreasing the load on airway smooth muscle including airway cartilage softening, decreased tethering of lung parenchyma, increased airway smooth muscle in proportion to circumference, increased wall thickness, or increased secretions in airway lumens (Moreno et al., 1986).

### Table 3

<table>
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<tr>
<th>Specific airway conductance in subjects with spinal cord injury.</th>
<th>sGaw (cm H2O -1 s -1)</th>
<th>Epinephrine level (μmol/L)</th>
</tr>
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<tbody>
<tr>
<td>Tetraplegia (n = 12)</td>
<td>0.14 ± 0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>High paraplegia (n = 11)</td>
<td>0.19 ± 0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Low paraplegia (n = 11)</td>
<td>0.19 ± 0.04</td>
<td>0.16</td>
</tr>
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Data adapted from Radulovic et al. (2008), and Schmid et al. (1998). sGaw values are mean ± S.D.

* p < 0.001 compared to high paraplegia and low paraplegia.
8. Pulmonary symptoms

A survey of respiratory symptoms among 180 subjects with SCI using a modified questionnaire developed for use in general epidemiological studies (Ferris, 1978) revealed that 68% of individuals reported one or more respiratory symptom (Spungen et al., 1997). Breathlessness, the most prevalent complaint, was associated with level of injury: 73% in high tetraplegia (C5 and above not requiring mechanical ventilation), 58% in low tetraplegia (C6–C8), 43% in high paraplegia (T1–T7), and 29% in low paraplegia (T8–L3). The prevalence of chronic cough (18%), chronic phlegm production (30%), cough combined with chronic phlegm production (20%), and chronic wheeze (24%) did not differ significantly among the four groups. Of note and of potential importance, subjects with high tetraplegia reported increased breathlessness when exposed to hot air or second-hand cigarette smoke. Independent predictors of breathlessness were level of injury, cough combined with phlegm and/or wheeze, TLC (<60% predicted) and ERV (<0.6L), but not age, duration of injury, completeness of injury, a history of asthma, or current smoking (Spungen et al., 2002). Independent predictors of cough combined with phlegm and/or wheeze included current smoking, breathlessness, and FEV1 (<60% predicted), but not age, duration of injury, completeness of injury, level of injury, or a history of asthma. Other investigators have reported that breathlessness is more prevalent among those with neurologically complete cervical injury, those who need a motorized wheelchair for daily activities, and those with SCI considered non-athletes (Ayas et al., 1999; Wien et al., 1999; Grandas et al., 2005). It was determined that the use of a custom girdle significantly lowered breathlessness in patients with SCI, presumably by optimizing operating lung volumes and by decreasing abdominal compliance secondary to enhanced diaphragm performance (Hart et al., 2005). The quality and intensity of breathlessness during methacholine-induced bronchoconstriction and dynamic hyperinflation is comparable among patients with tetraplegia or asthma (Loughhead et al., 2002).

9. Methods to improve pulmonary function

As detailed in several recent review papers, a number of studies have been performed to determine if resistive inspiratory muscle training improves pulmonary function parameters in SCI (Brooks and O’Brien, 2005; Van Houtte et al., 2006). Two studies were randomized with a comparison group (Loveridge et al., 1989; Liaw et al., 2000). Meta-analysis could not be performed due to differences in study design and outcomes. Therefore, the benefit of inspiratory muscle training in tetraplegia remains unclear, and spontaneous recovery cannot be excluded as being responsible for some of the observed improvements (Stiller and Huff, 1999; Brooks and O’Brien, 2005). Recently it was reported that among 14 subjects with acute SCI (time between lesion and inclusion in the study at least 6 weeks) randomized to receive either normocapnic hyperpnea or sham training for 8 weeks, that normocapnic hyperpnea training was associated with an increase in maximum voluntary ventilation, and improved MIP and MEP (Van Houtte et al., 2008).

Two studies have evaluated the role of expiratory muscle training among individuals with SCI (Estenne et al., 1989; Gounden, 1990). Training of the pectoralis major by repetitive, strenuous, isometric contractions for 6 weeks among subjects with tetraplegia was associated with marked increases in maximal isometric muscle strength and ERV, and a decrease in RV (Estenne et al., 1989). A recent review assessing the effectiveness of expiratory muscle training (excluding electrical stimulation) concluded that training tended to improve expiratory muscle strength, VC and RV, but insufficient data was available to make conclusions concerning the effects on inspiratory muscle strength, respiratory muscle endurance, quality of life, exercise performance and respiratory complications (Van Houtte et al., 2006).

