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Systemic Inflammation and Reduced Pulmonary Function in Chronic Spinal Cord Injury

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Abstract

Objective—To evaluate the relationship between systemic inflammation and pulmonary function in persons with chronic spinal cord injury (SCI).

Design—Cross-sectional study.

Setting—Veterans Affairs Medical Center.

Participants—Fifty-nine men with chronic SCI participating in a prior epidemiologic study.

Methods—Standardized assessment of pulmonary function and measurement of plasma C-reactive protein (CRP) and interleukin-6 (IL-6).

Main Outcome Measurements—Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC).

Results—Persons with the highest values of IL-6 had the lowest %-predicted FEV_1 and FVC. There was a significant inverse linear trend between quartile of IL-6 and %-predicted FEV_1 ($P <$.

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001) and FVC ($P < .006$), unadjusted and adjusted for SCI level and completeness of injury, obstructive lung disease history, smoking, and body mass index ($P = .010$-$.039$). Although not as strong as for IL-6, there also were similar trends for %-predicted FEV_1 and FVC with CRP.

Conclusions—In chronic SCI, higher levels of IL-6 and CRP were associated with a lower FEV_1 and FVC, independent of level and completeness of injury. These results suggest that the reduction of pulmonary function after SCI is related not only to neuromuscular impairment but also to factors that promote systemic inflammation.

INTRODUCTION

Chronic spinal cord injury (SCI) is an example of a chronic medical condition associated with clinical characteristics that promote systemic inflammation [1-8]. These characteristics include an increase in central fat deposition after injury [1-3]; decreased mobility due to muscle paralysis; and recurrent skin, pulmonary, and urinary tract infections. The implications of systemic inflammation as a mechanism that contributes to chronic disease in chronic SCI have not been studied specifically. Although the mechanisms are not known, recent epidemiologic studies in persons without SCI indicate that C-reactive protein (CRP), a circulating marker of systemic inflammation, is associated with reduced pulmonary function in patients with chronic obstructive pulmonary disease (COPD) [9-12] in general population samples [13-20], including nonsmokers [21], and in young adults without known lung disease [22,23]. Inverse relationships between circulating interleukin-6 (IL-6) and forced expiratory volume in 1 second (FEV_1) also have been reported [15,19,20].

In 1994, we established the Veterans Affairs (VA) Boston SCI cohort study to define the effect of neurologic level and completeness of injury on pulmonary function and respiratory illnesses in chronic SCI [24,25]. As expected, the higher the level and more neurologically complete the injury, the greater the degree of respiratory muscle dysfunction and the lower the %-predicted forced vital capacity (FVC) and FEV_1. Assessed longitudinally, decline in FEV_1 and FVC was associated with a higher body mass index (BMI), which is associated with systemic inflammation [25]. In a subset of the VA Boston SCI cohort, we found that systemic inflammation as assessed by CRP was not significantly related to neurologic level and completeness of SCI but was related to a reduction in physical activity (as suggested by motorized wheelchair use), a higher BMI, and recurrent skin and urinary tract infections [26]. In this study, we explore novel relationships between circulating markers of systemic inflammation and pulmonary function in chronic SCI in this subset.

METHODS

Participants

Starting in 1994, in the VA Boston SCI study [24,25], participants with SCI were recruited from VA Boston or the community; they completed a health questionnaire, and a spirometry was obtained. If indicated, testing was scheduled 8 weeks or more after a respiratory illness other than a mild cold. In October 2003, the participants were asked to provide a blood sample. We previously conducted an assessment of the relationship between CRP and mobility mode in 64 men who were not using statins, who provided a blood sample between October 2003 and June 2005, and who were 2 or more years after injury [26]. We reviewed the availability of pulmonary function data in these participants. The study was approved by the VA Boston Healthcare System and Harvard Medical School institutional review boards, and all the subjects gave informed consent.

SCI Classification

SCI motor level and completeness were assessed by using the American Spinal Injury Association Impairment Scale [27]. Incomplete motor SCI was categorized as American Spinal Injury Association Impairment Scale (AIS C, majority of key muscles grade, <2/5 below the neurologic level) or AIS D (majority of key muscles, ≥3/5). The study subjects were classified into 3 groups based on injury level and severity: cervical motor complete and AIS C tetraplegia (severe tetraplegia), motor complete and AIS C paraplegia (severe paraplegia), and AIS D tetraplegia or paraplegia.

