Longitudinal Change in FEV_1 and FVC in Chronic Spinal Cord Injury

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***Rationale*: Although respiratory dysfunction is common in chronic spinal cord injury (SCI), determinants of longitudinal change in FEV_1 and FVC have not been assessed.**

***Objectives*: Determine factors that influence longitudinal lung function decline in SCI.**

***Methods*: A total of 174 male participants (mean age of 49 and 17 yr after injury) completed a respiratory questionnaire and underwent spirometry over an average follow-up of 7.5 years (range, 4–14 yr).**

***Measurements and Main Results*: In multivariate models, longitudinal decline in FEV_1 was significantly related to continued smoking, persistent wheeze, an increase in body mass index, and respiratory muscle strength. Aging was associated with an accelerated decline in FEV_1 (for ages <40, 40–60, >60 yr: -27, -37, and -71 ml/yr, respectively). Similar effects were observed for FVC.**

***Conclusions*: Longitudinal change in FEV_1 and FVC was not directly related to level and severity of SCI, but was attributable to potentially modifiable factors in addition to age. These results suggest that weight control, smoking cessation, trials directed at the recognition and treatment of wheeze, and efforts to improve respiratory muscle strength may slow lung function decline after SCI.**

Keywords: respiratory function; longitudinal studies; smoking; body mass index

Diseases of the respiratory system are an important cause of morbidity and mortality in persons with chronic spinal cord injury (SCI) (1–3). Although there is improvement in pulmonary function over the first postinjury year, the natural history of change in pulmonary function after this time period has not been described. We established the VA Boston SCI Health Study to assess determinants of respiratory health and pulmonary function in chronic SCI and have reported that a lower FEV_1 and FVC at study entry was associated with an increased risk of dying over a median of 4.5 years (3). In addition to age and SCI level and completeness of injury, significant cross-sectional determinants of pulmonary function were lifetime pack-years smoked, persistent wheeze, respiratory muscle performance, and years since injury (4).

Because SCI results in muscle paralysis that is determined by the neurologic level and completeness of injury, higher neurologic level and more complete injury will result in a greater degree of respiratory muscle dysfunction and a reduction in pulmonary function (i.e., FEV_1 and FVC) (5). However, there are not any reports describing whether persons with a higher neurologic level and more complete injury will have a more rapid longitudinal decline in FEV_1 and FVC than persons with less severe SCI or if other risk factors are important. In this study, we have extensively characterized potential risk factors for lung function decline with the goal of prospectively identifying factors associated with longitudinal change in FEV_1 and FVC in a cohort of persons with chronic SCI. Some of these results have been previously reported in the form of an abstract (6).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Respiratory dysfunction is common in chronic spinal cord injury; however, determinants of longitudinal change in FEV_1 and FVC have not been assessed.

What This Study Adds to the Field

Longitudinal change in FEV_1 and FVC was not directly related to level and severity of SCI, but was attributable to potentially modifiable factors in addition to age. These results suggest that weight control, smoking cessation, trials directed at the recognition and treatment of wheeze, and efforts to improve respiratory muscle strength may slow lung function decline after SCI.

METHODS

Between 1994 and 2001, 426 participants free from acute illness, 1 year or more post-SCI, and without tracheostomy or requiring ventilation were recruited. Recruitment methodology has been described previously (4). Participants with other neurologic conditions (n = 23), lung resection (n = 1), and without a detectable SCI level (n = 5) were excluded. Follow-up started in 1998 with efforts to conduct tests every 2 years. This report includes participants with at least 4 years of follow-up through December 2005. There were 37 participants who had their first test as part of a feasibility study using the same methodology (1989–1993), and these tests were included (7). Because the relationship between pulmonary function and stature depends on race and sex, nonwhite males (n = 19) and females (n = 8) were excluded. The cohort included 174 white males with two to six tests performed a mean of 3.2 years apart over a mean of 7.5 years (4–14 yr). There were 577 test

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sessions and 403 intervals where change in FEV_1, FVC, and FEV_1/FVC were evaluated. Approval was obtained from the institutional review boards of VA Boston Healthcare System, Harvard Medical School, and Brigham and Women's Hospital, and informed consent was obtained.

Motor level and completeness of injury were assessed by exam using American Spinal Injury Association (ASIA) guidelines (8). Participants with incomplete motor SCI were categorized as ASIA C (majority of key muscles below the neurologic level grade <2 [of 5]) or ASIA D (most muscles graded ≥3 [of 5]). The cohort was further grouped into quadriplegia (cervical complete motor and ASIA C), paraplegia (other complete motor and ASIA C), and all others (ASIA D).