Methods available to remove patients from ventilatory support and/or increase inspired volumes include conventional phrenic nerve pacing, intramuscular diaphragmatic pacing, and intercostal nerve pacing (Glenn et al., 1984; DiMarco, 2005; DiMarco et al., 2005a). Combined intercostal and unilateral diaphragmatic pacing may be a therapeutic option in selected individuals (DiMarco et al., 2005b). Of potential importance, subjects with tetraplegia have increased diaphragmatic fatigability with sustained pacing or during ventilatory threshold loading (Nava et al., 1996; Hopman et al., 1997), which has been attributed to a combination of loss of ribcage inspiratory muscles and alterations in chest-wall properties rather than to changes in diaphragmatic function (Fugl-Meyer and Grimby, 1984).

Electrical stimulation methods to improve expiratory muscle function and cough include magnetic stimulation of the expiratory muscles by placement of a stimulation coil over the lower back, stimulation of abdominal muscles directly by placement of electrodes over the surface of the abdominal wall, and electrical stimulation applied in the region of the lower thoracic spinal cord (DiMarco, 2005). Magnetic stimulation of abdominal muscles by placement of a stimulation coil over the lower back caused increases in esophageal pressure and expiratory flow rates, increases deemed greater than those required to initiate dynamic airway compression (Estenne et al., 2000). Magnetic stimulation of the lower thoracic spine among 8 subjects with tetraplegia for 4 weeks was associated with an increase in MEP, ERV, and forced expiratory flow rate (Lin et al., 2001). The benefits, however, disappeared within 2 weeks after discontinuation of stimulation. Increases in tidal volume, MEP, FVC, FEV1 and PEF occur with direct stimulation of abdominal muscles, with coughs produced by electrical stimulation being approximately as effective as those obtained by manual assistance (Jaeger et al., 1993; Linder, 1993; Stanic et al., 2000; Langbein et al., 2001). In a randomized 4-week controlled trial, whereby neuromuscular electrical stimulation was applied to the clavicular portion of the pectoralis major and abdominal muscles there was a significant increase in PEF, FEV1, VC, MEP and MIP compared to controls (Cheng et al., 2006) that persisted for at least 3 months after cessation of therapy. Abdominal binding alone has small effects on forced expiration as assessed by expiratory flow rate and esophageal pressure and is unlikely to improve the efficiency of cough (Estenne et al., 1998). A systematic review and meta-analysis found a lack of sufficient evidence to either support or discourage the use of an abdominal binder to improve respiratory function in SCI (Wadsworth et al., 2008).

β2 adrenergic agonists have been evaluated in SCI. Signorile et al. determined in a double-blind, placebo controlled, crossover study among subjects with tetraplegia given an oral short-acting β2 adrenergic agent (metaproterenol) that forearm muscle strength and size increased significantly during the time of active drug administration (Signorile et al., 1995). Also, a placebo-controlled study of 3 individuals with SCI (two with tetraplegia and one with paraplegia) demonstrated that total work output during functional electrical stimulation cycling increased 64% during salbutamol treatment as compared to a 27% increase with placebo treatment (27%) (Murphy et al., 1999). A randomized, prospective, double-blind, placebo-controlled crossover study was performed to determine if long-term administration of a long-acting β2-adrenergic agonist improved pulmonary function parameters and static mouth pressures among subjects with tetraplegia (Grimm et al., 2006) (Table 4). During the 4-week period of salmeterol administration, PEF, FEV1, PEF, MEP and MIP increased significantly. Although the increase in MIP and MEP suggest improvement in respiratory muscle strength, this cannot be stated with certainty.
because MIP and MEP values are dependent on volume parameters at which they are measured, some of which also increased. Regardless of the mechanism, improvement in pulmonary parameters and static mouth pressures with salmeterol indicate that long-term administration of a B<sub>2</sub> adrenergic agonist should improve cough effectiveness in tetraplegia, and possibly improve respiratory symptoms.

With regard to alternative agents, a randomized study with crossover demonstrated that administration of oral theophylline at which they are measured, some of which also increased. Regard-

**Table 4**

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<th>Baseline</th>
<th>Placebo</th>
<th>Salmeterol</th>
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<tr>
<td>FVC (L)</td>
<td>3.11 ± 0.38</td>
<td>3.22 ± 0.41</td>
<td>3.36 ± 0.41†</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>2.40 ± 0.51</td>
<td>2.52 ± 0.49</td>
<td>2.74 ± 0.52‡</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>4.63 ± 1.13</td>
<td>5.01 ± 1.06</td>
<td>5.78 ± 1.20‡</td>
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<tr>
<td>MIP (cm H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>72.5 ± 18.6</td>
<td>73.9 ± 21.5</td>
<td>81.6 ± 20.8‡</td>
</tr>
<tr>
<td>MEP (cm H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>40.9 ± 16.1</td>
<td>45.9 ± 19.2</td>
<td>51.3 ± 20.0‡</td>
</tr>
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</table>

The data are mean ± S.D. Data adapted from Grimm et al. (2006). † p < 0.001 compared to baseline. ‡ p < 0.05 compared to placebo.

