ORIGINAL ARTICLE

Influence of neurological lesion level on heart rate variability and fatigue in adults with spinal cord injury

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Study design: Group cohort design.
Objectives: To determine the influence of spinal cord injury (SCI) and neurological level on heart rate variability (HRV) and associations with fatigue.
Setting: SCI rehabilitation outpatient and community settings in New South Wales, Australia.
Methods: Participants included 45 adults with SCI living in the community and 44 able-bodied controls. Socio-demographic, neurological injury, psychological, HRV and eye blink variables were assessed. Multivariate analysis of variance and *post hoc* protected *t*-tests were used to determine differences in HRV and fatigue as a function of the neurological level. Pearson's correlation analysis was used to determine the relationships between these factors.
Results: Participants with SCI had significantly reduced sympathetic activity. Those with tetraplegia had lowered sympathetic activity compared with those with paraplegia and able-bodied controls. Neither were differences in parasympathetic activity found between groups nor were there any significant differences found for the time domain or non-linear domains. Higher levels of fatigue were found in the SCI sample, and participants with tetraplegia had higher fatigue levels compared with those with paraplegia. Fatigued participants were more likely to have altered autonomic function—that is, reduced sympathetic activity.
Conclusions: Higher levels of neurological impairment in people with SCI are more likely to result in disordered cardiovascular control involving reduced sympathetic activity, whereas elevated fatigue was found to be associated with increased sympathetic dysfunction. Findings highlight the need to address risks associated with this dysfunction, such as improved HRV and fatigue screening for people with SCI and improved education on cardiovascular risk factors.
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INTRODUCTION

Spinal cord injury (SCI) involves damage to the nervous system and structures within the spinal canal (spinal cord and cauda equina), either by bruising, lacerations or severing as a result of traumatic injury or non-traumatic causes such as intervertebral disc disease, tumours, cysts and infections.[1,2] Among other complications, SCI results in disordered cardiovascular control believed to be due to autonomic nervous system (ANS) imbalance and dysregulation of homeostatic mechanisms.[2] Generally, dysregulation is likely to be more severe the higher and more complete the lesion,[1,3,4] although inactivity associated with being wheelchair dependent may result in disordered cardiac control in lesions as low as T10.[5] In cervical and high thoracic lesions, disruption of sympathetic nervous system (SNS) pathways to the heart is associated with bradycardia, orthostatic hypotension, reduced blood pressure, as well as autonomic dysreflexia and a reduced capacity to thermoregulate.[3] In lesions around the T5 level and below, there is increased likelihood of problems such as uncontrolled hypertension and tachycardia.[3,5] Increased cardiovascular risks in lower level lesions may be due to increased compensatory sympathetic activity.[5] The mechanisms for ANS dysfunction are complex and require further investigation.[1–5]

Physical inactivity, metabolic syndrome and being overweight or obese increase cardiovascular risks,[2,5] and arguably these problems are likely to be associated with chronic fatigue. Fatigue has been defined as a state of excessive chronic tiredness involving pervasive feelings of exhaustion and negative emotions such as anxiety and poor mood.[6,7] It is the excessive and chronic nature of fatigue that distinguishes it from commonly experienced 'tiredness' related to daily physical or mental exertion, sometimes called acute fatigue.[6] Chronic fatigue has been shown to be associated with problems like significantly reduced quality of life, chronic pain and mental distress.[8,9] Fatigue has been found to be associated with dominant sympathetic activity in an able-bodied (AB) sample.[10]

Autonomic function changes can be measured by heart rate variability (HRV).[10–12] HRV is a measure of the variability of the normal-to-normal QRS complexes of the PQRST waveform of the electrocardiogram (ECG), which reflects innervation of the heart by the sympathetic and parasympathetic divisions of the ANS. It provides a measure of the relative contribution and activity of these divisions based on beat-to-beat interval variations of the heart.[11] HRV measures in the frequency domain have been shown to be highly reproducible in adults with SCI and therefore represent a potentially valid measure of