A respiratory health questionnaire (ATS-DLD-78) (9) was used to define chronic cough, chronic phlegm, any wheeze and persistent wheeze, physician-diagnosed asthma, heart disease treated in the past 10 years, hypertension, and chronic obstructive pulmonary disease (COPD) at each test session.

Spirometry was based on ATS standards (10) modified for use in SCI (7, 11). We have demonstrated that short expiratory efforts and excessive back extrapolation are more common than in the able-bodied and that the FVC and FEV_1 are reproducible (11). Therefore, we accepted excessive back extrapolation and efforts lasting less than 6 seconds if the effort appeared maximal, there was an acceptable flow–volume loop, and at least a 0.5-second plateau at residual volume. A 10-L water seal (80%) or an 8-L portable spirometer (6%) was used through March 2004, when a dry-rolling seal spirometer (14%) was used. Ninety percent (521) of the test sessions had at least three acceptable efforts with the two best values of FEV_1 and FVC each within 200 ml, 9% (49) had two acceptable efforts (approximately half reproducible), and 1% (7) performed one acceptable effort. The highest values were used and predicted values were calculated (12). Maximum inspiratory pressure (MIP) measured at FRC was the maximum of three values (13). Supine stature was measured in 90% of subjects, and if the subject declined to be measured or if there were joint contractures, self-report was used. Additional details are provided in the online supplement.

Linear mixture models (PROC MIXED, SAS version 9.1; SAS Institute, Cary, NC) with a first-order autoregressive covariance structure were used. Change in FEV_1, FVC, and FEV_1/FVC was calculated, and the corresponding change in age, body mass index (BMI), smoking (current, started, stopped, former, or never), and respiratory symptom (current, started, stopped, or never) assessed. We also assessed whether change in FEV_1 and FVC and FEV_1/FVC (between an initial test [t] and the subsequent test [$t + 1$]) was related to characteristics (i.e., years since injury, MIP, pack-years, age) at test $t + 1$. Quadratic terms for age and stature were assessed (12, 14). Residual plots were examined. Results are expressed as change in FEV_1 and FVC in milliliters and change in FEV_1/FVC × 100 over an average duration of 3.2 years between tests.

RESULTS

Baseline Model

Characteristics at study entry are presented in Table 1. Mean age was 49.3 ±14.1 years, participants had been injured a mean of 17.0 ±12.6 years, and 25% were current smokers, 41% were former smokers, and 35% were never-smokers. We defined a baseline regression model that included stature and age. Stature was a significant predictor of change in FVC (−4.7 ml; 95% confidence interval [CI], −8.6 to −0.8; $P = 0.02$) and a borderline predictor of change in FEV_1 (−2.6 ml; 95% CI, −5.6 to 0.3; $P = 0.08$). The effect of age on FEV_1 and FVC was best described by including terms for age and age squared at test $t + 1$ and for change in age, which is consistent with an age-related acceleration in the rate of decline in FEV_1 and FVC. There was no significant effect of age ($P = 0.52$), age squared ($P = 0.59$), change in age ($P = 0.81$), or stature ($P = 0.18$) on change in FEV_1/FVC and these were not included in subsequent models.

When added to the baseline model, neurologic level and completeness of SCI (quadriplegia, paraplegia, all others) was not a significant predictor of change in FEV_1 ($P = 0.99$), FVC ($P = 0.85$), or FEV_1/FVC ($P = 0.68$). Other factors not contributing to the baseline regression model for FEV_1, FVC, or FEV_1/FVC