Clinical Data

A history of smoking, physician-diagnosed asthma, COPD (emphysema or chronic bronchitis), hypertension, diabetes, and heart disease treated within 10 years were obtained by standardized respiratory questionnaire [28,29]. Spirometry was based on 1994 American Thoracic Society standards [30] modified for use in SCI, as previously published [31]. Short expiratory efforts and excessive back extrapolated volume are common in SCI, but the FVC and FEV_1 are reproducible. Therefore, we accepted excessive back extrapolation and efforts that lasted less than 6 seconds if the effort was maximal and if there was an acceptable flow-volume loop and at least a 0.5-second plateau at residual volume [31]. Starting in March 2004, a dry-rolling seal spirometer (CPL; nSpire Health, Longmont, CO) was used, but, previously, a 10-L water-seal (DSII in 8 persons) or an 8-L portable spirometer (Survey III in 2 persons) was used (DSII, Survey III; Collins Pulmonary Diagnostics, currently, nSpire Health, Longmont, CO). In 3 persons, recent pulmonary function data were unavailable, and 2 persons with a history of stroke were excluded. The final cohort included 59 persons with pulmonary function data, and the best FEV_1 and FVC were used in the analysis. Fifty-six of these subjects (95%) had at least 3 acceptable efforts, with the best values of FEV_1 and FVC each within 200 mL. Spirometry and a blood sample were available within 1 month in one person, within 12 months in another, and on the same day in all others. Weight and supine length were measured [32]. Self-report of length was used in 2 participants, and weight was available by either self-report or an SCI clinic note in 4 participants.

Biochemical Analyses

Blood was drawn into an ethylediaminetetraacetic acid tube, stored with a cooler pack in an insulated container, shipped overnight to a core blood laboratory, and processed and stored as previously described [26]. Plasma CRP was determined by using a high-sensitivity immunoturbidimetric assay, and IL-6 was determined by an ultra-sensitive enzyme-linked immunosorbent assay by batch analysis at the Clinical and Epidemiologic Research Laboratory, Children's Hospital, Boston.

Statistical Analysis

General linear models (PROC GLM, SAS 9.1; SAS Institute Inc, Cary, NC) were used to model relationships between CRP and IL-6 in quartiles and %-predicted [33] FVC, FEV_1, and FEV_1/FVC. Linear trends were assessed by treating each quartile of CRP or IL-6 as an ordinal variable. In separate analyses, we adjusted for COPD history, neurologic level, and completeness of SCI, lifetime cigarette consumption (pack years), and BMI. Age was included as a covariate in analyses that assessed FEV_1/FVC and noted in Tables 2 and 3.

RESULTS

Mean (standard deviation [SD]) age was 56.2 ± 14.9 years, and mean (SD) injury duration was 20.9 ± 12.6 years (Table 1). Fifty-eight men were white, and 1 was black. One person was found to be 1.6 years after SCI. Most persons had AIS D SCI (52.5%), 32.2% had

severe paraplegia, and 15.2% had severe tetraplegia. A slightly higher proportion had a normal BMI (39%) than persons who were obese (BMI ≥ 30 kg/m^2; 30.5%) or overweight (BMI 25 kg/m^2 to <30 kg/m^2; 30.5%), and 15% reported diabetes. Median values of CRP and IL-6 were similar across SCI motor level and completeness of injury groups. As in our previous report [24], persons with severe tetraplegia had the lowest %-predicted FEV_1 and FVC, and had a higher FEV_1/FVC, findings consistent with neuromuscular weakness. Six persons reported a history of physician-diagnosed COPD (10.2%), and 8 persons reported a history of physician-diagnosed asthma (13.6%).

There was a significant inverse linear relationship between %-predicted FEV_1, %-predicted FVC, and FEV_1/FVC with IL-6 quartile (Table 2, unadjusted values, $P < .001$ to .006). When adjusting for COPD history, neurologic level and completeness of SCI, lifetime cigarette consumption (pack years) and BMI, and age in the analysis of FEV_1/FVC, the relationship between reduced pulmonary function and IL-6 did not meaningfully change. The exception to this was FEV_1/FVC, where the pattern was similar; but the association was not significant in all models ($P = .004$-.123). Although additional multivariate modeling was limited by sample size, when adjusting for neurologic level and completeness of SCI and when including lifetime cigarette consumption (pack years) and BMI as covariates, the same inverse linear trend between %-predicted FEV_1 ($P = .019$) and %-predicted FVC ($P = .052$) across IL-6 quartiles was observed.