10. Sleep apnea in SCI

In middle-aged adults, the estimated prevalence of sleep-disordered breathing without regard to symptoms, defined as an apnea-hypopnea index (AHI) of ≥15 events/h of sleep, is 9.1% in men and 4% in women (Young et al., 1993). In four cross-sectional screening studies that included between 22 and 50 subjects with SCI, results from polysomnographic data employing the same AHI threshold to define sleep apnea yielded a prevalence ranging from 22% to 62% (Short et al., 1992; McEvoy et al., 1995; Stockhammer et al., 2002; Leduc et al., 2007). In another investigation, a diagnosis of sleep apnea was made in 9 of 20 participants (45%) based upon an apnea index of ≥5 events/h of sleep (Burns et al., 2000). Findings from screening evaluations in persons with SCI that relied upon overnight pulse oximetry with or without monitoring of body movement identified a pattern of episodic oxygen desaturation characteristic of sleep apnea in a significant number of subjects (Braun et al., 1982; Flavell et al., 1992; Cahan et al., 1993; Bach and Wang, 1994). Notwithstanding differences in methodological design and patient selection, including little representation by women and subjects with paraplegia, findings from the above studies suggest a prevalence of sleep apnea in association with SCI at least twice that reported in the general population. Obstructive sleep apnea (OSA) rather than central sleep apnea predominates; to which individuals with tetraplegia appear particularly prone. In a retrospective analysis of 584 male patients served by a Veterans Affairs SCI Service, previously diagnosed sleep apnea was identified in significantly more patients with tetraplegia (14.9%) than those with paraplegia (3.7%) (Burns et al., 2001). An association between tetraplegia and sleep apnea was also strongly suggested by findings from a longitudinal assessment of sleep disordered breathing in 25 men following acute cervical SCI, among whom sleep apnea defined as an AHI ≥10 events/h of sleep developed in 62% of subjects within 1 month of injury, and varied little during 1 year of follow-up (Berlowitz et al., 2005).

Excessive daytime sleepiness coupled with OSA is indicative of the obstructive sleep apnea syndrome (OSAS). In larger scale studies of persons with SCI that incorporated assessment of daytime sleepiness, the prevalence of OSAS ranged from 9% to 53% (Klebeck et al., 1998; Burns et al., 2000; Stockhammer et al., 2002; Leduc et al., 2007). These values exceed prevalence estimates of 4% in men and 2% in women reported in the general adult population based upon minimal diagnostic criteria (AHI ≥5 events/h plus symptoms) (Young et al., 1993). The 53% prevalence of OSAS recently reported by Leduc and colleagues from a relatively large sample of 41 subjects with tetraplegia (Leduc et al., 2007) applied diagnostic criteria recommended by the American Academy of Sleep Medicine (American Academy of Sleep Medicine Task Force, 1999); the symptom of excessive daytime sleepiness, though lacking specificity, was reported in a significantly greater proportion of subjects with (19 of 22) than without OSA (10 of 19). In other studies, symptom assessment was either non-discriminatory (Klebeck et al., 1998; Burns et al., 2000) or helped to identify only those patients with severe OSA (AHI >40 events/h of sleep) (Stockhammer et al., 2002). Given that sleep disruption is relatively common in persons with SCI, as is the use of sedative-hypnotic medication, screening for OSAS based upon a complaint of excessive daytime sleepiness has limitations (Bonekat et al., 1990; Biering-Sorensen and Biering-Sorensen, 2001). In one survey, neurogenic pain, spasticity, and voiding difficulties were cited by respondents, approximately one half of whom had cervical injury, as the greatest contributors to sleep disruption (Biering-Sorensen and Biering-Sorensen, 2001). The ability to correctly identify symptomatic OSA in persons with SCI could have important therapeutic implications if treatment was associated with improvement in sleep quality and potentially in health related quality of life as has been reported in able-bodied subjects (Jenkinson et al., 1999; Sin et al., 2002).

