

A Center's Experience: Pulmonary Function in Spinal Cord Injury

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Received: 20 December 2013 / Accepted: 10 March 2014 / Published online: 11 April 2014
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Abstract Traumatic spinal cord injury (SCI) is associated with significant psychological and physical challenges. A multidisciplinary approach to management is essential to ensure recovery during the acute phase, and comprehensive rehabilitative strategies are necessary to foster independence and quality of life throughout the chronic phase of injury. Complications that beset these individuals are often a unique consequence of SCI, and knowledge of the effects of SCI upon organ systems is essential for appropriate management. According to the National SCI Statistical Center (NSCISC), as of 2010 there were an estimated 265,000 persons living with SCI in the United States, with approximately 12,000 incidence cases annually. Although life expectancy for newly injured individuals with SCI is markedly reduced, persons with chronic SCI are expected to live about as long as individuals without SCI; however, longevity varies inversely with level of injury. Since 2005, 56 % of persons with SCI are tetraplegic, and due to paralysis of respiratory muscles, these individuals may be especially prone to pulmonary complications, which remain a major cause of mortality among persons with chronic SCI. We at the VA Rehabilitation Research and Development Center of Excellence for the Medical Consequences of SCI at the James J. Peters VA Medical Center have devoted more than 25 years to the study of secondary medical conditions that complicate SCI. Herein, we review

pulmonary research at the Center, both our past and future endeavors, which form an integral part of our multidisciplinary approach toward achieving a greater understanding of and improving care for veterans with SCI.

Keywords Spinal cord injury · Tetraplegia · Pulmonary function · Respiratory muscle function · Nonspecific airway hyperreactivity · Airway inflammation · Obstructive sleep apnea

Historical Perspective

Fifty years ago, Drs. Stone and Keltz from the Respiratory Division at the Bronx Veterans Affairs Medical Center were among the first to describe restrictive pulmonary dysfunction in 15 individuals with cervical and thoracic spinal cord injury (SCI) [1]. Since then, multiple investigators have confirmed their findings, and it is now well known that paralysis of respiratory muscles leads to diminution in lung capacity with higher levels of injury [2–12]. Stone and Keltz [1] also surmised that “changes in the components of vital capacity [between persons with tetraplegia and paraplegia] are probably related to the differential muscle loss.” Specifically, the relative preservation of function of the diaphragm, the principal muscle of inspiration supplied by phrenic nerve roots C3–C5, distinguishes pulmonary functional abnormalities among subjects with tetraplegia and high paraplegia (T1–T6) from those associated with low paraplegia and other neuromuscular diseases affecting the respiratory system. Greater preservation of inspiratory as compared to expiratory muscle function in persons with tetraplegia translates into lower percent predicted values for forced vital capacity (FVC) compared to total lung capacity (TLC) given the

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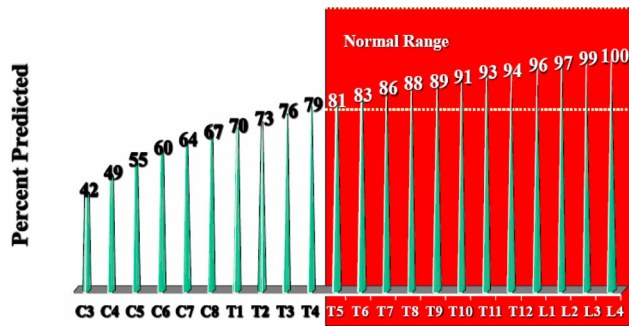