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ANS dysregulation in this population.[13] Research employing HRV as a measure of ANS dysfunction in adults with SCI has found altered fluctuations in autonomic function in response to various activities such as tilt tests, exercise and digestion.[14,15] In comparison with AB controls, reduced sympathetic activity was found in adults with SCI, with no differences found for parasympathetic activity.[3,5,16] Grim et al.[3] studied the influence of the neurological level with small samples of adults with tetraplegia ($n=10$ with complete lesions; $n=10$ with incomplete lesions) and adults with paraplegia ($n=10$) on sympathovagal balance with comparisons with a small sample of AB controls ($n=10$). They employed tilt, cold pressor and isometric tests to investigate the ANS function. They found significant differences in low-frequency HRV (mostly associated with sympathetic activity) between tetraplegia, paraplegia and AB groups. They also found high-frequency HRV (mostly associated with parasympathetic activity) differences between the paraplegia and the AB groups. Recent research has also found significantly reduced sympathetic activity in adults with tetraplegia,[4] whereas no HRV differences were found between adults with paraplegia (T2-T12) and AB controls in sympathetic activity.[5]

The purpose of this report is to extend the research conducted in the area of HRV and SCI by, for instance, investigating the influence of SCI, on cardiovascular function using standard and non-linear HRV measures, as well clarifying the relationship between fatigue and HRV as a function of the neurological lesion level in adults with SCI. The specific aims of this study were as follows: (i) determine differences in short-term HRV measures between adults with SCI and AB controls; (ii) examine these HRV differences as a function of the neurological lesion level; and (iii) determine associations between SCI, HRV and fatigue. It was hypothesised that SCI results in altered HRV patterns and that greater dysfunction in HRV would occur at higher neurological levels. It was also hypothesised that elevated fatigue will be more likely to occur in participants with SCI and that in the SCI sample fatigue will be associated with disruption to the sympathetic nervous system.

Table 1 Injury characteristics of spinal cord injury participants ($n=45$)

	Frequency	Percentage
Level of injury		
Cervical	21	46.7
Thoracic	20	44.4
Lumbar/Sacra	4	8.9
Completeness		
Tetraplegia		
Complete	7	15.6
Incomplete	14	31.1
Paraplegia		
Complete	20	44.4
Incomplete	4	8.9

Severity of injury			
	C1–C4	C5–C8	T1–S5
Number of patients	13	8	24
ASIA A	3	4	20
ASIA B	1	1	—
ASIA C	5	2	—
ASIA D	3	0	—
Unknown	1	1	4

Abbreviation: ASIA, American Spinal Injury Association.

MATERIALS AND METHODS

Study participants

Participants included 45 adults with a SCI (mean age = 50.4 years, s.d. = 18; 38 males, 7 females) and 44 AB adults (mean age = 48.9 years, s.d. = 19; 37 males, 7 females). All SCI participants were recruited after discharge from inpatient rehabilitation, and sources of recruitment included outpatients at a SCI rehabilitation unit in Sydney, or from contacts of people with SCI living in the community. Mean age at injury was 40.0 years (s.d. = 18.6, median = 37.6, range = 17–77), and mean time since injury was 10.4 years (s.d. = 12.9, median = 2.5, range = 0.6–47). The study was advertised by placing brochures in the outpatient clinic or by placing advertisements in SCI self-help newsletters. Inclusion criteria for the participants with SCI consisted of the following: (i) aged between 18 and 80 years; (ii) understand instructions in English; (iii) sustained an acute SCI; and (iv) at least 6 months post injury from inpatient rehabilitation. As the purpose of the study was to investigate HRV in people with SCI and its associations with fatigue, SCI and AB participants with disorders like diabetes and cardiovascular disease were not excluded from the study. At the time of assessment, participants' medications included the following: 12 in the SCI group and 12 in the AB group were taking cardiac medications including ace inhibitors, angiotensin II, anti-platelet, beta blockers and calcium channel blockers. One participant in the SCI group and two in the AB group were taking anti-diabetic medication. Four in the SCI group and three in the AB group were taking statin medication. The most commonly prescribed medications were muscle relaxants ($n=24$) and anti-convulsants ($n=19$), which were used only within the SCI group. Inclusion criteria for the AB controls included the first two conditions for the SCI sample, as well as (iii) no history of neurological injury and (iv) no evidence of a current severe psychiatric disorder such as a bipolar disorder or psychoses as determined by a structured psychiatric interview. Injury characteristics are shown in Table 1. Approximately 58% of the SCI and 66% of the AB participants had a diploma, trade or tertiary level education. There were no significant differences in the level of education between the groups ($P=0.32$). Falls were the most common cause of SCI (42.2%) followed by a motor vehicle crash (30.4%). Completeness of the lesion was assessed by a medical specialist based on International Standards for Neurological Classification of SCI (http://ais.emsci.org/). SCI participants received a $50 gift voucher to compensate for their time and effort while AB participants were not remunerated.

