Research Article

# Exploring 5-minute heart rate variability in spinal cord injury during acute inpatient rehabilitation

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**Objective:** To explore the use of 5-minute heart rate variability (HRV) during inpatient rehabilitation in the acute phase of traumatic spinal cord injury (SCI).
**Design:** Longitudinal observational study.
**Setting:** Acute inpatient rehabilitation (AIR).
**Participants:** 10 patients with acute traumatic SCI.
**Interventions:** 5-minute HRV supine recordings twice daily on three different days per patient.
**Outcomes Measures:** HRV values were evaluated (1) within a single day (Early versus Late); (2) across the inpatient admission (initial, mid, and discharge); (3) by SCI phenotypes and by clinical outcomes (ex. pressure injuries (PI)).
**Results:** Patients had an average age of 38 years, 80% male, and 40% with tetraplegia. There were no HRV differences between Early and Late recordings, across the inpatient admission, demographics, or SCI phenotype. However, improvement in neurologic exam was accompanied by increased parasympathetic tone (mean RR increased by 172 ms SD 61, P = .005). Patients with PI demonstrated lower sympathetic (SNS) activity (decreased LF by 472 $ms^2$ SD 240, P = .049) and lower PNS activity (decreased RMSSD by 1.2 ms SD 0.5, P = .02), compared to no PI. Comparisons to uninjured reference values and chronic SCI suggest a changing autonomic nervous system (ANS) from uninjured to acute to chronic as measured by HRV.
**Conclusions:** This preliminary evidence suggests HRV in acute SCI is stable across time and day during inpatient rehabilitation and may be correlated to clinical sequalae of ANS dysfunction and neurologic recovery. Comparisons to published work suggest that HRV may measure the progression in the ANS from acute to chronic phase after SCI.

**Keywords:** Spinal cord injuries, Autonomic nervous system, Heart rate variability, Electrocardiography

## Introduction

With approximately 17,700 cases annually, acute spinal cord injury is a clinical disorder that causes significant functional impairment.[1] While classically associated with partial or complete paralysis, acute spinal cord injury (SCI) can also dysregulate the intrinsic cardiovascular, urinary, thermoregulatory, gastrointestinal and bronchopulmonary functions of the autonomic nervous system (ANS). These changes to the ANS represent a major cause of increased morbidity and mortality and often reduce the quality of life for these patients.[2] Not surprising, research of the ANS has been a top priority in those living with SCI for the past 16 years in the U.S.[3] Measurement of ANS function and impairment is therefore an important observation in the evaluation of SCI but has remained a challenge to measure objectively.

Heart Rate Variability (HRV) is a non-invasive means of indirectly measuring the balance of

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sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) contributions of the ANS. HRV refers to the variation in the time interval present between heart beats, which can be detected using a two-electrode electrocardiogram (ECG) with 5-minute recordings. Measurements are affected by the SNS and PNS, as well as regulatory mechanisms that control heart rate (e.g. the baroreceptor reflex), rhythmic changes in vascular tone, and vagal inputs mediating respiratory drive.[4] HRV has classically been described as an individual indicator, where low HRV is associated with increased morbidity and mortality.[5] However, the individual measurements reflect the PNS and SNS activity, with well-defined guidelines for recording and interpreting HRV data, analyzed using both frequency-domain and time-domain variables.[6] Time domain methods measure the interval of time between successive normal complexes. Frequency domain methods describe the heartbeat components as how their variance distributes as a function of frequency.

Frequency-domain variables include: low frequency (LF), high frequency (HF), and the ratio of low frequency to high frequency (LF:HF). The LF spectral component reflects sympathetic modulation and cardiac autonomic outflows by baroreflexes, commonly considered the indirect representation of the SNS tone.[7] The HF spectral component, a surrogate for PNS activity, represents the vagally mediated cardiac parasympathetic control. LF/HF has been used to reflect sympathovagal balance and overall variations in SNS and PNS. Time domain variables include: mean RR interval (interval of time between two consecutive R waves of the QRS complex), SDNN (standard deviation of normal sinus heart beats), and RMSSD (the root mean square of successive differences). PNS activity is represented by mean RR and RMSSD, while SDNN has been used as a surrogate for overall sympathetic and parasympathetic activity influencing HRV.[6]