Fig. 1 Correlation of forced vital capacity (FVC) with level of SCI

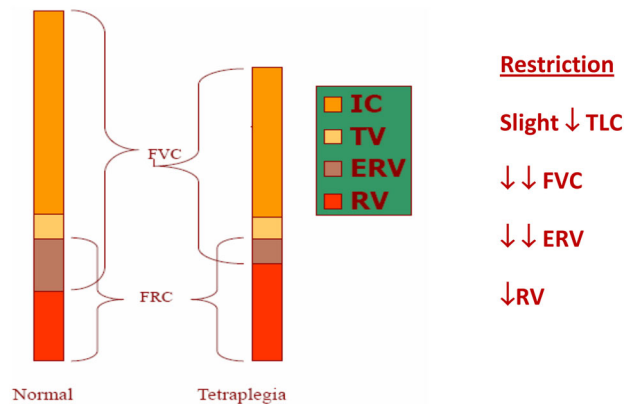


Fig. 2 Lung volume changes in persons with tetraplegia

greater dependence of FVC maneuvers on expiratory muscle strength. The inverse association between FVC and level of SCI was later corroborated in 2001 by our laboratory and collaborators at Rancho Los Amigos National Rehabilitation Hospital in Downey, CA, by cross-sectional analysis of two large outpatient populations (455 subjects); a decrease in percent predicted FVC (FVC %) was noted with increasing levels of SCI, falling below the normal range (FVC < 80 % predicted) at injury level T6 and above (Fig. 1) [12]. In addition to injury level, other investigators found that incomplete lesions mitigated FVC loss [11, 12], whereas cigarette smoking led to acceleration in the rate of decline in FVC and forced expiratory volume in 1 second (FEV₁), similar to that observed in the able-bodied population [13].

Stone and Keltz [1] were also among the first to recognize that persons with cervical SCI had significant reduction in expiratory reserve volume (ERV) and elevation in residual volume (RV) due to decreased ability to exhale forcibly below functional residual capacity (FRC). This compromise in expiratory muscle function was the result of paralysis of expiratory intercostal and abdominal muscles [1]. In addition, these investigators noted reduced

static lung compliance that correlated with reduced FVC% in subjects with cervical SCI, a finding corroborated by other investigators and suspected due to microatelectasis and/or altered surfactant properties of the lung [1, 14, 15]. Dyssynchrony and altered respiratory mechanics were later shown to further contribute to the pulmonary function abnormalities associated with tetraplegia; excessive diaphragmatic shortening due to abdominal muscle paralysis during inspiration was associated with paradoxical inward displacement of the upper anterior rib cage [15–17]. With inspiratory muscle loading, these mechanical derangements resulted in inefficiency and increased oxygen cost of breathing in association with shorter mean operational diaphragm length and distortion of the elastic properties of the chest wall [18].

A representative schematic summarizing changes in pulmonary function associated with tetraplegia is shown in Fig. 2.

Pulmonary Complications

Based upon recent epidemiologic studies, pulmonary complications remain a significant cause for morbidity and mortality among persons with SCI [19]. Paralysis of intercostal and abdominal musculature predisposes to weak cough and retained pulmonary secretions, which in turn may increase risk for atelectasis and possibly pneumonia. The greatest risk for pulmonary complications, including pulmonary thromboembolism, is during the first year post injury, although pulmonary complications remain a predominant cause of death in later years [19].

An Airway Perspective

Bronchodilator Responsiveness

In 1993, an unexpected observation was reported by our research team. A significant number of spontaneously breathing individuals with tetraplegia (14 of 34; 41 %), despite exhibiting no airflow obstruction on baseline spirometry, manifested bronchodilator responsiveness as defined by a significant increase in FEV₁ following administration of a short-acting β_2 adrenergic agonist [20]. It was postulated that heightened responsiveness in tetraplegia was due to interruption of sympathetic (bronchodilating) innervation to the lung arising from the upper six thoracic nerve roots, thereby resulting in unopposed parasympathetic (bronchoconstrictive) innervation to airways carried by vagal nerve fibers. Two years later, further support for this hypothesis was obtained when inhalation of ipratropium bromide, an anticholinergic agent, was found to elicit similar

Table 1 Effects of aerosolized ipratropium bromide on pulmonary function in persons with SCI