Research ethics

Full compliance with the Code of Ethics of the World Medical Association occurred, and research ethics approval was granted by the local institutional research ethics committee. All institutional regulations concerning the ethical use of human volunteers were followed during this research. Written consent was obtained prior to participation in the study.

Study design and procedure

A group cohort design was employed. The study involved all participants completing a 40-min fatigue-inducing task during which electrophysiology recording occurred. In addition, all participants completed a battery of psychosocial measures three times: the first at baseline before the fatiguing task, the second immediately after the task and the third after a 5-min recovery period. However, only the baseline measures and the HRV data from the initial 5 min of ECG recording will be presented in this paper. All participants were requested to refrain from consuming caffeinated and alcoholic beverages on the morning of the assessment. To control for circadian influences on HRV and for fatigue status,[10] assessments were conducted over a 4-h period between 9 am and 1 pm. Assessment was conducted in a quiet, relaxed environment, in a semi-darkened room to induce sleep, and was conducted either in the participant's home, a health clinic or a dedicated room in a research institution. The participants with SCI were seated in their wheelchair, and AB participants were seated in a chair with armrests while electrophysiological assessment occurred.

Assessment

The Biosemi Active-Two System (http://www.biosemi.com) was used in this study for recording electrophysiological signals from each participant, including

electrooculography (EOG) and ECG, from which HRV data were obtained. For the ECG, a sampling rate of 512 Hz was used, being the recommended sampling rate for time domain methods and the minimal recommended sampling rate for nonparametric spectral analysis.[11,17] Signal processing was performed using Kubios HRV Analysis software (Version 2.0 beta 2, Department of Applied Physics, University of Kuopio, Kuopio, Finland).[10] HRV analyses were performed in the time, frequency and non-linear domains.

In the HRV time domain, measures included the mean normal-to-normal intervals, the standard deviation of the N-N interval (SDNN; the variability of the heart) and the square root of the mean squared differences of successive N-N intervals. For short-term measures, SDNN reflects overall HRV, and square root of the mean squared differences of successive N-N intervals reflects vagal (parasympathetic) outflow.[11] The frequency domain of HRV methods uses the power spectral density that measures how power (or variance) distributes as a function of frequency.[11] In the frequency domain, low frequency (LF) and high frequency (HF) mostly reflect sympathetic and vagal modulations of HRV, respectively.[4,11]

In the time domain, decreased variation is often associated with a shift from sympathovagal balance to sympathetic predominance, whereas in the frequency domain this is often reflected in an increase in the LF/HF ratio. The two frequency components (LF, 0.04–0.15 Hz and HF, 0.15–0.35 Hz), expressed in absolute values (ms^2), largely represent the degree of sympathetic and parasympathetic control, respectively.[11] In the non-linear domain, entropy analyses quantify the degree of regularity, or periodicity, of the physiologic time series. Periodicity of the HR data is determined by complex interactions between multiple variables influenced by many systems, including haemodynamic, electrophysiological, humoral, autonomic and central nervous system.[11] In the non-linear domain, measures include approximate entropy and sample entropy. These measures of entropy are among the most suitable non-linear analyses for short-term HRV recordings.[11]