TABLE 1. CHARACTERISTICS OF COHORT AT STUDY ENTRY

Characteristics	Motor Level and Severity of Injury: Quadriplegia Motor Complete and ASIA C (*n = 44*)	Paraplegia Motor Complete and ASIA C (*n = 83*)	ASIA D (*n = 47*)	Total (*n = 174*)
Age, yr (SD)	47.3 (13.0)	49.4 (15.2)	51.1 (13.2)	49.3 (14.1)
Stature, cm (SD)	178.8 (8.7)	176.9 (7.3)	178.7 (8.1)	177.9 (7.9)
Body mass index, kg/m² (%)				
Normal (<25)	21 (47.7)	34 (41.0)	19 (40.4)	74 (42.5)
Overweight (25 to <30)	10 (22.7)	30 (36.1)	20 (42.6)	60 (34.5)
Obese (≥30)	13 (29.6)	19 (22.9)	8 (17.0)	40 (23.0)
Years postinjury (SD)	18.8 (12.1)	18.5 (13.5)	12.7 (10.3)	17.0 (12.6)
Smoking, n (%)				
Current smoker	9 (20.5)	12 (14.5)	22 (46.8)	43 (24.7)
Past smoker	22 (50.0)	34 (41.0)	15 (31.9)	71 (40.8)
Never smoker	13 (29.6)	37 (44.6)	10 (21.3)	60 (34.5)
Lifetime pack-years (for ever-smokers) (SD)	26.3 (23.3)	24.0 (21.9)	35.0 (28.7)	28.2 (24.9)
Chest injuries/operations, n (%)	9 (20.5)	33 (39.8)	11 (23.4)	53 (30.5)
COPD, n (%)	5 (11.4)	7 (8.4)	5 (10.6)	17 (9.8)
Asthma, n (%)	4 (9.1)	8 (9.6)	5 (10.6)	17 (9.8)
Heart disease, n (%)	2 (4.6)	4 (4.9)	3 (6.4)	9 (5.2)
Hypertension, n (%)	7 (15.9)	27 (32.5)	9 (19.2)	43 (24.7)
Chronic cough, n (%)	8 (18.2)	13 (15.7)	13 (27.7)	34 (19.5)
Chronic phlegm, n (%)	10 (22.7)	11 (13.3)	18 (38.3)	39 (22.4)
Any wheeze, n (%)	20 (45.5)	32 (38.6)	25 (53.2)	77 (44.3)
Persistent wheeze, n (%)	6 (13.6)	11 (13.3)	12 (25.5)	29 (16.7)
MIP*, cm H_2O (SD)	78.0 (27.5)	102.0 (33.1)	87.6 (32.4)	91.6 (32.9)
FEV_1, L (SD)	2.6 (0.9)	3.3 (0.8)	3.2 (0.7)	3.1 (0.8)
FVC, L (SD)	3.3 (1.0)	4.2 (0.9)	4.3 (0.9)	4.0 (1.0)
FEV_1/FVC, % (SD)	79.4 (10.8)	79.3 (8.4)	75.9 (8.1)	78.4 (9.1)
Percent-predicted FEV_1 (SD)	64.9 (18.4)	85.1 (15.7)	80.8 (10.6)	78.8 (17.3)
Percent-predicted FVC (SD)	63.9 (16.9)	83.7 (14.4)	83.2 (12.0)	78.6 (16.8)

Definition of abbreviations: ASIA = American Spinal Injury Association; MIP = maximum inspiratory pressure.

* Thirty-nine persons are missing baseline MIP.

were a history of chest injury or chest operation, asthma, COPD, hypertension, and heart disease ($P = 0.36$ to 0.97). Few persons were using bronchodilators (8 subjects over 577 test sessions), and there was no effect on change in FEV_1, FVC, or FEV_1/FVC.

Multivariate Models

In a model including age, stature, and change in BMI, current smokers had a significant decline in FEV_1 of −68.6 ml ($P = 0.04$) (Table 2). Among current smokers there was a decline in FEV_1 of 1.3 ml/pack-year assessed at test $t + 1$ (95% CI, −2.6 to 0.04; $P = 0.06$). An increase in BMI was a significant predictor of decline in FEV_1 (−23.8 ml/kg/m^2; $P < 0.001$) and FEV_1/FVC (−0.5; $P < 0.0001$) (Table 2). Because we found that the BMI of obese and overweight participants increased on average by 0.88 kg/m^2 and 0.35 kg/m^2, respectively, across a test session, and participants with a normal BMI had an average decrease in BMI of −0.36 kg/m^2, we examined change in FEV_1,FVC within BMI category. An increase in BMI among obese and overweight participants was associated with a significant decline in FEV_1 (−31.1 ml/kg/m^2; 95% CI, −48.0 to −14.1; and −55.4 ml/kg/m^2; 95% CI, −78.6 to −32.2, respectively) and FVC (−32.3 ml/kg/m^2; 95% CI, −53.8 to −10.8; and −53.8 ml/kg/m^2; 95% CI, −83.2 to −24.4, respectively). In obese and overweight participants, an increase in BMI was also associated with an overall decrease in FEV_1/FVC (−0.27; 95% CI, −0.52 to −0.01). In contrast, within the normal BMI category, the relationship with change in BMI was positive and an increase in BMI was associated with a significant increase in both FEV_1 and FVC (28.9 ml/kg/m^2; 95% CI, 3.2 to 54.6; and 81.8 ml/kg/m^2; 95% CI, 49.4 to 114.2, respectively).

