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Long-term change in respiratory function following spinal cord injury.

Article

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TITLE PAGE

Title: Long term change in respiratory function following spinal cord injury

Running title: Vital capacity change after spinal cord injury

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ABSTRACT

Study design

Retrospective study.

Objectives

To model the effect of time since injury on longitudinal respiratory function measures in spinal cord injured-individuals and to investigate the effect of patient characteristics.

Setting and Subjects

173 people who sustained a spinal cord injury between 1966 and April 2013 and who had previously participated in research or who underwent clinically indicated outpatient respiratory function tests at the Austin Hospital in Melbourne, Australia were included in the study. At least two measurements over time were available for analysis in 59 patients.

Methods

Longitudinal data analysis was performed using generalised linear regression models to determine changes in respiratory function following spinal cord injury from immediately post-injury to many years later. Secondly, we explored whether injury severity, age, gender and body mass index at injury altered the time-dependent change in respiratory function.

Results

The generalised linear regression model showed no significant change ($p=0.276$) in respiratory function measured in (forced) vital capacity ((F)VC) after the spinal cord injury. However, significant ($p<0.05$) differences in respiratory function over time were found when categorising age and body mass index.

Conclusion

This clinical cohort with long-term, repeated measurements of respiratory function showed no significant overall change in respiratory function over 23 years. However, a decline in respiratory function over time was observed in subgroups of individuals older than 30 years at the onset of injury and in those with a BMI greater than 30 kg/m^2.

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Key words

Spinal cord injury, respiratory function, body mass index, vital capacity, injury severity

INTRODUCTION

Lesion-dependent loss of respiratory muscle innervation caused by spinal cord injury (SCI) leads to the immediate impairment of respiratory muscle functioning and an associated reduction in lung volume.[1] Respiratory impairment after SCI causes respiratory complications[2] such as pneumonia, atelectasis, pleural effusions, sleep-disordered breathing or symptoms such as dyspnoea, in 50-67% of the patients.[3] Garshick et al.[4] showed that during the first year post-injury the respiratory system was the cause of death in 28% of the cases and in 22% of the cases thereafter. Pneumonia has been shown to be the most common cause of death in patients with a SCI.[5] These respiratory complications during the first two years post-injury have substantially decreased over the last 30 years, whilst respiratory complication rates in chronic SCI have not altered.[6]

Multiple factors may influence the high rate of respiratory complications in this population. Some of these include poor a priori respiratory function[7, 8], changes in breathing mechanics[9], and reduction of the elastic properties of the thorax with increasing time post-injury. [10, 11] Lesion level also seems to be involved, as it has been shown that lung function decreases[7] and respiratory tract infections increase[8] with higher lesion level. However, patients with a SCI are able to train their remaining muscles, which can result in substantial variability in respiratory function measures across time in patients with the same lesion level.[12]

Sinderby et al.[13] showed no significant change in vital capacity from early (1-3 years) to later (10 or more years) time post-injury in patients with tetraplegia. Other studies even showed large improvements in lung function during the first 6 months post-injury, which became smaller thereafter.[14-17] Resolution of the impact of spinal shock, usually during the first 4-6 months post-injury, and thus lung function, could explain these findings.[18] Nonetheless, there are little data describing the effect of time since injury on respiratory function in SCI.[19] Therefore, the first aim of the study was to describe the change in respiratory function following the early changes after a spinal injury in a clinical cohort.

In persons with a SCI, similar to the able-bodied population, respiratory function is influenced by parameters such as gender, body mass index (BMI), age, and severity of the injury.[13, 20-22] However, whether these parameters influence the changes in (F)VC following a SCI have not yet been investigated. The bulk of the literature is based on cross-sectional comparison. Currently, little is known about factors influencing the change in pulmonary function across time in SCI individuals. A better understanding of these factors may improve therapeutic interventions and approaches (e.g. patient selection or identification) to prevent respiratory complications and potentially decrease respiratory morbidity and mortality. Therefore, the second aim of this paper was to investigate the effect of age at injury, gender, BMI and severity of injury on the change in (F)VC after a SCI.