Recording of the baseline HRV time series was based on a 5-min sample recording per participant, which is considered sufficient to measure HRV validly.[11] However, unwanted activity in the HRV, such as mechanical and central effects of breathing and the influence of dominant very low-frequency activity, can cause distortion to time and frequency analyses, leading to possible misinterpretation of the data.[12,18,19] Therefore, to distinguish changes in HR that are of interest in the investigation from these sources, an advanced detrending method was used, shown not to affect HRV statistical outcomes.[18] The smoothing parameter was selected so that the HRV components of interest were not significantly affected by the detrending process. However, in the time domain, detrending results in reduced values for the SDNN, LF ms2 and Total power.[19] For these reasons, the SDNN values reported in this paper cannot be used for medical diagnosis, especially where consistent normative values have not been well established.[20]

Fatigue was assessed using a psychometric scale called the Iowa Fatigue Scale (IFS),[21] as well as an electrophysiological measure of eye blink rate duration.[22]

The IFS was used to measure self-reported fatigue and is composed of 11 Likert items covering 4 subscales: cognitive, fatigue, energy and productivity.[21] The purpose of using the IFS was to determine the impact of a SCI on subjective fatigue levels, as well as determine whether associations exist between fatigue and HRV. To complete the IFS, participants were rated on a five-point scale of 1 'not at all' to 5 'extremely' to each item—for example, 'I feel worn out' and 'I have trouble concentrating.' The IFS has demonstrated homogeneity and internal consistency with Cronbach's coefficients over 0.90. Correlations between the four subscales ranged from 0.49 to 0.66. An IFS total score of around 30 or higher indicates severe fatigue.[21]

Fatigue was also assessed by eye blink duration, provided by EOG, which has been shown to provide a sensitive physiological measure of fatigue.[6,22,23] Eye blink duration was counted and measured from the unfiltered EOG raw signal at 500 mV in 2-s intervals on a low-pass filter. For the purposes of this study, eye blink duration included both the closing and reopening times. For all participants, three cutoff times were noted and recorded: those under 300 ms, shown to be within normal blink closure duration; those between 300–500 ms, shown to be long lasting spontaneous blink rate, and those above 500 ms, which included eyes closed, believed to be associated with fatigue.[10,22] Baseline EOG was taken from the second minute of the 5-min baseline measure.

Statistical methods

Using Lilliefors P-values for the Kolmogorov–Smirnov tests, variables not normally distributed were logarithmically transformed. Consequently, all HRV variables were logarithmically transformed, except mean R–R and sample entropy. Multivariate analysis of variance was performed to determine whether significant differences existed among the subgroups across all HRV and fatigue domains. If the multivariate analysis of variance was significant, post hoc Bonferroni protected t-tests were used to determine where differences existed. To determine the influence of the neurological level on HRV, the SCI group was further divided into those with tetraplegia and paraplegia, with comparisons with the AB group. On the basis of prior work on the differences in psychological (for example, fatigue) and physiological measures (for esample, HRV) between people with SCI and AB controls,[7,10] a medium effect size was assumed (Cohen's d), and, with a sample size of 45, 'a priori' statistical power was estimated to range between 60 and 70%. Partial eta-squared (η^2) effect size values are provided as an estimate of the size of the difference among the groups. A partial η^2 of around 0.03 is considered small, 0.13 is considered a medium difference and over 0.2 is considered a large and a substantial difference.[24] Post hoc or retrospective statistical power of the tests is also provided. Pearson's correlation analyses were also conducted to examine associations between self-reported fatigue, eye blink duration times and HRV. All analyses were performed using Statistica Software (Version 12, Statsoft http://www.statsoft.com).