Pulmonary function parameter	Paraplegia (<i>n</i> = 6)			Tetraplegia (<i>n</i> = 6)		
	Pretreatment	Post-treatment	Change (%)	Pretreatment	Post-treatment	Change (%)
FVC						
L	4.00 ± 0.63	4.00 ± 0.57	0 ± 3	2.85 ± 0.83	3.07 ± 0.94*	7 ± 6
% predicted	79 ± 11	78 ± 10	0 ± 3	55 ± 12	60 ± 14*	7 ± 6
FEV₁						
L	3.24 ± 0.64	3.30 ± 0.66	2 ± 3	2.11 ± 0.57	2.37 ± 0.64*	12 ± 6
% predicted	84 ± 15	85 ± 15	2 ± 3	56 ± 14	68 ± 14*	13 ± 6
FEV ₁ /FVC ratio	82 ± 7	82 ± 0.7	0 ± 2	75 ± 4	79 ± 7	5 ± 7
FEF_{25-75%}						
L/s	3.56 ± 1.96	3.80 ± 2.01	7 ± 8	1.76 ± 0.38	2.25 ± 0.64*	27 ± 21
% predicted	89 ± 43	95 ± 45	7 ± 9	47 ± 11	60 ± 15*	27 ± 21
Vtg. L	3.82 ± 0.51	3.55 ± 0.56*	-7 ± 4	3.13 ± 0.89	2.83 ± 0.68	-9 ± 11
TLC						
L	5.97 ± 0.32	5.88 ± 0.50	-2 ± 4	4.96 ± 1.24	4.85 ± 1.18	0 ± 5
% predicted	86 ± 6	85 ± 8	-2 ± 4	68 ± 16	68 ± 14	1 ± 6
RV						
L	2.07 ± 0.68	1.96 ± 0.77	-6 ± 16	2.04 ± 0.67	1.83 ± 0.49	-8 ± 20
% predicted	102 ± 35	96 ± 39	-6 ± 15	95 ± 39	86 ± 32	-8 ± 20
RV/TLC ratio	0.35 ± 0.11	0.33 ± 0.11	-4 ± 15	0.42 ± 0.09	0.38 ± 0.08	-7 ± 17
FRC						
L	3.16 ± 0.58	3.00 ± 0.68*	-5 ± 4	2.67 ± 1.02	2.61 ± 0.86	0 ± 10
% predicted	83 ± 16	79 ± 19*	-5 ± 74	70 ± 27	68 ± 23	0 ± 10
ERV (L)	1.09 ± 0.45	1.04 ± 0.44	-7 ± 30	0.63 ± 0.56	0.78 ± 0.57*	57 ± 63
sGaw (cm H ₂ O/s)	0.26 ± 0.02	0.31 ± 0.03*	19 ± 7	0.13 ± 0.03	0.31 ± 0.11*	135 ± 47

Values given as mean ± SD

Change is percentage change in pulmonary function parameter following ipratropium bromide. Statistical significance established at $P < 0.05$

* Significant change in pulmonary function parameter following ipratropium bromide

bronchodilator responsiveness in 12 of 25 (46 %) of subjects [21].

Because individuals with tetraplegia might have difficulty performing effort-dependent forced expiratory maneuvers, we chose to investigate specific airway conductance (sGaw), an alternative to spirometry for assessment of airway caliber and bronchodilator responsiveness. The inverse of airway resistance corrected for lung volume, sGaw is determined via body plethysmography and requires little effort. As originally described by Butler et al. in 1960 [22], sGaw is felt to represent the number, length, and patency of conducting airways and is a sensitive measure of bronchodilator responsiveness [23]. Among 15 subjects with tetraplegia and 15 subjects with low paraplegia (injury level T7 and below), we found that compared to individuals with low paraplegia, baseline sGaw was significantly reduced among those with tetraplegia, and following inhalation of ipratropium bromide, a significant bronchodilator response occurred in all subjects (Table 1) [24]. This study demonstrated reduction in baseline airway