HRV analysis has been found to be both consistent and reproducible in the chronic SCI population.[8] Several studies have used HRV as a tool to study physiologic changes in people with chronic SCI. Karri *et al.* demonstrated that SCI patients with neuropathic pain have a lower baseline HRV and reduced PNS tone compared to those without neuropathic pain.[9] People with SCI and orthostatic hypotension (OH) appear to have both time and frequency-domain variable changes compared to those without OH.[10] Kyriakides *et al.* found greater HRV changes in chronic paraplegia compared to tetraplegia following sitting maneuvers.[11] It is unclear whether these measures are similar in the acute SCI population.

The objective of this study is to explore the use of HRV during the acute phase of SCI. In this exploratory trial, we performed longitudinal HRV and BP recordings in people with acute SCI during inpatient rehabilitation. We evaluated for differences in HRV based on: (I) morning (Early) and evening (Late) recordings; (II) changes over time during inpatient rehabilitation (admission, 1 week after admission, and discharge). We also explored associations to clinical findings (SCI phenotype) and outcomes (*i.e.* infections, autonomic dysreflexia (AD), orthostatic hypotension (OH)). Additionally, for contrast, we provide HRV values in persons with chronic SCI[10] and uninjured adult reference values.[12]

## Materials and methods

All patients with acute traumatic SCI admitted to an acute inpatient rehabilitation hospital between July 2018 and January 2019 were screened using the electronic medical record (EMR) and excluded if they had a history of cardiac dysrhythmia, chemotherapeutic medications, and diseases that can affect the ANS function (e.x. diabetes mellitus, hypertension, peripheral neuropathies, and sleep disorders). There were no inclusion/exclusion criteria based on neurologic level of injury or AIS. Recruitment stopped after a convenience sample of 10 patients and no sample size calculation was performed due to an inherent lack of data in acute SCI HRV. All enrolled patients received the usual SCI acute inpatient rehabilitation care and management at our facility. This study was approved by the Institutional Review Board and informed consent was obtained in participating patients.

5-minute ECG readings were collected at approximately 7AM (Early) and 7PM (Late) for each subject at three time points during their rehabilitation: (1) within 3 days of admission (Admission); (2) one week into rehabilitation (Mid); and (3) within 1 week of discharge (Discharge). All recordings were obtained in a standardized manner with subjects lying supine, resting for at least 5 minutes, with minimized exposure to environmental stimuli, including turning off televisions and fluorescent lights, and refraining from cellular phone or tablet use. Adhesive electrodes were placed at the midclavicular region of the first intercostal space on both the right (white lead) and left (black lead) chest wall. Over the course of the 5-minute ECG recordings, patients were asked to remain silent and motionless. ECG recordings were performed with a wireless ECG heart rhythm scanner (Biocom 5000 Wireless ECG

Recorder, Biocom Technologies, Poulsbo, WA). Blood pressures were collected immediately after ECG recordings using a Welch Allyn Spot Vitals Signs BP monitor with an adult-sized cuff. HRV analysis was performed offline with Kubios HRV Software (University of Eastern Finland, Joensuu, FIN).

Chart review was utilized to obtain information on patient demographics, SCI phenotypes (tetraplegia v paraplegia, complete injury versus incomplete, and neurologic level), physical exam motor scores, and medications that may influence HRV recordings, including vasopressors and inotropes. Pain was assessed prior to each ANS recording via numerical pain scores (NPS) scaled from 0–10 (no pain to severe). The International Standards for Neurological Classification of SCI (ISNCSCI) exam was used to categorize neurological improvement from rehabilitation admission to discharge based on (1) improved motor and/or sensory levels, and/or (2) improved American Spinal Injury Association (ASIA) impairment scale (AIS). Patients were categorized based on the presence or absence of improvement (Improved or Not improved).