Table 2 Comparison of mean (s.d.) differences between HRV measures for the SCI and AB controls

Variable	SCI group		AB controls		F	η^2
	Mean(s.d.)	95% CI	Mean (s.d.)	95% CI		
Mean HR	67.03 (12.9)	10.7–16.4	66.38 (12.6)	10.4–16.0	0.05	0.00
Mean NN	979.04 (171.7)	142.1–216.8	936.32 (159.2)	131.5–201.7	0.04	0.00
SDNN (ln)	29.38 (0.5)	12.6–19.2	36.42 (23.1)	19.1–29.2	1.67	0.02
RMSSD (ln)	29.33 (20.5)	16.9–25.8	37.26 (33.5)	27.7–42.5	0.77	0.01
LF ms^2 (ln)*	469.30 (546.4)	452.3–690.2	829.25 (990.6)	818.4–1255.1	4.80	0.05
HF ms^2 (ln)	435.64 (717.5)	594.0–906.4	512.61 (723.3)	597.6–916.5	0.28	0.00
Total ms^2 (ln)	1035.71 (1200.2)	993.6–1516.1	1421.13 (1703.8)	1407.7–2158.8	0.92	0.01
LF/HF (ln)*	1.97 (1.9)	1.6–2.5	2.95 (4.5)	3.7–5.7	4.23	0.05
ApEn (ln)	1.05 (0.1)	0.1–0.2	1.06 (0.1)	0.08–0.09	0.26	0.00
SampEn	1.40 (0.3)	0.3–0.4	1.44 (0.3)	0.2–0.4	0.52	0.01

Abbreviations: AB, able bodied; ApEn, approximate entropy; CI, confidence interval; HF, high-frequency band; HR, heart rate; HRV, HR variability; LF, low-frequency band; LF/HF, ratio between low-frequency and high-frequency power; LN, natural logarithm; NN, mean of the RR interval; RMSSD, root mean squared of the difference of successive RR intervals; SCI, spinal cord injury; SDNN, standard deviation of the RR interval; SampEn, sample entropy.
*Significant difference at $P<0.05$.

Table 3 Comparison of mean (s.d.) HRV measures between tetraplegia, paraplegia and AB groups

	Tetraplegia (n = 21)			Paraplegia (n = 24)			AB (n = 44)		
	Mean (s.d.)	95% CI		Mean (s.d.)	95% CI		Mean (s.d.)	95% CI	
Mean RR	959.75 (197.9)	151.4	285.8	902.17 (143.8)	111.8	201.8	936.32 (159.2)	131.5	201.7
STD RR	27.10 (15.8)	12.1	22.8	31.38 (14.6)	11.4	20.5	36.42 (23.1)	19.1	29.2
Mean HR	65.51 (14.9)	11.5	21.6	68.37 (11.1)	8.6	15.6	66.38 (12.6)	10.4	16.0
STD HR	2.28 (0.8)	0.6	1.2	3.03 (1.3)	0.9	1.8	3.40 (3.4)	2.8	4.3
RMSSD	30.16 (24.1)	18.4	34.8	28.61 (17.2)	13.3	24.1	37.26 (33.5)	27.7	42.5
LF (ms^2)[a]	296.95 (319.5)	244.4	461.3	620.11 (656.9)	510.6	921.5	829.25 (990.6)	818.4	1255.1
HF (ms^2)	518.67 (876.8)	670.8	1266.2	362.98 (551.9)	428.9	774.2	512.61 (723.3)	597.6	916.5
Total (ms^2)	940.24 (1159.9)	887.4	1675.1	1119.25 (1253.1)	973.9	1757.8	1421.13 (1703.8)	1407.7	2158.8
LF/HF[b,c]	1.43 (1.3)	1.0	1.9	2.45 (2.3)	1.8	3.2	2.95 (4.5)	3.7	5.7
ApEn-1	1.06 (0.1)	0.1	0.2	1.05 (0.1)	0.1	0.2	1.06 (0.1)	0.1	0.1
SampEn-1	1.43 (0.3)	0.2	0.4	1.37 (0.3)	0.2	0.4	1.44 (0.3)	0.2	0.4

Abbreviations: AB, able bodied; ApEn, approximate entropy; CI, confidence interval; HF, high-frequency band; HR, heart rate; HRV, HR variability; LF, low-frequency band; LF/HF, ratio between low-frequency and high-frequency power; RMSSD, root mean squared of the difference of successive RR intervals; SampEn, sample entropy.
The data are presented as mean and s.d. of the raw scores.
Analyses were based on log-transformed data using natural logarithm.
[a]$P = 0.014$ between tetraplegia and AB in LF power.
[b]$P = 0.006$ between tetraplegia and AB in LF/HF.
[c]$P = 0.047$ between paraplegia and AB in LF/HF.