The association between reduced %-predicted FEV_1 and FVC with CRP ($P = .034$-.050) was similar to the pattern observed for IL-6 but was not as consistent, particularly after adjustment for lifetime smoking and BMI ($P = .045$-.216) (Table 3). There was no significant relationship between FEV_1/FVC and CRP quartiles. When any obstructive lung disease history was included in regression models (ie, physician-diagnosed COPD or asthma) instead of physician-diagnosed COPD, the results were similar.

We considered whether the time of the blood draw could influence the results. In contrast to CRP, in which there is no diurnal variation [34], lower concentrations of IL-6 during the day compared with 7 AM values have been reported [35]. The blood was drawn within a narrow time range (median, 1:30 PM; interquartile range, 12 PM to 3 PM), and there was no significant relationship between the time of day and IL-6 ($P = .99$).

DISCUSSION

In this study, which assessed relationships between pulmonary function and systemic inflammation in chronic SCI, higher levels of IL-6 were significantly associated with lower %-predicted FEV_1, FVC, and FEV_1/FVC. Overall, these relationships persisted after adjustment for previously diagnosed obstructive lung disease, neurologic level and completeness of SCI, smoking history, and BMI. For CRP, relationships with %-predicted FEV_1 and FVC were similar but not as strong, and, with FEV_1/FVC, not significant. Although all covariates assessed were not statistically significant, they were included because of their potential effects on pulmonary function, as found in our larger SCI cohort [24,25]. Our sample size was relatively small in the current study, so it was not possible to meaningfully include all variables (Tables 2 and 3) in a single regression model. Although relationships between reduced pulmonary function and systemic inflammation in all regression models were not statistically significant, the consistency of the results suggests an inverse association between FEV_1 and FVC and systemic inflammation in chronic SCI.

Our findings in chronic SCI are consistent with the recent literature that describes inverse relationships between systemic inflammation and reduced pulmonary function in able-bodied individuals independent of COPD [10] and other factors that could contribute to

pulmonary dysfunction [13-23]. For example, in the Third National Health and Nutrition Examination survey, higher values of CRP were associated with a reduced FEV_1, in persons with an obstructive or a restrictive pattern, independent of age, BMI, smoking status, and previous cardiovascular disease [9]. In persons assessed at the time of a general physical examination, a significant inverse association between CRP and FEV_1 was observed both in smokers and in persons who never smoked [21]. The relationship between CRP and reduced pulmonary function was not meaningfully influenced after adjustment for age, history of coronary artery disease, statin use, or obesity. Inverse relationships between CRP and FEV_1 were also noted in young adults ages 26-32 years old [22]. In another study, a higher value of CRP at age 20 years was associated with greater decline in FEV_1 and FVC measured at age 29 years [23]. Fewer studies have assessed relationships between IL-6 and reduced pulmonary function, but the results have been similar [15,19,20].

The biologic mechanisms that account for relationships between systemic inflammation and reduced pulmonary function are not known. In COPD, as an example of a disease characterized by pulmonary inflammation, it has been speculated that the pulmonary inflammatory changes are responsible for higher levels of circulating markers of inflammation [10]. However, based on the inverse relationships between CRP and pulmonary function in young adults, in persons without known lung disease, independent of smoking, and based on the results that we obtained in the current study in individuals with chronic SCI, it also appears possible that the systemic inflammatory state may have a deleterious impact on pulmonary function. For example, in persons without COPD, an inflammatory milieu attributable to extrapulmonary sources, for example, adipose tissue, has been proposed to be a risk factor for asthma [36-38]. Our data demonstrate an inverse relationship between inflammatory markers and both FEV_1 and FVC when COPD and smoking have been accounted for (Tables 2 and 3). Further evidence of a link between systemic inflammation and pulmonary dysfunction comes from the report of an attenuation of pulmonary function decline attributable to statins because they may have systemic anti-inflammatory effects [39]. Similarly, because physical activity also may have an anti-inflammatory effect, the finding that regular exercise reduces longitudinal decline in FEV_1 in smokers also supports an inverse relationship between systemic inflammation and pulmonary function [40].