caliber due to heightened cholinergic tone, and restoration of airway caliber as suggested by normalization in sGaw following inhalation of ipratropium bromide. Further support for the hypothesis that interruption of sympathetic innervation affects airway tone came from a recent study utilizing spirometry, impulse oscillometry (IOS), and body plethysmography to assess FEV₁, respiratory resistance, and sGaw in persons with tetraplegia, high paraplegia, low paraplegia, and control subjects [25]. Among subjects with tetraplegia, sGaw was again noted to be lower than in the other groups, consistent with reduced baseline airway caliber, and by use of minimal difference to assess bronchodilation to ipratropium bromide, changes in IOS and sGaw were more sensitive than spirometry at detecting bronchodilation [25].

Airway Hyperresponsiveness (AHR)

Contemporaneously with our initial spirometric studies, the following question was posited: If obstructive physiology

could be unmasked by bronchodilator administration in persons with tetraplegia, might the opposite occur, namely, would cervical SCI be associated with nonspecific airway hyperresponsiveness (AHR) following provocation with agents such as methacholine or histamine? A finding historically associated with asthma, a positive response is defined by a $\geq 20\%$ fall in FEV₁ following increasing inhaled concentrations of the provocative agent according to established protocols. In 1994, our group found that inhalational challenge testing with the cholinergic agonist methacholine was associated with AHR in eight never-smoking individuals with tetraplegia [26]. A follow-up study examining the effects of methacholine in never-smokers, smokers, and ex-smokers with tetraplegia, high paraplegia (injury level T1–T6), and low paraplegia revealed AHR in those with tetraplegia regardless of smoking status, and in three of the six subjects with high paraplegia who had comparatively lower lung volumes; AHR was not observed in subjects with low paraplegia [27]. Subjects with tetraplegia, but not those with low paraplegia, were also found in separate studies to demonstrate AHR in response to histamine and ultrasonically nebulized distilled water [28, 29].

In a study involving 32 subjects with tetraplegia, AHR to histamine was observed in 25 subjects (78%), and these individuals had significantly lower values for spirometric indices of airway size and airway size relative to lung size [forced expiratory flow between 25 and 75% of the outflow curve (FEF_{25–75}), FEF_{25–75}% predicted, FEV₁% predicted, and the FEF_{25–75}/FVC ratio] [30]. AHR might therefore be explained by preexisting airway narrowing in that a small further reduction in airway caliber induced by a bronchoconstrictor agent would lead to marked increases in airway resistance; this is in accordance with the principal that resistance in an airway varies inversely with the fourth power of the radius [31]. Thus, similar to the mechanism postulated to account for bronchodilator responsiveness, AHR might stem from reduction in baseline airway caliber among persons with tetraplegia due to overriding cholinergic airway tone. This hypothesis was further supported by findings that pretreatment with inhaled ipratropium bromide blocked AHR in response to methacholine and ultrasonically nebulized distilled water, and that pretreatment with the γ -aminobutyric acid (GABA) agonist baclofen and oxybutynin chloride (both with anticholinergic properties) blocked methacholine-induced AHR [26, 28, 32, 33]. In addition, pretreatment with the aerosolized β_2 adrenergic agonist metaproterenol sulfate blocked methacholine- and histamine-induced AHR [34]. Not all studies, however, could explain histamine-induced AHR solely on the basis of reduction in airway caliber, because pretreatment with aerosolized ipratropium bromide, baclofen, or oxybutynin

chloride did not attenuate the bronchoconstrictor response to subsequent provocative stimulation with histamine [28, 29, 33].