RESULTS

HRV differences as a function of SCI
HRV measures for the two groups are presented in Table 2. The SCI group was found to have significantly different HRV scores when compared with the AB group: Wilk's lambda $= 0.70$, $F_{10,78} = 3.29$, $P = 0.001$, $\eta^2 = 0.30$, power $= 98\%$. Bonferroni's *post hoc* analyses showed that differences were in the frequency domain—that is, the LF ms^2 and LF/HF ratio ($P < 0.05$). The SCI group had lower LF ms^2 and LF/HF scores. No significant differences were found between the two groups for the time and non-linear domains.

HRV differences as a function of the neurological level
Table 3 shows comparisons of HRV variables for the time, frequency and non-linear domains for the tetraplegia, paraplegia and AB groups. Multivariate analyses showed no differences in the HRV time and non-linear domains for the SCI subgroups and the AB group (Wilk's Lambda $= 0.86$, $F_{10,164} = 1.33$, $P = 0.22$, $\eta^2 = 0.07$, power $= 66\%$; Wilk's Lambda $= 0.98$, $F_{4170} = 0.32$, $P = 0.86$, $\eta^2 = 0.01$, power $= 12\%$, respectively). However, in the HRV frequency domain, there were significant differences among the tetraplegia, paraplegia and AB groups: Wilk's Lambda $= 0.76$, $F_{8166} = 2.98$, $P = 0.004$, $\eta^2 = 0.13$, power $= 95\%$. Bonferroni's *post hoc* analyses indicated that differences occurred between the tetraplegia and the AB group in the LF ms^2 ($P = 0.014$), between the tetraplegia and the AB group in the LF/HF ratio ($P = 0.006$) and the paraplegia and the AB group in the LF/HF ratio ($P = 0.047$). There were no significant differences found among the groups in the HF measures.

Fatigue and eye blink duration as a function of the neurological level
Table 4 shows descriptive statistics for the IFS scores and eye blink duration (<300 ms, 300 ms–500 ms, >500 ms) as a function of tetraplegia, paraplegia and the AB groups. Using the IFS cutoff score of 30 and above for an indication of severe fatigue, results suggest that 52.4% ($n = 11$ of 21) of the tetraplegia group was experiencing severe fatigue levels when assessed at baseline (mean $= 34.18$; s.d. $= 4$), compared with 33.3% ($n = 8$ of 24) of the paraplegia group

(mean 34.75; s.d. $= 5$) and 18% ($n = 8$ of 44) of the AB group (mean $= 34.25$; s.d. $= 5.33$). Similar rates of severe fatigue were found when using the eye blink duration rate >500ms as an indicator of fatigue, with 52.4% ($n = 11/21$), 41.6% ($n = 10/24$) and 11.4% ($n = 5/44$) of the tetraplegia, paraplegia and AB groups, respectively, categorised as having elevated levels of fatigue.

Multivariate analysis of variance conducted for differences between groups for all IFS and eye blink duration indicated significant differences: Wilk's Lambda $= 0.73$, $F_{14,160} = 1.95$, $P = 0.025$, $\eta^2 = 0.15$, power $= 93\%$. Univariate analyses showed that these differences were in IFS Total, Energy and Productivity domains, as well as eye blink duration >500 ms. *Post hoc* Bonferroni analyses showed that these differences occurred between the tetraplegia and the AB groups for the IFS total score ($P = 0.016$), energy ($P = 0.026$) and productivity ($P = 0.001$) and between paraplegia and AB in the >500 ms eye blink duration subgroup ($P = 0.034$). A trend occurred for a difference in >500 ms eye blink duration between tetraplegia and the AB group. Overall, the tetraplegia group had higher fatigue scores compared with the paraplegia group and significantly higher fatigue scores than the AB group. A trend existed for the paraplegia group to have higher fatigue scores compared with the AB group.