SUBJECTS AND METHODS

Study design and patient population

Clinical and research databases at the Austin Hospital in Melbourne, Australia were used to identify patients with SCI who had participated in previous research or had outpatient respiratory function tests (RFTs) completed. Only patients who had a SCI and one or more RFTs with a known time since injury were included in this study. This data audit was approved by the Austin Health Human Ethics Committee.

Lung function measurements

Lung function measurements were made in an accredited respiratory function laboratory at the Austin Hospital. Spirometers were calibrated daily and RFTs made in accordance with the relevant ATS(21) and ERS/ATS(23) recommendations at the time of data collection. Briefly, patients were instructed to exhale fully from total lung capacity, through a mouthpiece while wearing a nose clip, until three reproducible and acceptable measurements were registered. The highest measured value was quoted for further analysis. Analyses were performed on the forced vital capacity (FVC) if available. If the FVC was not reported, then the VC was substituted. Change over time was modelled from patients with at least two technically acceptable measures over time.

Statistical analysis

Descriptive statistics (mean, standard deviation (SD), median and range) for group characteristics of all the included patients and the subset of patients who were included in the analysis were calculated separately. Severity of injury was categorised according to the DeVivo et al(24) recommendations. Comparisons between the total sample and the subset with at least two repeated FVC values within 23 years since injury were made to examine any differences using t-tests and chi-squared as appropriate.

The longitudinal data was initially visualized in Microsoft Excel to explore how the available data were spread over time since injury at the date of the RFT. Stata12 was used to create a generalised linear regression model (GLM) to describe the change in (F)VC over time. In this model the (F)VC is the outcome variable, the time since injury is the predictor and the patient is the random variable, to account for all patient characteristics and individual variables.

Subsequently, regression interaction analyses were performed in Stata12 to investigate the influence of age and BMI at the time of injury, gender and injury severity on the change in (F)VC over time. Age at injury was split into three groups for the ages 18-30 years, 31-60 years and older than 60 years; following the recommendations of DeVivo.(24) BMI at the time of injury was also split into three groups according to standard BMI classification(25); BMI <25, BMI 25-30 and BMI >30. Severity of injury was categorised according to DeVivo et al(24) recommendations, however in the subgroup of patients selected for analysis, there were no patients with an AIS E injury. For each of the categories the individual slopes of the change over time were calculated and then compared to determine whether the variable has a significant influence on the change over time in (F)VC.

RESULTS

In this study 180 patients with one or more RFT measurements were identified. The time since injury was known for 173 patients who sustained a spinal cord injury between 1966 and April 2013. The corresponding RFTs were conducted between 1996 and September 2014. Of the 311 RFTs conducted, FVC was not available for 19 and therefore VC was substituted. The characteristics of the 173 patients are described in Table 1.

For analysis of the longitudinal data, we included the 59 patients (34%) who underwent two or more RFTs. Figure 1 illustrates the selection process of patients in this study.

The frequency of RFT measures was anticipated to decrease over time after injury and the "density" or "frequency" of the measures of (F)VC would affect the validity of the regression modelling. There is no agreed statistical technique to determine the optimum frequency of data samples in time series analysis such as that proposed for these data. As such, Figure 2 was constructed to facilitate visual inspection of data density and to select a cut-point for analysis of the effect of time after injury. As illustrated below, there is a clear reduction in the frequency of data collection after 23 years and therefore this time was chosen as the censoring time post-injury.

Change in pulmonary function in SCI

Characteristics of the sample of those with two or more RFTs performed up to 23 years post injury (n=59) are described in Table 1 and compared to the total sample (n=173). Comparison of this subgroup with the total group shows patients in the subgroup were on average 4 years older (p=0.04) and slightly more overweight (p<0.001).

Results from the linear model analysis showed a slope of -0.01 (SE 0.01, 95%-CI [-0.03, 0.01]; p=0.28) indicating there was no significant change in (F)VC over time.