Respiratory Symptoms

In a model including age, stature, change in BMI, and smoking status, persistent wheeze (reported at test t and $t + 1$) was associated with a significant decline in FEV_1 (−95.4; $P = 0.02$) and FEV_1/FVC (−1.8%; $P = 0.02$) (Table 3). In a separate model, cessation of any wheeze was associated with a significant improvement in FEV_1 (+102; $P = 0.02$) (Table 4). The effect of wheeze on change in FVC was similar ($P = 0.09$ and 0.054, respectively) for persistent wheeze and cessation of any wheeze (Tables 3 and 4). Cough and phlegm were not significantly associated with change in FEV_1 ($P = 0.32$ and 0.80, respectively) or FVC ($p = 0.65$ and 0.87, respectively), but the onset of cough (31 test sessions) and the onset of phlegm reported at $t + 1$ (43 test sessions) were associated with a significant decline in FEV_1/FVC (−2.0; 95% CI, −4.0 to −0.1; $P = 0.04$; and −3.1; 95% CI, −4.7 to −1.5; $P = 0.0003$, respectively).

Respiratory Muscle Strength

To explore the relationship between respiratory muscle strength and lung function, we divided MIP at test $t + 1$ into quartiles (373 test intervals in 167 participants). Persons in the lowest MIP quartile (<61 cm H_2O) had a greater decline in FEV_1 (−75.0 ml/cm H_2O; 95% CI, −157.1 to 7.1; $P = 0.073$) and FVC (−137.0 ml/cm H_2O; 95% CI, −245.5 to −28.5) compared with persons in the highest quartile (>118 cm H_2O) after adjusting for age, stature, change in BMI, and smoking status. Effects on decline in FVC and FEV_1 in the other quartiles were not significant ($P > 0.57$). There was no significant difference in FEV_1/FVC by MIP quartiles ($P > 0.12$). Participants in the lowest MIP quartile had the greatest average decline in MIP (−22.0 cm H_2O), whereas in the second and third quartiles the change was less (−10 and −4 cm H_2O, respectively). Participants in highest MIP quartile had an average increase in MIP of +23.5 cm H_2O.

Age

To further describe the effects of aging on decline in FEV_1 and FVC in ml/year, we included indicator variables for different age groups and adjusted for change in BMI, stature, and smoking status in multivariate models. For the age groups <40, 40–60, >60 years, change in FEV_1 was −27 ml/year (95% CI, −56.4 to 2.8), −37 ml/year (95% CI, −57.0 to −16.1), and −71 ml/year (95% CI, −93.5 to −48.5), and change in FVC was −39 ml/year (95% CI, −79.0 to 0.2), −29 ml/year (95% CI, −56.0 to −1.5), and −73 ml/year (95% CI, −103.0 to −42.9), respectively.

Effect Modification

Among subjects with motor complete or ASIA C quadriplegia and paraplegia, there was a suggestion of a greater decline in FEV_1 with greater duration of injury assessed at test $t + 1$ (−1.9 ml for each yr of injury; 95% CI, −4.0 to 0.2), adjusting for age, stature, change in BMI, and smoking status. The effect of years since injury among persons with ASIA D SCI was not significant (−0.4 ml for each yr of injury; 95% CI, −3.3 to 2.4).

DISCUSSION

This study is the first of which we are aware that assesses relationships between clinical factors and longitudinal change in FEV_1 and FVC in chronic SCI. Previous investigations of pulmonary function in SCI have focused on cross-sectional relationships (4, 15–22). There was an age-related acceleration

TABLE 2. MULTIVARIATE EFFECTS OF BASELINE VARIABLES, BODY MASS INDEX, AND SMOKING STATUS ON CHANGE IN FEV_1, FVC, AND FEV_1/FVC

	ΔFEV_1		ΔFVC		$\Delta(FEV_1/FVC)$	
Covariate	β*	95% Confidence Limits	β*	95% Confidence Limits	β*	95% Confidence Limits
Change in age	−26.3	−44.3, −8.3	−35.2	−58.4, −12.1		
Age	11.1	−1.1, 23.3	21.0	4.5, 37.6		
Age^2	−0.1	−0.2, −0.02	−0.2	−0.4, −0.1		
Stature, cm	−2.8	−5.6, 0.1	−4.8	−8.7, −0.8		
Change in BMI, kg/m^2	−23.8	−36.2, −11.4	−11.4	−27.5, 4.8	−0.5	−0.7, −0.3
Smoking status†						
Current (obs = 93)	−68.6	−133.3, −4.0	−45.0	−133.1, 43.1	−1.0	−2.2, 0.2
Started (obs = 7)	−94.4	−314.1, 125.4	−7.1	−293.5, 279.3	−2.5	−6.6, 1.6
Stopped (obs = 15)	−59.0	−213.5, 95.5	−31.7	−234.2, 170.9	−1.4	−4.2, 1.4
Ex (obs = 151)	−22.3	−80.3, 35.6	−32.8	−111.7, 46.1	0.1	−1.0, 1.1

Definition of abbreviations: β = regression coefficient; BMI = body mass index; ΔFEV_1 = change in FEV_1 in ml (between two tests); $\Delta(FEV_1/FVC) = \Delta(FEV_1/FVC) \times 100$ (between two tests); ΔFVC = change in FVC in ml (between two tests).