Respiratory Symptoms

In 1997, we investigated the prevalence of respiratory symptoms in persons with chronic SCI stratified by level of injury [35]. A standard respiratory questionnaire was modified for subjects with limited mobility and was completed by 180 subjects. Overall, 68% of subjects reported at least one respiratory symptom. Of particular significance, a report of breathlessness, the most common symptom, was associated with level of lesion. Specifically, 73% of subjects with high tetraplegia (C5 and above not requiring mechanical ventilation) reported breathlessness compared to 58, 43, and 29% of subjects with low tetraplegia (C6–C8), high paraplegia (T1–T6), and low paraplegia (T7–L3), respectively. The prevalence of chronic cough (18%), chronic phlegm production (30%), cough combined with phlegm production (20%), and wheeze (24%) did not differ significantly among the groups. Breathlessness occurred more significantly in the group with high tetraplegia during rest or following exposure to hot air or passive smoke [35]. Among the subjects with tetraplegia, a complaint of breathlessness appeared to have no significant relationship with smoking status, whereas among subjects with paraplegia, phlegm and wheeze were reported more frequently in current smokers [32]. Altered respiratory mechanics associated with tetraplegia appear to contribute to the sensation of breathlessness and may overshadow adverse effects caused by smoking [36]. Interestingly, Loughheed et al. [37] found that the quality and intensity of breathlessness during methacholine-induced bronchoconstriction and dynamic hyperinflation were similar in subjects with tetraplegia and asthma.

Cough Effectiveness and Respiratory Muscle Strength

The most commonly performed noninvasive surrogate measures of global inspiratory and expiratory muscle strength are maximal static mouth inspiratory and expiratory pressure (MIP and MEP, respectively). Compared to normal subjects, both MIP and MEP are reduced in subjects with tetraplegia, although MEP is comparatively more reduced than MIP due to greater compromise of expiratory muscle function [4, 38]. Paralysis in subjects with cervical and high thoracic cord injury leads to loss of function of the major muscles of expiration, including the anterolateral abdominal wall, the expiratory intercostals, and the triangularis sterni [39], thus contributing to weak cough.

Table 2 Effect of salmeterol on respiratory parameters among subjects with tetraplegia ($n=11$)

	Baseline	Placebo	Salmeterol
FVC (L)	3.11 ± 0.38	3.22 ± 0.41	3.36 ± 0.41*†
FEV ₁ (L)	2.40 ± 0.51	2.52 ± 0.49	2.74 ± 0.52*†
PEF (L/s)	4.63 ± 1.13	5.01 ± 1.06	5.78 ± 1.20*†
MIP (cmH ₂ O)	−72.5 ± 18.6	−73.9 ± 21.5	−81.6 ± 20.8*†
MEP (cmH ₂ O)	40.9 ± 16.1	45.9 ± 19.2	51.3 ± 20.0*†

The data are expressed as mean ± SD

* $p < 0.001$ compared to baseline; † $p < 0.05$ compared to placebo

Residual expiratory function has been attributed to the clavicular portion of the pectoralis major muscle originating from the fifth through seventh cervical nerve segments, and the pectoralis major [40, 41]. Reduced expiratory muscle strength and cough may lead to retention of secretions and atelectasis, and consequently increased risk of pneumonia and respiratory failure.

In a systematic review of subjects with tetraplegia, it was concluded that there are insufficient data to describe the effects of resistive respiratory muscle training on inspiratory muscle strength, endurance, quality of life, exercise performance, and respiratory complications, although improvement in expiratory muscle strength has been demonstrated more consistently [42]. In one study, Estenne et al. [43] found that 6 weeks of training of the pectoralis major by repetitive strenuous isometric contractions by persons with tetraplegia was associated with a marked increase in isometric muscle strength, as well as an increase in ERV and a decrease in RV. The benefit of resistive muscle training as a noninvasive means to improve respiratory muscle strength and cough effectiveness in persons with higher levels of SCI might prove to be substantial if reduction in pulmonary complications such as atelectasis and pneumonia were realized. Electrical stimulation to improve expiratory muscle function and cough has also been shown to be beneficial in select individuals [44].