Recognized risk factors for OSA in the general adult population including male gender, obesity, and advancing age have been variably linked to the high prevalence of OSA among subjects with tetraplegia, although findings are not uniform due to limited sample sizes and differences in study design, patient recruitment, and diagnostic methods. Body mass index, a strong predictor of OSA severity in the general population, directly correlated with apnea severity in four (Flavell et al., 1992; Burns et al., 2001; Stockhammer et al., 2002; Leduc et al., 2007) of the seven (Short et al., 1992; Klebeck et al., 1998; Burns et al., 2000) studies involving patients with SCI in which it was evaluated. Further inspection reveals that the association between BMI and OSA appears to be stronger if analysis is limited to studies that enlisted only subjects with tetraplegia screened by polysomnography (Stockhammer et al., 2002; Leduc et al., 2007). Similarly, neck circumference, which has been applied in a prediction rule to estimate a patient’s probability of having OSA in able-bodied subjects (Flemons et al., 1994), directly correlates with apnea severity in the three studies that included only subjects with tetraplegia (McEvoy et al., 1995; Stockhammer et al., 2002; Leduc et al., 2007), and not in the two reports that included subjects with paraplegia (Short et al., 1992; Burns et al., 2000). Possible reasons for why exclusion of subjects with paraplegia appears to strengthen associations between either BMI or neck circumference and OSA in persons with tetraplegia include the greater prevalence of obesity in persons with paraplegia despite an apparently lower risk of OSA (Burns et al., 2001) and increases in neck mass that occur following cervical spinal cord injury (Frisbie and Brown, 1994). Habitual snoring, another important marker of OSA in the general population, and an independent predictor of cardiovascular disease risk (Koskenvuo et al., 1987), appears to be more prevalent, of greater intensity, and present for more years in subjects with SCI compared to a control population (Biering-Sorensen and Biering-Sorensen, 2001). In another survey, habitual snoring was reported in 42.6% of respondents, and appeared to be more common in obese subjects and those taking antispasticity medication (baclofen, diazepam) (Ayas et al., 2001). Snoring was equally represented, however, across all levels of spinal cord injury, and there is no evidence to suggest that persons with tetraplegia snore to any greater or lesser degree than persons with lower level SCI. With regard to other factors, there is insufficient evidence to link OSA prevalence in persons with SCI
to age, smoking status, alcohol consumption, duration of injury, level of injury, completeness of injury, pulmonary function, or use of antispasticity medications.

In addition to respiratory muscle weakness, several potential factors have been proposed to explain the pathophysiology underlying OSA in persons with tetraplegia. These include poor coordination between respiratory and pharyngeal dilator muscles (Cahan et al., 1993), decreased pharyngeal cross-sectional area in association with reduced lung volumes (Hoffstein et al., 1984), and possibly thickening of the oropharyngeal wall through unopposed parasympathetic stimulation of mucosal and vessel walls (Wasicko et al., 1990). Preferred adoption of a supine sleeping position common among persons with tetraplegia could impose increased gravitational stress upon the upper airway. A decrease in upper airway patency could also result from loss of lean tissue mass and fat redistribution given evidence that persons with SCI have greater adiposity for any given BMI compared to able-bodied subjects (Spungen et al., 2003). Alternatively, the possibility exists that the increased neck circumference observed in persons with tetraplegia is the result of neck muscle hypertrophy in response to increased respiratory loads (Burns et al., 2001).