* Change over an average of 3.2 years.

† Reference is never-smokers (137 test intervals).

TABLE 3. EFFECTS OF PERSISTENT WHEEZE ON CHANGE IN FEV_1, FVC, AND FEV_1/FVC ADJUSTED FOR BASELINE VARIABLES*, SMOKING, AND BODY MASS INDEX

	ΔFEV_1		ΔFVC		$\Delta FEV_1/\Delta FVC$	
Covariate	β†	95% Confidence Limits	β†	95% Confidence Limits	β†	95% Confidence Limits
Change in BMI	−25.2	−37.6, −12.7	−12.7	−28.9, 3.6	−0.5	−0.7, −0.3
Persistent wheeze‡						
Current (obs = 40)	−95.4	−176.2, −14.7	−93.2	−202.7, 16.3	−1.8	−3.3, −0.3
Started (obs = 26)	−58.9	−170.5, 52.8	−66.8	−212.7, 79.0	−0.9	−3.0, 1.2
Stopped (obs = 25)	1.0	−113.0, 114.9	−1.9	−151.7, 147.9	0.8	−1.3, 2.9

For definition of abbreviations, *see* Table 2.

* Stature (cm), age at time $t + 1$, age squared at time $t + 1$, and change in age.

† Change over an average of 3.2 years.

‡ Reference is no report of persistent wheeze (312 test intervals).

in the rate of decline in FEV_1 and FVC. After adjusting for stature and age, significant determinants of longitudinal decline in FEV_1 included current smoking, an increase in BMI among persons who were obese or overweight, and wheeze. Participants with the lowest MIP had a greater decline in FEV_1 and FVC compared with persons with the greatest MIP.

The results of this study suggest a model of pulmonary function loss after SCI in which neurologic completeness and level of injury account for a reduction in the *level* of FEV_1 and FVC, but do not directly influence longitudinal decline. Decline in FVC and FEV_1 in persons without SCI is known to accelerate with age, and although the effect of age cannot be directly compared with previous studies, our results indicate that effect is of similar magnitude as in able-bodied persons (23). Cross-sectional studies, including our own, have described a significant age-independent association between years of injury and lower values of FEV_1 and FVC that were greatest in persons with higher and more neurologically complete SCI (4, 14, 15). After SCI, lung and rib cage compliance decrease, a process that could account for an effect of injury duration on decline in FEV_1 and FVC (24, 25). In the current study, we also describe an effect of years postinjury on FEV_1 in persons with motor complete and ASIA C quadriplegia and paraplegia. The effect was small and of borderline significance, probably because the rate of change of lung and rib cage compliance is slow relative to the average follow-up time of the cohort.

As in able-bodied persons, continued smoking was associated with a greater loss of FEV_1 and FVC compared with never-smokers, and the rate of decline was similar to that of able-bodied individuals (26). In our previous cross-sectional analysis, we demonstrated with each pack-year smoked a decrease in FEV_1 of similar magnitude to our current study (4).

We also found that an increase in BMI was a significant predictor of decline in FEV_1 and FVC in persons who were obese or overweight. Overall, an increase in BMI was a significant predictor of a decline in FEV_1/FVC. In our cross-sectional study, an increase in BMI was also associated with a reduction in FEV_1/FVC (4). Several longitudinal studies in able-bodied individuals have demonstrated an inverse relationship between BMI or weight gain and pulmonary function (27–30). Lazarus and colleagues (31) found that both obesity itself and the pattern of body fat distribution had independent effects on ventilatory function, and a central pattern of fat distribution was associated with lower values of FEV_1 and FVC after adjusting for BMI. After SCI there is also is an increase in fat mass and a decrease in lean tissue mass. Central fat, fat in the limbs below the level of injury, and in some studies an increase in fat in nonparalyzed limbs above the level of injury have been described (32, 33). Studies assessing body fat distribution in SCI have demonstrated an 8 to 18% increase in fat mass compared with that in able-bodied persons (33, 34). Although a greater BMI may result in mechanical loading of the chest wall and reduced pulmonary function, adiposity is also associated with greater levels of circulating markers of systemic inflammation that have been linked to reduced pulmonary function in able-bodied individuals (35–39). In participants with a normal BMI, an increase in BMI was associated with a significant increase in FEV_1 and FVC. It is possible that, in these individuals, changes in BMI are a surrogate for differences in respiratory muscle strength.