To assess the validity of substituting VC when FVC was unavailable, we performed a sensitivity analysis on the original dataset, whereby we repeated the analysis using only those with two or more FVC measurement (n=54) and only those with two or more VC measurements (n=42). As with the primary analysis, these models showed no change in respiratory function using either measure, with a FVC slope of 0.01(SE 0.01, 95%-CI [-0.03, 0.01]; p=0.48) and a VC slope of 0.00(SE 0.01, 95%-CI [-0.02, 0.02]; p=0.99).

Factors related to change in pulmonary function in SCI

The characteristics of the different age, gender, BMI and injury severity categories of the subgroup of 59 patients are described in Table 2. Injury severity was unknown for one patient, who was therefore excluded from this analysis (n=58). The individual slopes for every category regarding change in (F)VC for every variable are plotted in Figure 3.

A significant difference was found when comparing the slopes between 18-30 year olds and 31-60 year olds (p=0.003). There were no differences between 18-30 year olds and those older than 60 (p=0.222), nor 31-60 year old and those older than 60 (p=0.799).

There was no difference in change in (F)VC over time between males and females (p=0.16).

When comparing BMI categories, a significant difference in change over time was found between people with a BMI <25 kg/m^2 and >30 kg/m^2 (p<0.001) and people with a BMI of 25-30 kg/m^2 and

>30 kg/m^2 (p=0.024). People with a BMI >30 kg/m^2 showed a decline in (F)VC over time. No significant difference was found when comparing people with a BMI <25 kg/m^2 and 25-30 kg/m^2 (p=0.511).

When comparing the different categories of injury severity, no differences were found in change in (F)VC over time. Those with AIS D had higher baseline pulmonary function than those AIS A,B,C with high cervical injuries.

DISCUSSION

This paper provides novel information regarding the change in respiratory function, specifically the (F)VC over time after SCI. We were able to model change over time in participants up to 23 years after injury and have demonstrated that, after the initial drop in pulmonary function, little further changes are observed. However, specific groups of participants demonstrated particular patterns. Those participants with a BMI in the obese range at baseline and middle-aged subjects at the age of SCI onset showed a substantial decline in pulmonary function over time. This study provides novel and important insight into factors that alter the change in pulmonary function across time in a group of SCI individuals.

There have been few studies addressing issues regarding ageing and SCI in respiratory function.[26] Available data on this topic suggests that inspiratory capacity, and therefore FVC[27], reduces after a SCI due to higher abdominal compliance. Consequently, this impacts functional residual capacity as the diaphragm is less elevated due to the lack of tone in the abdominal muscles. This is pronounced in persons with tetraplegia and high-level paraplegia.[28] Mueller et al[29] showed a decline in respiratory function with ageing in persons with a SCI of -0.012 to -0.021 liters per year, which is less than that reported in able-bodied people (-0.026 to -0.043 liters per year).[30] Postma et al.[31] showed that many patients with SCI have a larger decline in respiratory function in the first 5 years post-injury, than can be explained by age-related decline. The results from both studies are in contrast with the finding of this study that respiratory function after SCI does not significantly decline. However, Mueller[29] and Postma[31] only investigated a short follow-up of one year post-discharge and five years post-injury respectively, which differs substantially from the current study follow-up timeframe of up to 23 years post-injury. Tow et al.[32] however had a follow-up time of 20 years in their study, which did show a significant decline in vital capacity over the years. However, those authors only included tetraplegic patients while in this study both tetra- and paraplegic patients were included.

In the second part of this study we aimed to identify factors that may alter the change across time. Interestingly, we found significant changes over time between patients younger than 30 years old and patients older than 30 years and between patients with a BMI of less than 30 and those with a BMI over 30. The fact that there was no statistically significant difference between age 18-30 and >60 was probably due to the small sample (n=9) of the oldest age group in this study and an associated poor statistical power. As such, it may be concluded that age >31 and a BMI >30 have a greater effect on the (F)VC decline over time.