Clinical outcomes of interest throughout their admission were obtained from the EMR. The definition used for OH was a decrease of systolic (SBP) and/or diastolic blood pressure (DBP) by 20 mmHg or 10 mmHg, respectively, upon standing from a seated position.[13] The definition of AD is considered a sudden increase in systolic blood pressure ≥ 20 mmHg above baseline.[14] Because the SNS is implicated in the immune system dysregulation that occurs after SCI, we recorded all infections in the participating patients.[15] Infection was defined by the presence of at least one of the following: urinary tract infection (UTI), pneumonia, cellulitis, surgical infection, or other stated infection. UTI was defined by symptoms known to occur in SCI, a positive UA with bacterial growth in urine culture, with symptom improvement after appropriate antibiotic treatment.[16] Pneumonia was diagnosed by pathologic chest X-ray infiltrates. Surgical infections were diagnosed by fever greater than 100.8 degrees Fahrenheit with erythema, tenderness, and/or discharge originating from surgical incision site.[17]

Uninjured reference values[12] were plotted for juxtaposition against the acute SCI data from this manuscript and chronic SCI data from our previous work.[10] The uninjured reference values were developed from a systematic review of the literature of 5-minute HRV values in healthy adults.[12] Data from subjects with chronic (> 1 year) traumatic SCI was collected from routine SCI clinic visits and excluded if they had a history of cardiac dysrhythmia, orthostatic hypotension, or active medical concerns.[10] Because the uninjured reference values were from single recordings, rather than serial recordings, we used the first recordings from both the chronic and acute SCI data.

## Statistical analysis

Continuous variables were described as means and Standard Deviation (SD) or median and interquartile range (IQR). The coefficient of variation (CV) was calculated (SD/mean x 100) for the HRV and BP measures. Categorical values were reported as frequency and percentage. Patients that experienced OH also experienced AD, reported together as OH/AD. Mean comparisons were made using T-test or Mann–Whitney test for normal or nonparametric data, respectively. Mixed-effects models were used to evaluate HRV changes over time, with the fixed effects the autonomic measures and the random effects as the subject differences and duration of injury. Associations to clinical measures and outcomes were individually added to the mixed-effects model. STATA version 14.2 was used for analyses.

## Results

Ten patients participated in the study (eight male and two female) with a mean age (SD) of 38 (11.3) years (Table 1). Recordings were collected within 13–86 days from injury. The mean duration of injury on initial recording was 28 (10.6) days, and final recording was 48 (16.4) days. There were four patients with tetraplegia (40%) and five with complete injury AIS A (50%), all of which had paraplegia. There was a total of 58 HRV recordings, with 29 Early recordings (missing one recording from patient #5) and 29 Late recordings (missing one recording from patient #7). None of the patients were administered inotropic or vasopressor medications that may alter the heart rate or blood pressure recordings.

(I) Time of day, early versus late recording differences

We compared the means of the Early and Late recordings (Table 2) and found no significant differences. However, the Late measures were increased compared to the Early measures, with the frequency band (HF, LF) at least 2x greater than the Early measures. Late HRV recordings tended to show greater variability as calculated by the CV.

(II) HRV changes over time

We evaluated whether the HRV measures changed over time using mixed-effects modeling, accounting

**Table 1 Patient demographics.**

| Patient | Age | Sex | NLI | AIS | Recording 1 | Recording 2 (Days from injury) | Recording 3 |
|---|---|---|---|---|---|---|---|
| 1 | 45 | M | T8 | A | 39 | 46 | 58 |
| 2 | 47 | M | C4 | C | 38 | 45 | 52 |
| 3 | 47 | F | T2 | A | 13 | 23 | 31 |
| 4 | 27 | M | T2 | A | 19 | 30 | 39 |
| 5 | 20 | M | T12 | A | 29 | 36 | 43 |
| 6 | 25 | M | C2 | B | 41 | 76 | 86 |
| 7 | 33 | F | T10 | B | 24 | 31 | 37 |
| 8 | 52 | M | C4 | B | 39 | 47 | 56 |
| 9 | 36 | M | T12 | A | 17 | 25 | 32 |
| 10 | 48 | M | C4 | C | 21 | 34 | 42 |

M, male; F, female; NLI, neurologic level of injury; C1-8, cervical levels 1-8; T1-12, thoracic levels 1-12; AIS (American Spinal Cord Injury Association Impairment Scale) A, complete; B, sensory incomplete; C, motor incomplete.