β_2 Agonists have anabolic properties, and two relatively small studies in persons with SCI using agents in this class of medication are briefly discussed [45, 46]. In the first report, by Signorile et al. [45], administration of the oral β_2 adrenergic agonist metaproterenol for 4 weeks to subjects with tetraplegia in a double-blind, placebo-controlled crossover design was associated with a significant increase in forearm muscle size and strength. In the second study, conducted by Murphy et al. [46], total work output during functional electrical stimulation cycling by three individuals with SCI increased 64 % during salbutamol treatment compared to a 27 % increase with placebo treatment. Stimulated by these preliminary studies, we performed a randomized, prospective, double-blind, placebo-controlled

crossover study to determine if administration for 4 weeks of the long-acting β_2 adrenergic agonist salmeterol improved pulmonary function parameters and static mouth pressures in subjects with tetraplegia [47]. During salmeterol administration, FVC, FEV₁, MIP, and MEP increased significantly (Table 2). Although increases in MIP and MEP suggest improvement in respiratory muscle strength, given that these measurements are also dependent on lung volume, it is possible that bronchodilation might also account for some of the observed increase [47]. Regardless of the cause, significant improvement in pulmonary function parameters following administration of salmeterol suggests that long-term use of β_2 agonists might improve cough effectiveness and reduce pulmonary complications in persons with cervical or high thoracic SCI.

To further investigate the anabolic and bronchodilator effects of β_2 agonists in persons with tetraplegia and high paraplegia, we are near completion of a randomized, double-blind, placebo-controlled trial to assess the effects of the oral β_2 agonist albuterol repetabs on spirometric parameters, static mouth pressures, and cough strength. In a second arm of the study, we are examining whether the addition of expiratory muscle training to a study drug (i.e., placebo or albuterol) affords additional gains in pulmonary function and cough effectiveness. We anticipate that administration of an oral β_2 agonist in concert with expiratory muscle training will lead to greater salutary effects on pulmonary function and cough strength than either one alone.

Role of Inflammation

As our prior work has shown, obstructive airway physiology in persons with tetraplegia is similar to that associated with mild asthma. Physiologic correlates in persons with tetraplegia include a decrease in baseline airway caliber [24], significant bronchodilator responsiveness following inhalation of a β_2 adrenergic agonist [48] or anticholinergic agent [21], and increased evidence of AHR [26–28]. In asthma, these responses are closely related to airway inflammation. In persons with tetraplegia, we hypothesized that reduced airway caliber and exaggerated bronchoconstriction are a consequence of overriding parasympathetic influence, although the role of airway inflammation is less understood. Airway inflammation could stem from recurrent respiratory infections as a result of ineffective pulmonary clearance [49], be associated with systemic inflammation as a consequence of the acute injury [50, 51], or may arise from chronic microaspiration due to esophageal dysmotility and/or gastroesophageal reflux disorder (GERD).

To investigate the potential role of airway inflammation, a preliminary investigation was performed demonstrating

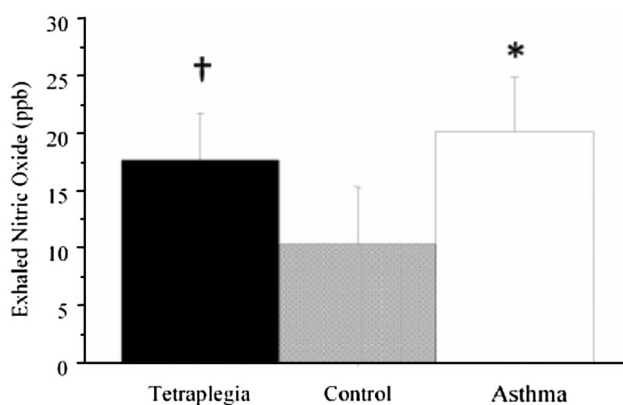


Fig. 3 Difference in exhaled nitric oxide in persons with tetraplegia or asthma versus controls. Values presented as group mean \pm SD. †Tetraplegia versus control: 17.72 ± 3.9 ppb versus 10.37 ± 4.9 ppb; $p \leq 0.01$. *Asthma versus control: 20.23 ± 4.64 ppb versus 10.37 ± 4.9 ppb; $p \leq 0.001$