Persistent wheeze was a significant predictor of FEV_1 decline, and cessation of any wheeze was associated with a significant increase in FEV_1. In able-bodied persons, wheeze has been associated with lower values of FEV_1, both cross-sectionally (40) and longitudinally (41), and is a risk factor for developing asthma later in life (42). The onset of cough and phlegm was associated with a significant decline in FEV_1/FVC. An early study by Fletcher and coworkers in able-bodied individuals found that chronic cough and phlegm were not associated with lung function decline (43), whereas more recent studies have reported significant associations (44, 45).

TABLE 4. EFFECTS OF ANY WHEEZE ON CHANGE IN FEV_1, FVC, AND FEV_1/FVC ADJUSTED FOR BASELINE VARIABLES*, SMOKING, AND BODY MASS INDEX

	ΔFEV_1		ΔFVC		$\Delta FEV_1/\Delta FVC$	
Covariate	β†	95% Confidence Limits	β†	95% Confidence Limits	β†	95% Confidence Limits
Change in BMI	−21.5	−33.8, -9.1	−9.2	−25.4, 6.9	−0.5	−0.7, -0.3
Any wheeze‡						
Current (obs = 116)	−30.9	−88.4, 26.6	−19.8	−98.4, 58.8	−0.9	−2.0, 0.2
Started (obs = 38)	−62.5	−155.9, 30.8	−83.5	−206.5, 39.5	−0.4	−2.2, 1.3
Stopped (obs = 51)	102.2	17.0, 187.3	109.9	−1.9, 221.8	0.5	−1.1, 2.0

For definition of abbreviations, *see* Table 2.

* Stature (cm), age at time $t + 1$, age squared at time $t + 1$, and change in age.

† Change over an average of 3.2 years.

‡ Reference is no report of any wheeze (198 test intervals).

Persons in the lowest MIP quartile had a greater decline in FVC and FEV_1 and also had the greatest decline in MIP across each test interval. This is consistent with an effect of respiratory muscle performance on FVC and FEV_1 and can be understood by considering the pressure–volume characteristic of the respiratory system (46, 47). In our cross-sectional analysis, a greater MIP was associated with a greater FEV_1 and FVC (4). Near the extremes of the vital capacity, the pressure–volume characteristic of the respiratory system is curvilinear. As a result, changes in MIP produce only small changes in vital capacity (applicable to our subjects with the greatest MIP and who are likely to have the largest FVC and FEV_1). In the midrange of the vital capacity (applicable to our subjects with the weakest respiratory muscles and likely to have a lower FVC and FEV_1), the pressure–volume characteristic of the respiratory system is more linear. Compared with persons with the greater MIP, similar changes produce more substantial changes in vital capacity due to a more linear pressure–volume relationship, thereby accounting for the greater decline in FVC and FEV_1 seen in the subjects with the lowest MIP.

Some limitations need to be considered. The analysis was limited to white male subjects with SCI who live primarily in New England. However, we are not aware of data showing that clinical effects on FEV_1 and FVC vary widely based on race, sex, or location. We also included test sessions for which persons did not produce three acceptable and two reproducible values for FVC and FEV_1. As described in able-bodied individuals (48, 49), there was concern that excluding these sessions would exclude persons with greater impairment. Although these persons tended to have lower values of FVC and FEV_1, analyses using an indicator variable to adjust for these test sessions did not influence results. Although some studies have found that self-reported stature may be overestimated (50), analyses conducted adjusting for whether stature was measured or stated also did not influence results. Additional analyses adjusting for whether weight was measured or stated at time $t + 1$ (using an indicator variable) in the regression did not influence results.

Although SCI results in impairment of pulmonary function, our study demonstrates that decline in FEV_1 and FVC in chronic SCI is not directly related to SCI neurologic level and severity. As in able-bodied persons, longitudinal decline in those with SCI is accounted for by aging and current smoking. Factors less appreciated but also described in able-bodied individuals include an increase in BMI and wheeze. We also describe an effect of respiratory muscle performance on longitudinal decline in FEV_1 that has not been previously described. These results suggest that, in SCI, studies to reduce longitudinal decline in FEV_1 and FVC and perhaps improve survival should focus on smoking cessation, weight reduction, recognition and management of wheeze, and improvements in respiratory muscle strength.