**Table 2 Comparison of Time of Day BP and HRV recordings in acute SCI.**

| | Acute SCI (Early) | | | Acute SCI (Late) | | | Early v Late *p*-value |
|---|---|---|---|---|---|---|---|
| | Median | IQR | CV | Median | IQR | CV | |
| SBP (mmHg)* | 118 | 20 | 17 | 124 | 18 | 15 | 0.26 |
| DBP (mmHg)* | 67 | 18 | 27 | 73 | 13 | 18 | 0.174 |
| Mean HR (bpm) | 75 | 70–89 | 17 | 71 | 62–87 | 21 | 0.211 |
| HRV variables | | | | | | | |
| Mean RR (ms)* | 787 | 125 | 16 | 838 | 164 | 19 | 0.193 |
| SDNN (ms) | 22 | 15–31 | 59 | 27 | 18–38 | 120 | 0.158 |
| RMSSD (ms) | 2.3 | 1.6-2.8 | 41 | 2.3 | 1.8-3.2 | 89 | 0.273 |
| LF ($ms^2$) | 77 | 59–241 | 149 | 110 | 67–213 | 217 | 0.141 |
| HF ($ms^2$) | 74 | 18–127 | 149 | 108 | 31–331 | 193 | 0.127 |
| LF:HF | 1.6 | 1.1-2.3 | 60.2 | 1.4 | 1-2.5 | 219.1 | 0.382 |

SCI, spinal cord injury; BP, blood pressure; HRV, heart rate variability; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, interval of time between two consecutive R waves of the QRS complex; SDNN, standard deviation of normal sinus heart beats; RMSSD, root mean square of successive differences; LF, low frequency; HF, high frequency; LF:HF, the ratio of LF to HF; CV, coefficient of variation; * mean and SD

for repeated patient measures. We did not find significant changes of the HRV or BP values over the entirety of the recording sessions.

(III) Clinical correlations to HRV recordings

Using the mixed-effects model, we compared the HRV data over time to demographics and we found no significant differences based on age and sex. Clinical measures and outcomes (Table 3) were individually entered into the mixed-effects model for comparisons to the HRV and BP measures. We did not find a significant difference between the HRV measures in tetraplegia and paraplegia, complete and incomplete injury, or neurologic level of injury among the 58 recordings. Similarly, we did not find HRV associations to the upper, lower, and total motor scores. There were 3/10 patients who improved their neurologic exam (Improved) during rehabilitation. Compared to those who did not improve, mean RR was increased (172 ms, SD 61, P = .005) and mean HR was decreased by 16 bpm (SD 6.4, P = .015) in Improved. Increased parasympathetic activity in Improved compared to not improved as measured by HF nearly approached significance (400 $ms^2$, SD 208, P = .055).

There were four patients (40%) who experienced OH and AD. There were no significant associations found between these groups and the BP/HRV variables. There were four patients (40%) who had PIs. The group with PIs demonstrated lower SNS activity as measured by decreased LF by 472 $ms^2$ (SD 240, P = .049) and lower PNS activity as measured by decreased RMSSD by 1.2 ms (SD 0.5, P = .02). There were two patients (20%) with DVTs and we found no correlation to the HRV or BP measures between those with and without DVTs. There were four patients (40%) who developed an infection during their rehabilitation admission. We found increased PNS activity as measured by increased HF of 394 $ms^2$ (SD 191, P = .04) in those that developed an infection compared to those that did not. We did not find BP measures to be associated with any of these clinical correlates.

**Table 3 Clinical outcomes used for associations to BP and HRV recordings.**

| Subject | NLI | AIS | UEMS | LEMS | TMS | Improved | OH/AD | PI | DVT | Infection |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | T8 | A | 50 | 2 | 52 | No | Yes | Yes | No | No |
| 2 | C4 | C | 11 | 2 | 13 | No | No | Yes | No | No |
| 3 | T2 | A | 50 | 0 | 50 | Yes | Yes | No | No | No |
| 4 | T2 | A | 50 | 0 | 50 | Yes | Yes | No | No | Yes |
| 5 | T12 | A | 50 | 0 | 50 | No | No | No | No | No |
| 6 | C2 | B | 0 | 0 | 0 | Yes | No | Yes | No | No |
| 7 | T10 | B | 50 | 0 | 50 | No | No | No | No | Yes |
| 8 | C4 | B | 8 | 0 | 8 | No | No | No | Yes | Yes |
| 9 | T12 | A | 50 | 1 | 51 | No | No | No | No | No |
| 10 | C4 | C | 5 | 7 | 12 | No | Yes | Yes | Yes | Yes |