The negative influence of a BMI >30 at baseline on the (F)VC over time is supported by the findings of Jones et al. [33], who have shown that a BMI >30 negatively influences the vital capacity in able-bodied participants. Chen et al[34] also showed that in an able-bodied population respiratory function is decreased when overweight. This suggests that obesity importantly affects changes in respiratory function across time, an effect that is not altered by the presence of a spinal cord injury. Stolzmann et al.[35] have also demonstrated that longitudinal change in FVC is attributable to factors such as age and BMI. However, that study was only performed in male patients with SCI. In our study, both male and female patients with SCI were included, therefore our results are applicable to all patients with SCI regardless of gender. Furthermore no effect of gender was observed.

Clinical relevance

This study has shown the effect of time since injury on respiratory function in patients with SCI. As there is currently very limited published data available on the impact of time since injury, a better understanding of the physiology of respiratory function after SCI may provide insights for improved therapeutic interventions and respiratory care. These study results suggest that a serial decline in respiratory function in a person with SCI may reflect a sign of disease, instead of normal ageing as typically observed in the able-bodied population. This study focused on the (F)VC because of its broad prognostic utility and relationship with possibly important outcomes like the need for intubation and tracheostomy.

Further, this study has shown that patients older than 30 at the time of their injury, and those with a BMI greater than 30 are likely to show a decline in respiratory function. In groups other than these, our data would suggest that any demonstrable decline in (F)VC may warrant clinical review.[36]

Study limitations

It was not possible to determine which RFTs were performed for diagnostic or research purposes, and therefore it is impossible to exclude the possibility that some of the RFTs were completed when the patient was experiencing a respiratory complication (and therefore the RFT may reflect an underestimation of the true respiratory function). Further, no distinction was made in patients with or without pre-existing pulmonary diseases at the time of the RFT. These effects would be expected to have occurred at random across the entire dataset and as such were unlikely to contribute to any systematic bias. Significant differences were found in age at injury and BMI when comparing the subset of 59 patients with the total group, however these were small and unlikely to be clinically relevant.

Due to sample size limitations we were only able to assess the interaction between one independent variable with time since injury at a time, and therefore cannot control for confounding between variables. A larger study population would allow for controlling of more potentially explanatory variables in a multivariate mixed model analysis.

This study involved analysing a retrospective dataset sourced from several databases at the Austin Hospital and we were therefore unable to obtain reliable data on smoking history, ethnicity and change in BMI over time.

Conclusion

Investigation of longitudinal data of RFTs after SCI showed no overall change in (F)VC over time. Our clinical cohort data suggests that respiratory function in people with SCI does not change significantly beyond their initial drop in lung function after injury. However, patients older than 30 years at the time of their injury and those with a BMI greater than 30 are more likely to show a decline in respiratory function over time.

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CONFLICTS OF INTEREST

We declare that we do not have any conflicts of interest.

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TITLES AND LEGENDS TO FIGURES

Figure 1
Title: Selection of patients

Figure 2
Title: Individual (F)VC records plotted against time since injury

Figure 3
Title: Interaction plots of (F)VC over time (A) by age category, (B) by gender, (C) by BMI category and (D) by injury severity category.

Title:

Table 1: Patients' characteristics of the whole sample (n=173) and the subset for analysis (n=59)

	Total group	**Group with two or more RFTs with cut point of 23 years post injury**	**P-value**
N	173[1]	59	
Gender			0.31
Male	131 (76%)	42 (71%)	
Female	42 (24%)	17 (29%)	
Mean age at injury in years (SD, median, range)	36 (16, 33, 1-84)	40 (16, 37, 18-71)	0.04
Mean BMI in kg/m^2 (SD, median, range)	26.3 (5.7, 25.4, 15.9-52.9)	28.2 (6.8, 26.8, 16.0-52.9)	<0.001
Smoking history			0.09
Never smoked	64 (37%)	20 (34%)	
Stopped smoking	70 (40%)	30 (51%)	
Currently smoking	39 (23%)	9 (15%)	
Severity of injury			0.27
C1-C4, AIS A, B, C	30 (17%)	10 (17%)	
C5-C8, AIS A, B, C	69 (40%)	30 (51%)	
T1-S5, AIS A, B, C	29 (16%)	9 (15%)	
AIS D	38 (22%)	9 (15%)	
AIS E	3 (2%)	0 (0%)	
Unknown	4 (3%)	1 (2%)	

Data are n (%) unless otherwise stated.