Factors specifically associated with chronic SCI promote systemic inflammation. For example, elevated CRP levels are related to pressure ulcers and indwelling bladder catheters [4]. Similarly, slowly healing pressure ulcers are associated with higher levels of IL-6 and soluble intercellular adhesion molecule-1, an adhesion molecule present in the endothelial cell wall [5]. Higher levels of CRP, IL-6, and vascular cell adhesion molecule-1 in peripheral blood have been described in 62 men with SCI compared with controls [41]. A history of heart disease, hypertension, a higher BMI, locomotive mode, and a history of pressure ulcers or urinary tract infections in the prior year were all predictors of CRP in our previous assessment of determinants of CRP in persons included in this report [26]. Motorized wheelchair users had higher CRP values compared with persons who walked with or without an assistive device. This is consistent with findings that, in persons without SCI, lesser degrees of physical activity and fitness are independently associated with higher levels of CRP and IL-6 [42-44]. These results suggest that, in addition to BMI, locomotive mode (likely as a surrogate for decreased physical activity), and recurrent infections contribute to systemic inflammation in chronic SCI.

A limitation of this investigation was its small sample size and cross-sectional nature. Nevertheless, taken together, our results and the previous observations regarding associations between reduced pulmonary function and systemic inflammation in persons without SCI suggest a novel disease pathway whereby systemic inflammation contributes to

chronic pulmonary dysfunction in SCI independent of the effects of neuromuscular impairment. Although speculative at this time, our results suggest that addressing factors that promote systemic inflammation in SCI may ameliorate longitudinal decline in pulmonary function.

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Table 1

Participant characteristics

	Motor Level and Completeness of Injury			
	Motor Complete and AIS C Tetraplegia	**Motor Complete and AIS C Paraplegia**	**All AIS D**	**Total**
Patients, n	9 (15.2%)	19 (32.2%)	31 (52.5%)	59
Age, y	51.8 [10.0]	52.0 [15.1]	60.1 [15.3]	56.2 [14.9]
Years since injury	26.3 [8.5]	20.4 [10.7]	19.6 [14.5]	20.9 [12.6]
Stature, cm	174.2 [6.3]	172.3 [8.1]	175.8 [6.7]	174.5 [7.2]
Weight, lb	174 [22.4]	178.6 [33.4]	192.1 [39.5]	185.0 [35.8]
BMI				
Normal (18.5 to <25 kg/m^2)	5 (55.6%)	7 (36.8%)	11 (35.5%)	23 (39.0%)
Overweight (25 to <30 kg/m^2)	3 (33.3%)	6 (31.6%)	9 (29.0%)	18 (30.5%)
Obese (≥30 kg/m^2)	1 (11.1%)	6 (31.6%)	11 (35.5%)	18 (30.5%)
Smoking				
Current	1 (11.1%)	2 (10.5%)	6 (19.4%)	9 (15.3%)
Former	5 (55.6%)	6 (31.6%)	16 (51.6%)	27 (45.8%)
Never	3 (33.3%)	11 (57.9%)	9 (29.0%)	23 (39.0%)
No. pack years (in ever smokers)	11.6 [9.8]	32.2 [33.8]	31.0 [22.1]	28.1 [24.3]
Heart disease	2 (22.2%)	2 (10.5%)	6 (19.4%)	10 (17.0%)
Hypertension	1 (11.1%)	5 (26.3%)	9 (29.0%)	15 (25.4%)
Diabetes	0 (0.0%)	3 (15.8%)	6 (19.4%)	9 (15.3%)
COPD	0 (0.0%)	3 (15.8%)	3 (9.7%)	6 (10.2%)
Asthma	1 (11.1%)	4 (21.1%)	3 (9.7%)	8 (13.6%)
COPD or asthma	1 (11.1%)	5 (26.3%)	5 (16.1%)	11 (18.6%)
FEV_1, L	2.7 [0.5]	3.1 [1.0]	2.9 [1.0]	2.9 [0.9]
FVC, L	3.4 [0.7]	3.9 [1.0]	3.7 [1.1]	3.7 [1.0]
FEV_1/FVC, %	81.2 [9.0]	79.6 [11.6]	76.0 [8.2]	78.0 [9.6]
%-Predicted FEV_1	74.2 [15.0]	87.9 [24.2]	82.4 [20.1]	82.9 [21.0]
%-Predicted FVC	71.1 [15.0]	84.3 [20.6]	82.0 [19.2]	81.1 [19.3]
Inflammatory markers, median [25th-75th percentile]				

	Motor Level and Completeness of Injury			
	Motor Complete and AIS C Tetraplegia	Motor Complete and AIS C Paraplegia	All AIS D	Total
CRP, mg/L	1.8 [1.0-5.3]	2.0 [0.7-4.7]	1.4 [1.0-3.6]	1.8 [1.0-4.0]
IL-6, pg/mL	2.0 [1.3-4.6]	2.0 [1.1-4.4]	2.2 [1.3-4.3]	2.1 [1.3- 4.4]

Values are expressed as mean [SD] unless otherwise indicated.