BP, blood pressure; HRV, heart rate variability; NLI, neurologic level of injury C1-8, cervical; T1-12, thoracic; AIS, American Spinal Injury Association Impairment Scale; A, complete; B, sensory incomplete; C, motor incomplete; UEMS, upper extremity motor score out of 50; LEMS, lower extremity motor score out of 50; TMS, total motor score out of 100; Improved, improved exam; OH/AD, orthostatic hypotension/ autonomic dysreflexia; PI, pressure injury; DVT, deep venous thrombosis.

NPS were collected prior to each of the 58 recording sessions and divided into thirds for analysis: NPS Category I (score 0, sessions = 20); NPS Category II (scores 1–5, sessions = 21); NPS Category III (scores 6–10, sessions = 19). We found SBP was increased in NPS Category II compared to I by 11 mmHG (SD 5.5, P = .043), but no significant difference between Category III and I. There were no associations to other BP or HRV measures.

(IV) HRV values from acute SCI, chronic SCI, and uninjured reference values

We present the HRV values obtained in acute SCI along with known reference values in uninjured adults[12] and in our sample of patients with chronic SCI.[10] The SCI groups were younger than the uninjured reference population, but sex was relatively matched between groups (Table 4). Sex, age, and percentages of tetraplegia and completeness of injury were similar between the acute and chronic SCI groups. There were many differences seen in the HRV values between these groups (Table 5). In general, there was reduced HRV in both SCI groups compared to the uninjured reference values. The variability of these measurements were similar for mean RR, SDNN, and LF:HF. The acute SCI values showed high variability with LF and HF recordings (2150, 1287, respectively).

The progression of HRV values from uninjured reference values to the cohorts of acute SCI and chronic SCI is illustrated in Fig. 1(A and B). Reference values are depicted in bars with SD, whereas the SCI groups were arranged in box plots. In Fig. 1(A), overall HRV as measured by SDNN shows a significant reduction in acute SCI which then increases in chronic SCI to within normal range of the reference values. RMSSD, a marker of PNS tone, follows the same pattern. The balance between SNS and PNS as reflected in LF:HF does not appear to change between the groups. In Fig. 1(B), mean RR remains lower in SCI compared to reference values. Both LF and HF are reduced in SCI, with chronic SCI reduced compared to acute SCI.

**Table 4 Demographics of Uninjured reference, chronic SCI and acute SCI.**

| | Uninjured reference [12] n = 21,438 | Acute SCI n = 10 | Chronic SCI[10] n = 18 |
|---|---|---|---|
| Mean (SD) | | | |
| Age (years) [missing] | 57.3 (9.7) [5, 159] | 38 (11.3) | 41.8 (14) |
| Median (IQR) | | | |
| DOI (days) | – | 26.5 (19-39) | 1395 (708-3591) |
| n (%) | | | |
| Male [missing] | 12729 (59%) [192] | 8 (80%) | 18 (72%) |
| Tetraplegia | – | 4 (40%) | 11 (44%) |
| Complete | – | 5 (50%) | 10 (40%) |

SCI, spinal cord injury; DOI, duration of injury.

## Discussion

In this limited sample size of 10 subjects with early SCI, serial ECG recordings did not reveal differences in HRV or BP parameters based on sex, age, or SCI phenotypes, nor were we able to detect HRV changes over time. Our data suggest that 5-minute HRV may be sensitive to clinical outcomes like improvement in the ISNCSCI exam and occurrence of pressure injury and infections. Furthermore, this novel data of HRV in early SCI provides missing data to help define the changes that occur to the ANS from uninjured to early injury to chronic SCI. We present data that suggests that the autonomic nervous system is changing over time after spinal cord injury, reflecting the clinical presentation of people with SCI.