Associations between socio-demographic, HRV and fatigue measures
For the SCI group, no socio-demographic variables significantly correlated with any fatigue or HRV variable. Table 5 shows Pearson's correlation results for associations between IFS scores, eye blink duration and LF and LF/HF measures for the SCI group. All IFS measures significantly and negatively correlated with LF power ($P < 0.05$), except for the IFS cognitive domain. Only the IFS total ($P < 0.05$) and productivity ($P < 0.01$) scores significantly and negatively correlated with the LF/HF ratio. High self-reported fatigue was associated with low levels of sympathetic activity. For eye blink duration, no significant relationships were found. No significant relationships were found between IFS or eye blink durations with LF power or LF/HF ratios for the AB group.

Table 4 Comparison of mean (s.d.) of IFS scores and eye blink duration between the tetraplegia, paraplegia and the AB groups

	Tetraplegia		Paraplegia		AB	
	Mean (s.d.)	95% CI	Mean (s.d.)	95% CI	Mean (s.d.)	95% CI
IFS total[a]	29.29 (6.8)	5.2–9.8	25.63 (8.5)	6.6–11.9	23.86 (6.5)	5.3–8.2
IFS cognitive	9.29 (3.2)	2.5–4.6	8.33 (2.9)	2.2–4.0	8.25 (2.8)	2.3–3.5
IFS fatigue	4.14 (1.5)	1.2–2.2	3.79 (1.9)	1.5–2.6	3.30 (1.4)	1.1–1.7
IFS energy[b]	10.05 (2.6)	1.9–3.7	8.63 (3.0)	2.4–4.3	8.20 (2.3)	1.9–2.9
IFS productivity[c]	5.81 (1.7)	1.3–2.4	4.88 (1.9)	1.5–2.7	4.11 (1.6)	1.3–1.9
EBD (<300 ms)	14.05 (12.1)	9.3–17.5	14.96 (8.9)	6.9–12.5	12.56 (9.1)	7.5–11.5
EBD (300–500 ms)	2.43 (3.1)	2.4–4.5	2.42 (3.3)	2.5–4.6	1.27 (2.1)	1.7–2.6
EBD (>500 ms)[d]	0.90 (1.1)	0.8–1.6	0.96 (1.6)	1.3–2.3	0.23 (0.7)	0.6–0.9

Abbreviations: AB, able bodied; CI, confidence interval; EBD, eye blink duration; IFS, Iowa Fatigue Scale.
Data are presented as mean and standard deviation (s.d.).
[a]$P = 0.016$ between tetraplegia and AB.
[b]$P = 0.026$ between tetraplegia and AB.
[c]$P = 0.001$ between tetraplegia and AB.
[d]$P = 0.034$ between paraplegia and AB.

Table 5 Pearson's correlation coefficients between the fatigue-related variables (IFS and eye blink duration) and LF and LF/HF ratio HRV factors for the SCI group

Fatigue variables	LF ms^2 (ln)	LF/HF (ln)
IFS total	− 0.37*	− 0.30*
IFS cognitive	− 0.23	− 0.12
IFS fatigue	− 0.31*	− 0.24
IFS energy	− 0.34*	− 0.25
IFS productivity	− 0.37*	− 0.45**
EBD <300 ms	0.11	0.29
EBD 300–500 ms	− 0.09	0.14
EBD >500 ms	− 0.29	−0.16

Abbreviations: HF, high-frequency band; HRV, heart rate variability; IFS, Iowa Fatigue Scale; LF, low-frequency band; LF/HF: ratio between low-frequency and high-frequency power; SCI, spinal cord injury.
Data are presented as mean and standard deviation (s.d.).
*$P < 0.05$, **$P < 0.01$.

DISCUSSION

As found in prior research,[3–5,16] the SCI group was found to have autonomic dysfunction, that is, reduced sympathetic activity (reduced LF and LF/HF) compared with AB controls of a similar age, education and sex breakdown. Participants with tetraplegia were shown to have significantly reduced sympathetic activity when compared with the AB controls, also supporting the findings of prior research,[3,4] whereas a trend for the participants with paraplegia to have lowered sympathetic activity compared with the controls also occurred. No differences in HF (parasympathetic tone) were found between the SCI and the AB groups. In addition, no significant differences were found between the two groups in the time and non-linear domains.