that individuals with tetraplegia had elevated levels of exhaled nitric oxide (NO), comparable to levels associated with mild asthma (Fig. 3) [52]. It is now widely believed that NO generation in the airways of asthmatic subjects represents a physiologic mechanism that counteracts the bronchoconstriction caused by various stimuli, in which case NO may be a marker of the inflammatory response [53]. To expand upon these initial findings, we recently presented evidence that individuals with tetraplegia have significantly elevated levels of the inflammatory biomarker 8-isoprostane in exhaled breath condensate (EBC) when compared to mild asthmatics and able-bodied controls. In fact, the pH value of their EBC, although not significantly different than that of the mild asthmatics or controls, trended toward hyperacidity (6.03 ± 0.95 tetraplegia group vs. 6.89 ± 0.03 asthma group vs. 6.81 ± 0.28 control group) [54]. Both elevation in 8-isoprostane levels and airway acidification have been demonstrated in asthmatic patients with GERD [55, 56]. Moreover, decreased 8-isoprostane levels and normalization of EBC pH have been shown following treatment with proton pump inhibitors (PPI) in persons with GERD-induced asthma [57]. We have initiated a study in persons with SCI to determine the underlying mechanism and prevalence of GERD by investigating esophageal dysmotility and lower esophageal sphincter pressures, and to correlate findings with markers of airway inflammation obtained by EBC.

Obstructive Sleep Apnea

In four cross-sectional screening polysomnographic studies that each comprised between 22 and 50 subjects with SCI, the prevalence of obstructive sleep apnea (OSA), as defined

by an apnea–hypopnea index ≥ 15 events/h of sleep, ranged between 22 and 62 % [58–61]. Thus, the prevalence of OSA among persons with SCI appears to be far greater than that encountered in the general middle-aged population (9.1 % in men, 4 % in women) [62]. Subjects with tetraplegia appear to be more vulnerable to OSA than individuals with paraplegia, perhaps because of respiratory muscle paralysis and altered respiratory mechanics [63]. The cardiovascular and neurohormonal response to OSA in persons with tetraplegia has never been assessed, but we anticipate diminished adrenergic outflow in response to hypoxia at apnea termination, thus potentially blunting the rapid changes in cardiac output and blood pressure associated with intrathoracic pressure swings in this population compared to able-bodied controls. Overactivity of the sympathetic nervous system associated with OSA in the able-bodied population has been implicated in the development of hypertension and increased predisposition to stroke and cardiovascular disease if left untreated [64]. Due to interruption of sympathetic pathways, persons with tetraplegia have low circulating catecholamine levels and would not be expected to mount a catecholamine surge in response to apnea, nor would the rapid fluctuations in cardiac output be anticipated because of respiratory muscle paralysis and less negative intrathoracic pressure generation during apneic events. To investigate these hypotheses further, and to better define the implications of OSA in persons with tetraplegia, we have initiated a study to investigate the acute hemodynamic and neurohormonal changes accompanying obstructive apneas in persons with tetraplegia with documented OSA. The hemodynamic and neurohormonal responses to apnea will be compared among individuals with tetraplegia with and without OSA and able-bodied subjects with OSA matched for demographic characteristics and OSA severity.

Final Thoughts

Over the past 24 years, clinical investigation in our unit has greatly enhanced our understanding of respiratory system mechanics and fostered a greater appreciation of airway dynamics in subjects with SCI, particularly in regard to 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 may contribute to weakened cough, ineffective pulmonary clearance, increased work in breathing, and possibly to respiratory symptomatology and AHR. 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 OSA are largely unknown.

The ultimate goal of our investigation is to improve the health, well being, and quality of life for veterans with SCI. In our effort to attain this goal, a multidisciplinary approach to reduce the incidence of pulmonary complications is being vigorously employed.

Conflict of interest None.

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