1. Patients with known time since injury at each RFT, number used to calculate proportions for other characteristics.

Title:

Table 2: Results from regression interaction analysis regarding age, gender, BMI and injury severity.

Variable	Category	Patients (n)	RFTs (n)	Individual slopes	[95%-CI]	P-value[1]
Age (years)	**18-30**	21	53	0.027	[-0.004, 0.059]	0.092
	31-60	29	88	-0.029	[-0.049, -0.010]	0.003
	> 60	9	36	-0.020	[-0.089, 0.049]	0.570
Gender	**Male**	42	125	-0.014	[-0.034, 0.006]	0.156
	Female	17	52	0.001	[-0.025, 0.027]	0.934
BMI (kg/m^2)	**< 25**	19	57	0.020	[-0.005, 0.044]	0.115
	25-30	21	57	0.005	[-0.034,-0.043]	0.821
	> 30	19	63	-0.047	[-0.071, -0.024]	<0.001
Injury severity[2]	**C1-C4, AIS A,B,C**	10	28	-0.008	[-0.043, 0.027]	0.656
	C5-C8, AIS A,B,C	30	81	-0.002	[-0.029, 0.024]	0.857
	T1-S5, AIS A,B,C	9	34	0.001	[-0.029, 0.031]	0.929
	AIS D	9	30	-0.019	[-0.071, 0.032]	0.459

1. The listed p-value and confidence intervals in the table test whether the gradient of the regression is statistically different to zero, i.e. a straight (horizontal) line.

2. The analysis regarding injury severity is based on 58 patients, the 1 patients with unknown injury severity was excluded from this analysis.