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References

1. DeVivo MJ, Krause JS, Lammertse DP. Recent trends in mortality and causes of death among persons with spinal cord injury. *Arch Phys Med Rehabil* 1999;80:1411–1419.
2. Soden RJ, Walsh J, Middleton JW, Craven ML, Rutkowski SB, Yeo JD. Causes of death after spinal cord injury. *Spinal Cord* 2000;38:604–610.
3. Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gagnon D, Brown R. A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* 2005;43:408–416.
4. Jain NB, Brown R, Tun CG, Gagnon D, Garshick E. Determinants of FEV_1, FVC, and FEV_1/FVC in chronic spinal cord injury. *Arch Phys Med Rehabil* 2006;87:1327–1333.
5. Almenoff PL, Spungen AM, Lesser M, Bauman WA. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. *Lung* 1995;173:297–306.
6. Stolzmann KL, Gagnon DR, Brown R, Tun CG, Jain N, Garshick E. Determinants of longitudinal change in FEV_1 and FVC in spinal cord injury [abstract]. *J Spinal Cord Med* 2007;30:179–180.
7. Ashba J, Garshick E, Tun CG, Lieberman SL, Polakoff DF, Blanchard JD, Brown R. Spirometry–acceptability and reproducibility in spinal cord injured subjects. *J Am Paraplegia Soc* 1993;16:197–203.
8. Marino RJ, Barros T, Biering-Sorenson F, Burns SP, Donovan WH, Graves DE, Haak M, Hudson LM, Priebe MM. International standards for neurological classification of spinal cord injury. *J Spinal Cord Med* 2003; 26:S50–S56.
9. Ferris BG. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 1978;118:1–120.
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, *et al.* Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
11. Kelley A, Garshick E, Gross ER, Lieberman SL, Tun CG, Brown R. Spirometry testing standards in spinal cord injury. *Chest* 2003;123:725–730.
12. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
13. Tully K, Koke K, Garshick E, Lieberman SL, Tun CG, Brown R. Maximal expiratory pressures in spinal cord injury using two mouthpieces. *Chest* 1997;112:113–116.
14. Dockery DW, Ware JH, Ferris BG Jr, Glicksberg DS, Fay ME, Spiro A III, Speizer FE. Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never-smokers in six US cities. *Am Rev Respir Dis* 1985;131:511–520.
15. Linn WS, Adkins RH, Gong H Jr, Waters RL. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil* 2000;81:757–763.
16. Linn WS, Spungen AM, Gong H Jr, Adkins RH, Bauman WA, Waters RL. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord* 2001;39:263–268.
17. Fugl-Meyer AR, Grimby G. Ventilatory function in tetraplegic patients. *Scand J Rehabil Med* 1971;3:151–160.
18. Fugl-Meyer AR. Effects of respiratory muscle paralysis in tetraplegic and paraplegic patients. *Scand J Rehabil Med* 1971;3:141–150.
19. Kokkola K, Moller K, Lehtonen T. Pulmonary function in tetraplegic and paraplegic patients. *Ann Clin Res* 1975;7:76–79.
20. Ohry A, Molho M, Rozin R. Alterations of pulmonary function in spinal cord injured patients. *Paraplegia* 1975;13:101–108.
21. Linn WS, Spungen AM, Gong H Jr, Bauman WA, Adkins RH, Waters RL. Smoking and obstructive lung dysfunction in persons with chronic spinal cord injury. *J Spinal Cord Med* 2003;26:28–35.
22. Spungen AM, Grimm DR, Schilero G, Lenner R, Oei E, Bauman WA, Almenoff PL, Lesser M. Relationship of respiratory symptoms with smoking status and pulmonary function in chronic spinal cord injury. *J Spinal Cord Med* 2002;25:23–27.
23. Ware JH, Dockery DW, Louis TA, Xu X, Ferris BG, Speizer FE. Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. *Am J Epidemiol* 1990;132:685–700.
24. Estenne M, Heilporn A, Delhez L, Yernault JC, De Troyer A. Chest wall stiffness in patients with chronic respiratory muscle weakness. *Am Rev Respir Dis* 1983;128:1002–1007.
25. Scanlon PD, Loring SH, Pichurko BM, McCool FD, Slutsky AS, Sarkarati M, Brown R. Respiratory mechanics in acute quadriplegia: lung and chest wall compliance and dimensional changes during respiratory maneuvers. *Am Rev Respir Dis* 1989;139:615–620.
26. Xu X, Dockery DW, Ware JH, Speizer FE, Ferris B. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;146:1345–1348.
27. Bande J, Clement J, Van de Woestijne KP. The influence of smoking habits and body weight on vital capacity and FEV_1 in male air force personnel: a longitudinal and cross-sectional analysis. *Am Rev Respir Dis* 1980;122:781–790.
28. Chen Y, Horne SL, Dosman JA. Body weight and weight gain related to pulmonary function decline in adults: a six year follow up study. *Thorax* 1993;48:375–380.
29. Chinn DJ, Cotes JE, Reed JW. Longitudinal effects of change in body mass on measurements of ventilatory capacity. *Thorax* 1996;51:699–704.
30. Carey IM, Cook DG, Strachan DP. The effects of adiposity and weight change on forced expiratory volume and decline in a longitudinal study of adults. *Int J Obes* 1999;23:979–985.