Malmqvist et al.[4] found significantly reduced sympathetic activity in participants with tetraplegia compared with those with paraplegia (T6-T12), with no differences found between tetraplegia and those with lesions at T1-T5. Serra-Añó et al.[5] found adults with paraplegia to have altered HRV compared with AB controls, especially in those who were less active. These findings and those presented in this paper reinforce concerns of increased risk of cardiovascular morbidity and mortality in the SCI population, recently expressed in the research literature.[4,5] In response to this increased risk, our findings suggest that HRV spectral analysis should be considered more often as a screen for fatigue related to autonomic dysregulation in the SCI population. The lack of association between the non-linear HRV data

and SCI requires further examination to determine whether this type of HRV complexity analysis is worthwhile.

Elevated fatigue levels were found in the SCI sample, with more severe levels found in those with tetraplegia. These elevated self-reported fatigue levels were confirmed by eye blink duration data, whereby an eye blink duration rate of >500 ms (indicating fatigue or tiredness) was more likely in those with SCI. Results suggested that just over half of those with tetraplegia and around one-third of those with paraplegia had elevated/severe levels of fatigue. Significantly reduced energy and productivity were found in those with tetraplegia compared with the AB controls, with non-significant trends for this to occur between those with paraplegia and the AB controls. Fatigue in people with SCI has been linked with increased depressive mood, increased anxiety and pain.[7,8,25] Results indicate that fatigue is also associated with ANS dysfunction—that is, reduced sympathetic (LF and LF/HF) activity. The lack of association between HRV and fatigue in the AB participants contrasts with the association found between these variables in the SCI sample.

These findings are of concern, given risks of cardiovascular disease appear to be cumulative in the SCI population—for instance, from loss of supraspinal control of ANS function, increased risk of being overweight and lowered capacity of physical activity/exercise, as well as increased occurrence of chronic fatigue, in addition to higher risks of perceived hopelessness and low self-efficacy, depressive mood and anxiety.[7,8,26,27] It will be important for SCI rehabilitation programs to address these cumulative risks through self-management education concerning relationships between cardiovascular disease and lifestyle, a greater emphasis on increasing social and physical activities, as well as the establishment of psychosocial strategies that address mood, anxiety, pain and fatigue.

Limitations of the research need discussion. First, the findings presented in this paper are preliminary, based on cross-sectional data, and therefore cannot clarify time influences or causal relationships among fatigue, HRV and neurological level. There is therefore a need for experimental or prospective research to determine how fatigue contributes to HRV in people with SCI. Second, only 5-min HRV recordings were taken. However, 5-min recording of HRV is believed sufficient for valid assessment of the ANS function,[11] and the HRV results based on 5-min recordings are similar to those data in studies that used longer recordings of HRV.[4] This suggests that short HRV assessment could be considered a valid and a clinically pragmatic assessment of autonomic dysregulation in people with SCI.

Furthermore, advanced detrending analysis to remove unwanted activity was employed in the 5-min recordings, which is believed to improve the validity of the HRV data and analysis.[18] Third, neither were the participants screened for cardiovascular disorders nor were levels of activity/fitness assessed in the study. As described in the Materials and methods section, and perhaps as expected, there was widespread use of cardiovascular and other medications in the sample. Therefore, neither were these participants omitted nor asked to abstain from taking medications for ethical reasons. Although it is acknowledged that medications and physical fitness have a potential influence on HRV, spectral analysis results of the HRV were similar to those in other studies where these factors were considered.[2–4]

In conclusion, fatigue has been found to be associated with altered HRV and therefore a potential cardiovascular risk. It is hoped these results will encourage the incorporation of 'anti-fatigue and anti-cardiovascular risk' strategies that maintain or increase tonic sympathetic outflow by encouraging, for instance, appropriate levels of exercise, the use of aids such as compression stockings, improved diet and healthy sleep behaviour, and the consistent use of self-management strategies such as relaxation treatments.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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