**Table 5 HRV values of Uninjured reference, Acute SCI, and chronic SCI.**

| | Uninjured [12] | | Acute SCI # | | Chronic SCI [10] | |
|---|---|---|---|---|---|---|
| | n = 21,438 | | n = 10 | | n = 18 | |
| HRV | Mean (SD) | CV | Median (IQR) | CV | Median (IQR) | CV |
| Mean RR* (ms) | 926 (90) | 10 | 762 (129) | 17 | 824 (159) | 19 |
| SDNN (ms) | 50 (16) | 32 | 21 (12-26) | 62 | 41 (28-68) | 62 |
| RMSSD (ms) | 42 (15) | 37 | 2 (2-3) | 31 | 28 (11-38) | 130 |
| LF ($ms^2$) | 519 (291) | 56 | 72 (59-107) | 2150 | 0.06 (0.05-0.08) | 48 |
| HF ($ms^2$) | 657 (777) | 118 | 60 (13-120) | 1287 | 0.19 (0.16 −0.24) | 33 |
| LF:HF | 2.8 (2.6) | 93 | 1.6 (0.9-2.7) | 76 | 2 (1.4-2.6) | 95 |

SCI, spinal cord injury; RR, interval of time between two consecutive R waves of the QRS complex; SDNN, standard deviation of normal sinus heart beats; RMSSD, root mean square of successive differences; LF, low frequency; HF, high frequency; LF:HF, the ratio of LF to HF; # only first recordings used; CV, coefficient of variation; *mean and SD.

We expected to detect significant changes in the HRV measures over time during acute inpatient rehabilitation because clinically, healthcare providers have appreciated the changes in the ANS from the acute to chronic phase of SCI. Symptoms like bradycardia may reduce in frequency and intensity,[18] while AD may increase in frequency with time post-injury.[19] The highest risk of DVT and PE occurs within months after SCI and then declines.[20,21] However, objective measures of the changing ANS are lacking in routine clinical practice. In this pilot study, HRV data from patients were recorded between 13 and 86 days from injury, with an average of 10 days between recording sessions. It is quite possible that HRV is not sensitive enough to detect changes within this duration. To detect the ANS changes using HRV, more time between recordings is needed, as seen in the comparisons to people with chronic SCI.

Based on the limited available 5-minute HRV data, there seems to be a difference between the HRV measures from acute SCI and chronic SCI, ostensibly representing a change in the ANS. Our findings suggest that all HRV values decrease after SCI, while the ratio of SNS to PNS remain stable. Our comparisons suggest that as the SCI progress from acute to chronic, some HRV values trend towards returning to uninjured reference values (SDNN, RMSSD), some values remain low (mean RR), and some decrease even further (LF, HF). Findings from other studies in chronic SCI HRV further support the ANS progression after SCI. In studies of chronic SCI, a distinction can be seen in HRV analyses between tetraplegia and paraplegia, with increased SNS tone as measured by LF in paraplegia compared to tetraplegia,[10,11] as well as increased PNS tone measured by HF.[11] We did not find these HRV differences in our limited cohort of people with acute SCI, which may support the concept that the ANS changes over time after SCI, leading to differences in paraplegia versus tetraplegia in the chronic phase and further supporting the possibility that HRV can be used to measure these ANS changes. Longitudinal studies in SCI are needed to evaluate the changes in HRV over time.

We expected to find HRV differences in patients experiencing clinical sequela of autonomic dysfunction, like AD, OH, and pressure injuries. While we did not find a difference in those with AD and OH, we did find that those with pressure injuries had reduced SNS and PNS activity as measured by LF and RMSSD, respectively. Again, caution is needed in interpretating the results of this limited data set. However, the development of a tool that could predict or risk-stratify patients that may develop pressure injuries is an exciting idea that could lead to improved management, better outcomes, and cost-saving benefits for patients and the healthcare system.

We were also interested in using HRV to measure the potential for neurologic recovery. We were able to detect HRV differences between patients that we classified as having improved neurologic exam. Patients that exhibited improved neurologic exam while in acute rehabilitation had increased PNS activity as measured by mean RR and HF. Noteworthy, two of the three patients that improved their neurologic exam during inpatient rehabilitation had complete thoracic injuries. Measuring improvements in neurologic exam in thoracic spinal cord injuries rely on time-consuming, subjective measures of light touch and pin prick dermatomal tests that can be unreliable.[22] The development of a quick, reliable tool that can predict potential for neurologic improvement in SCI would be innovative. However, there were other clinical correlations to increased PNS activity, such as infection and high pain scores. One of the three patients with improved neurologic exam had an infection, confounding these findings. However, one of the Improved patients developed a pressure injury, which was associated with decreased PNS activity. A much larger