31. Lazarus R, Sparrow D, Weiss ST. Effect of obesity and fat distribution on ventilatory function. *Chest* 1997;111:891–898.
32. Maggioni M, Bertoli S, Margonato V, Merati G, Veicsteinas A, Testolin G. Body composition assessment in spinal cord injury subjects. *Acta Diabetol* 2003;40:S183–S186.
33. Spungen AM, Adkins RH, Stewart CA, Wang J, Pierson RN Jr, Waters RL, Bauman WA. Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. *J Appl Physiol* 2003; 95:2398–2407.
34. Buchholz AC, Bugaresti JM. A review of body mass index and waist circumference as markers of obesity and coronary heart disease risk in persons with chronic spinal cord injury. *Spinal Cord* 2005;43:513–518.
35. Aronson D, Roterman I, Yigla M, Kerner A, Avizohar O, Sella R, Bartha P, Levy Y, Markiewicz W. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. *Am J Respir Crit Care Med* 2006;174:626–632.
36. Shaaban R, Kony S, Driss F, Leynaert B, Soussan D, Pin I, Neukirch F, Zureik M. Change in C-reactive protein levels and FEV1 decline: a longitudinal population-based study. *Respir Med* 2006;100:2112–2120.
37. Sin DD, Man SF. Impaired lung function and serum leptin in men and women with normal body weight: a population based study. *Thorax* 2003;58:695–698.
38. Huang TS, Wang YH, Chen SY. The relation of serum leptin to body mass index and to serum cortisol in men with spinal cord injury. *Arch Phys Med Rehabil* 2000;81:1582–1586.
39. Bauman WA, Spungen AM, Zhong YG, Mobbs CV. Plasma leptin is directly related to body adiposity in subjects with spinal cord injury. *Horm Metab Res* 1996;28:732–736.
40. Enright PL, Kronmal RA, Higgins MW, Schenker MB, Haponik EF. Prevalence and correlates of respiratory symptoms and disease in the elderly. Cardiovascular Health Study. *Chest* 1994;106:827–834.
41. Jaakkola MS, Jaakkola JJ, Ernst P, Becklake MR. Respiratory symptoms in young adults should not be overlooked. *Am Rev Respir Dis* 1993;147:359–366.
42. Enright PL, McClelland RL, Newman AB, Gottlieb DJ, Lebowitz MD. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. *Chest* 1999;116:603–613.
43. Fletcher C, Peto R, Tinker C, Speizer FE. The natural history of chronic bronchitis and emphysema. New York: Oxford University Press; 1976.
44. Sherman CB, Xu X, Speizer FE, Ferris BG, Weiss ST, Dockery DW. Longitudinal lung function decline in subjects with respiratory symptoms. *Am Rev Respir Dis* 1992;148:855–859.
45. de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, Janson C, Sunyer J, Jarvis D, Chinn S, *et al.* Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med* 2007;175:32–39.
46. Saunders NA, Rigg JRA, Pengelly LD, Campbell EJM. Effect of curare on maximum static PV relationships of the respiratory system. *J Appl Physiol* 1978;44:589–595.
47. Kreitzer SM, Saunders NA, Tyler HR, Ingram RH. Respiratory muscle function in amyotrophic lateral sclerosis. *Am Rev Respir Dis* 1978; 117:437–447.
48. Eisen EA, Oliver LC, Christiani DC, Robins JM, Wegman DH. Effects of spirometry in two occupational cohorts. *Am Rev Respir Dis* 1985; 132:120–124.
49. Eisen EA, Robins JM, Greaves IA, Wegman DH. Selection effects of repeatability criteria applied to lung spirometry. *Am J Epidemiol* 1984; 120:734–742.
50. Garshick E, Ashba J, Tun CG, Lieberman SL, Brown R. Assessment of stature in spinal cord injury. *J Spinal Cord Med* 1997;20:36–42.