AIS = American Spinal Injury Association Impairment Scale; AIS C = most key muscles grade <2/5 below the neurologic level; AIS D = most muscles are ≥3/5; BMI = body mass index; COPD = chronic obstructive pulmonary disease; L = liters; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; CRP = C-reactive protein; IL-6 = interleukin-6.

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Table 2

IL-6 in quartiles (Q) and pulmonary function

Mean %- predicted FEV_1, adjusted for each factor listed

IL-6, pg/mL	Unadjusted	COPD	SCI level and completeness	Pack years, BMI
P for trend	<.001	.002	<.001	.014
Q 1 (≥4.4)	69.8	66.9	69.0	74.1
Q 2 (2.1 to <4.4)	78.3	74.5	76.0	78.7
Q 3 (1.3 to <2.1)	91.1	86.0	89.9	90.6
Q 4 (<1.3)	92.4	88.0	90.7	89.4

Mean %- predicted FVC, adjusted for each factor listed

IL-6, pg/mL	Unadjusted	COPD	SCI level and completeness	Pack years, BMI
P for trend	.006	.010	.007	.039
Q 1 (≥4.4)	71.5	70.8	70.1	74.5
Q 2 (2.1 to <4.4)	75.6	74.7	72.3	75.4
Q 3 (1.3 to <2.1)	90.4	89.2	88.8	91.1
Q 4 (<1.3)	86.9	85.8	84.5	84.8

Mean FEV_1/FVC, adjusted for each factor listed

IL-6, pg/mL	Unadjusted	COPD	Age, SCI level and completeness	Age, pack years, BMI
P for trend	.004	.013	.039	.123
Q 1 (≥4.4)	72.9	69.9	74.5	74.7
Q 2 (2.1 to <4.4)	77.5	73.6	79.5	78.9
Q 3 (1.3 to <2.1)	77.9	72.7	78.0	76.4
Q 4 (<1.3)	83.6	79.1	82.7	81.2

IL-6 = interleukin-6; FEV_1 = forced expiratory volume in 1 second; COPD = chronic obstructive pulmonary disease; SCI = spinal cord injury; BMI = body mass index; FVC = forced vital capacity.

Table 3

CRP in quartiles (Q) and pulmonary function

Mean %- predicted FEV_1, adjusted for each factor listed				
CRP, mg/L	**Unadjusted**	**COPD**	**SCI level and completeness**	**Pack years, BMI**
P for trend	.034	.062	.045	.216
Q 1 (≥4.0)	78.3	73.6	77.2	81.1
Q 2 (1.8 to <4.0)	77.7	70.9	76.0	80.6
Q 3 (1.0 to <1.8)	82.4	75.6	81.4	80.3
Q 4 (<1.0)	93.9	87.2	91.9	92.1

Mean %- predicted FVC, adjusted for each factor listed				
CRP, mg/L	**Unadjusted**	**COPD**	**SCI level and completeness**	**Pack years, BMI**
P for trend	.050	.068	.060	.172
Q 1 (≥4.0)	75.4	73.3	74.0	76.9
Q 2 (1.8 to <4.0)	78.5	75.5	76.4	81.2
Q 3 (1.0 to <1.8)	82.0	79.1	80.1	80.6
Q 4 (<1.0)	89.0	86.1	86.8	88.0

Mean FEV_1/FVC, adjusted for each factor listed				
CRP, mg/L	**Unadjusted**	**COPD**	**Age, SCI level and completeness**	**Age, pack years, BMI**
P for trend	.090	.165	.355	.794
Q 1 (≥4.0)	77.0	73.5	79.8	80.2
Q 2 (1.8 to <4.0)	74.9	69.8	74.4	74.3
Q 3 (1.0 to <1.8)	77.6	72.5	78.0	76.7
Q 4 (<1.0)	82.6	77.6	81.6	80.6

CRP = C-reactive protein; FEV_1 = forced expiratory volume in 1 second; COPD = chronic obstructive pulmonary disease; SCI = spinal cord injury; BMI = body mass index; FVC = forced vital capacity.

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