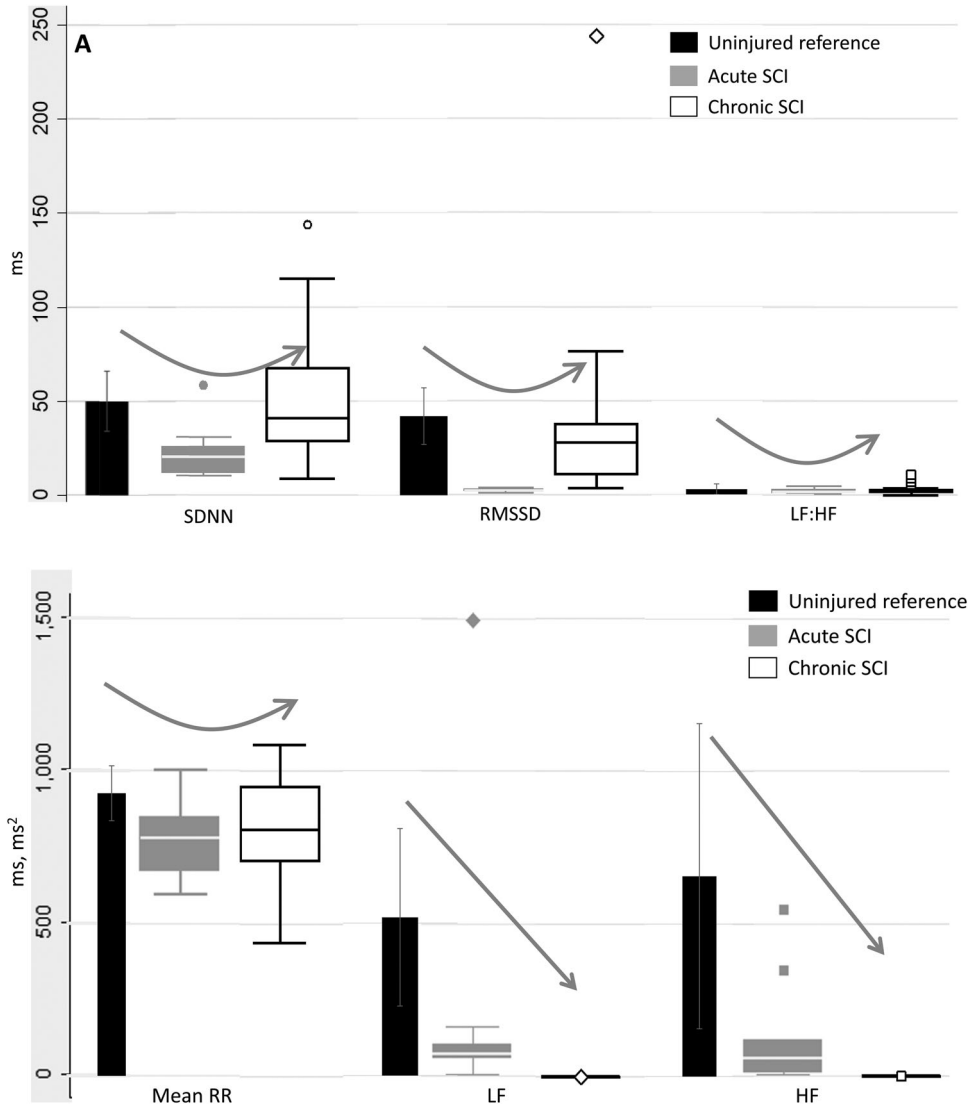


**Figure 1 Uninjured references, acute spinal cord injury (SCI) and chronic SCI arranged by HRV measures. (A) SDNN (standard deviation of normal sinus heart beats) and RMSSD (root mean square of successive differences) follow similar pattern of decreased values in acute SCI and increasing towards uninjured reference values in chronic SCI. (B) Mean RR (interval of time between two consecutive R waves of the QRS complex) follows the pattern of an acute decrease after SCI and increase towards uninjured reference values. LF (low frequency) and HF (high frequency) decrease after SCI and further decrease in chronic SCI. Grey arrows highlight the trends in HRV values from uninjured to acute SCI to chronic SCI. Data outliers, defined as a number which is greater than the third quartile by more than 1.5 times the interquartile range, are shown as separately plotted points (circle, diamond, square) above the box plot.**

sample size would be required to elucidate the ANS associations to clinical outcomes in order to control for confounding variables.