Figure 1

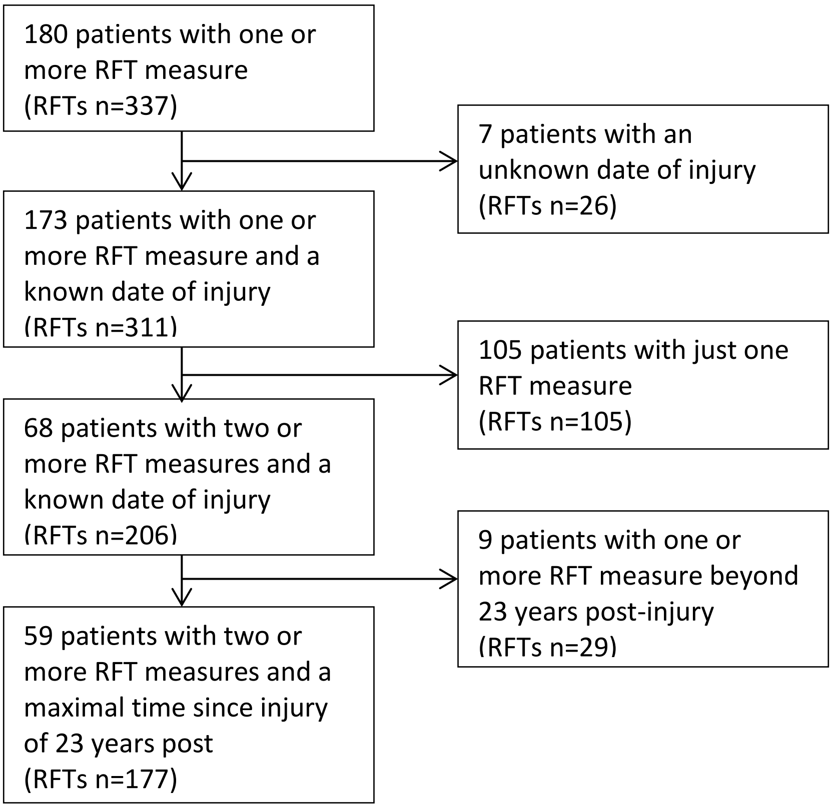
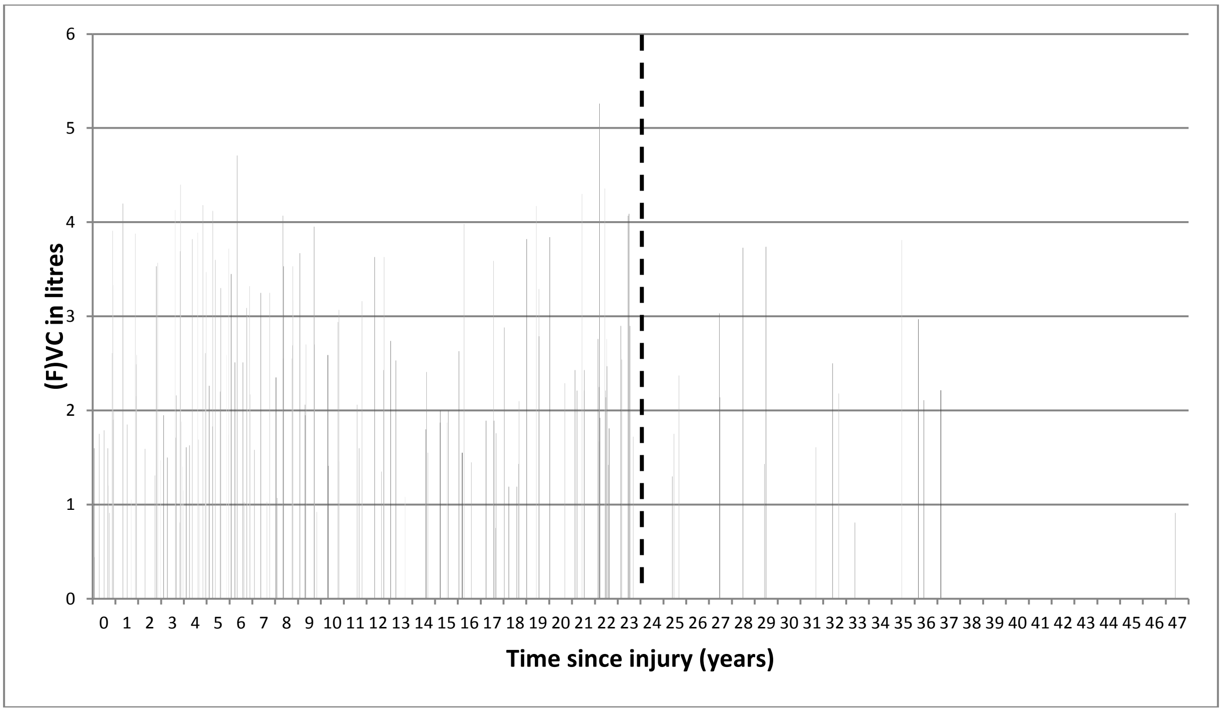

180 patients with one or more RFT measure (RFTs n=337)
7 patients with an unknown date of injury (RFTs n=26)
173 patients with one or more RFT measure and a known date of injury (RFTs n=311)
105 patients with just one RFT measure (RFTs n=105)
68 patients with two or more RFT measures and a known date of injury (RFTs n=206)
9 patients with one or more RFT measure beyond 23 years post-injury (RFTs n=29)
59 patients with two or more RFT measures and a maximal time since injury of 23 years post (RFTs n=177)

Figure 2



6
5
4
3
2
1
0
(F)VC in litres
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47
Time since injury (years)