Few studies have addressed treatment of OSA in persons with SCI (Biering-Sorensen et al., 1995; Burns et al., 2001, 2005; Stockhammer et al., 2002). Short term follow-up with nasal continuous positive airway pressure (CPAP) was addressed in 16 of 31 subjects with tetraplegia diagnosed with OSA in a screening study who subsequently accepted a trial of treatment (Stockhammer et al., 2002). Five discontinued therapy within 2 weeks; four because of mask discomfort, and one because of anxiety. Subjective benefit from CPAP treatment was reported in ten of 11 subjects who continued therapy, all of whom were symptomatic before therapy initiation. In a retrospective analysis of persons with tetraplegia and paraplegia, 47% of 49 subjects were receiving treatment (primarily CPAP or bi-level positive airway pressure; Bi-PAP), the remaining subjects were either intolerant of CPAP/Bi-PAP or refused treatment (Burns et al., 2001). The only study to address long-term treatment involved subjective responses to a mail-in survey sent to 72 patients with tetraplegia and paraplegia identified through a Department of Veterans Affairs SCI database, most previously diagnosed with OSA on clinical grounds rather than through participation in a random screening study (Burns et al., 2005). The response rate was 54%, amounting to 40 subjects (37 with tetraplegia) diagnosed with OSA a mean of 4.2 ± 3.0 years prior to the study. The survey indicated that the primary reasons for originally undergoing sleep apnea testing included witnessed apneas, severe snoring, and subjective sleepiness, and that of the 90% of patients (36 of 40) who had been offered CPAP/Bi-PAP therapy, 20 (54%) reported continued use for an average of 6.5 nights per week (range 3–7), 6.9 ± 1.9 h per night. The side effects of CPAP/Bi-PAP reported, which included nasal congestion, mask discomfort, throat and nasal dryness, and frequent awakenings were similar to those that have been reported in able-bodied subjects (Kakkar and Berry, 2007). Of the 17 participants who were not currently receiving any treatment, 13 had been offered CPAP and 12 had tried it, the principal reasons for non-adherence being inability to fall asleep with the mask, discomfort, and claustrophobia. Despite the realization that persons with tetraplegia often lack adequate hand function to readjust the mask, the acceptance and compliance rates for CPAP/Bi-PAP therapy compared favorably with what has been reported in able-bodied subjects (Mc Ardle et al., 1999). The acceptance rate, however, was likely an overestimation, as it was determined through medical record review that a significantly greater percentage of respondents to the survey were receiving CPAP/Bi-PAP treatment as compared to non-respondents (Burns et al., 2005). Of interest, the degree of daytime sleepiness as assessed by responses to a validated questionnaire developed in able-bodied subjects (Epworth Sleepiness Scale), revealed no differences between respondents on therapy and those receiving no treatment. A paucity of information exists regarding other forms of therapy for OSA in persons with SCI, including conservative treatments (i.e. weight loss regimens, body positioning), surgical approaches, and mandibular repositioning devices.

Obstructive sleep apnea has been associated with neurocognitive dysfunction both in the able-bodied population (Adams et al., 2001) and in persons with tetraplegia (Sajkov et al., 1998). More importantly, in the general population there is now strong evidence linking OSA to hypertension, stroke, and myocardial infarction (Nieto et al., 2000; Shahar et al., 2001). It is not yet known whether the same association exists in persons with SCI, although premature cardiovascular disease is prevalent and a major cause for mortality in this population (Myers et al., 2007).

11. Conclusions and future directions

Research performed over the past 25 years has greatly enhanced our understanding of respiratory system mechanics, the extent of compromise in pulmonary function, and the determinants of pulmonary functional decline among persons with SCI. More recent studies have fostered a greater appreciation of airway dynamics, particularly in reference to investigations of resting airway caliber, bronchial provocation, and bronchodilator responsiveness. Persons with tetraplegia, as compared to those with paraplegia or other neuromuscular diseases, appear to have a unique pattern of respiratory impairment characterized by lung volume restriction, greater compromise of expiratory compared to inspiratory muscle function, and baseline airway narrowing, all of which to varying degrees may contribute to weakened cough, ineffective pulmonary clearance, increased work of breathing, and possibly to respiratory symptomatology and bronchial hyperresponsiveness. In addition, these individuals appear to be highly susceptible to the development of OSA, although the underlying pathophysiology as it relates to respiratory muscle paralysis and/or neurogenic mechanisms, the acute hemodynamic response to obstructed apneas, the effects of treatment, and the long-term consequences of this condition are largely unknown. Despite a more global level of understanding of pulmonary physiology in other areas, however, we are still compromised in our ability to identify individuals with SCI who are at risk for development of recurrent atelectasis, pneumonia, and respiratory failure based upon known physiologic parameters, even when taking into account level and completeness of injury. This translates to a limited ability to identify at risk subgroups and to target specific therapies.

Further investigation is therefore warranted to identify the most accurate method for non-invasive measurement of respiratory muscle strength in persons with SCI, and on a larger scale to assess the subacute to long-term impact upon pulmonary function, respiratory symptoms, quality of life, and incidence of pulmonary complications associated with inspiratory/expiratory muscle training and use of anabolic agents (i.e. β2 adrenergic agonists). Ongoing research involving electrical stimulation of spinal cord segments and inspiratory/expiratory muscle groups holds promise for reducing respiratory complications and ventilatory dependence in persons with SCI, although at the present time the applicability of these techniques appears to be limited to highly selected individuals. The importance of airway obstruction and bronchial hyperreactivity in persons with tetraplegia also deserves further study, especially with regard to the potential roles of overriding cholinergic airway tone and airway inflammation in pathogenesis, and whether use of inhaled anticholinergic agents to reduce airway resistance leads to a reduction in respiratory symptoms, OSA severity, pulmonary complications, and improved quality of life.
To broadly facilitate answering these and other questions, there is a further need to develop a disease-specific respiratory questionnaire and quality of life instrument validated for use in persons with SCI.

References