Infections in early SCI can lead to permanent, decreased recovery, and the ANS, specifically the SNS, is implicated in the immune system dysregulation.[16,23] Although we did not see a change in LF, representing the SNS, we did find increased PNS activity as measured by HF in those with infections. It has been suggested that an inverse relationship exists between markers of PNS tone and inflammation.[24] We may postulate that our findings supports this mechanism, such that those that developed infection had a weakened immune system and a higher PNS tone. More research is needed to determine if such a relationship exists and whether HRV can be used to identify those at risk for infection.

There were several limitations to this observational study, primarily the small sample size of our cohort. More patients would be needed to help control for potential confounding variables that impact the HRV measurements. The small sample size may also account for the lack of differences seen, for example,

between tetraplegia and paraplegia. Furthermore, while ECG recordings were standardized, the clinical environment lacks many of the controls available in the laboratory setting. However, the longitudinal recordings of BP and HRV were surprisingly stable, regardless of time of day, which supports the possible use of HRV as clinical tool. Additionally, to truly appreciate changes of the ANS over time, many more days, perhaps tracking to the chronic stage, would be needed between recordings. Findings from this exploratory trial will help to develop larger informative trials.

In summary, HRV was stable in acute SCI and our results provide preliminary findings of the progression clinically seen in the ANS after SCI from acute to chronic stages. The use of HRV as a surrogate marker of ANS function may provide the much-needed objective data to help fill the gaps in knowledge. With further research, HRV parameters could be correlated with clinical sequalae in the SCI population which have long recognized the need for improved ANS research.

## Conflict of interest

No potential conflict of interest was reported by the author(s).

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## References

1 Birmingham UoAa. National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL, 2021.
2 Taylor JA. Autonomic consequences of spinal cord injury. Auton Neurosci 2018;209:1–3. doi:10.1016/j.autneu.2017.09.015.
3 Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 2004;21(10):1371–1383. doi:10.1089/neu.2004.21.1371.
4 Hagen EM, Faerestrand S, Hoff JM, *et al*. Cardiovascular and urological dysfunction in spinal cord injury. Acta Neurologica Scandinavica Supplementum 2011;191:71–78. doi:10.1111/j.1600-0404.2011.01547.x. [published Online First: 2011/07/08].
5 Tsuji H, Larson MG, Venditti Jr. FJ, *et al*. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94(11):2850–2855. doi:10.1161/01.cir.94.11.2850. [published Online First: 1996/12/01].
6 Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93(5):1043–1065. [published Online First: 1996/03/01].
7 Goldstein DS, Bentho O, Park MY, *et al*. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol 2011;96(12):1255–1261. doi:10.1113/expphysiol.2010.056259. [published Online First: 2011/09/06].
8 Ditor DS, Kamath MV, Macdonald MJ, *et al*. Reproducibility of heart rate variability and blood pressure variability in individuals with spinal cord injury. Clin Auton Res 2005;15(6):387–393.
9 Karri J, Zhang L, Li S, *et al*. Heart rate variability: A novel modality for diagnosing neuropathic pain after spinal cord injury. Front Physiol 2017;8:495. doi:10.3389/fphys.2017.00495.
10 Stampas A, Zhu L, Li S. Heart rate variability in spinal cord injury: asymptomatic orthostatic hypotension is a confounding variable. Neurosci Lett 2019;703:213–218. doi:10.1016/j.neulet.2019.03.020.
11 Kyriakides A, Poulikakos D, Galata A, *et al*. The effect of level of injury and physical activity on heart rate variability following spinal cord injury. Journal of Spinal Cord Medicine 2017;4:1–8.
12 Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. Pacing and Clinical Electrophysiology: PACE 2010;33(11):1407–1417. doi:10.1111/j.1540-8159.2010.02841.x. [published Online First: 2010/07/29].
13 Kanjwal K, George A, Figueredo VM, *et al*. Orthostatic hypotension: definition, diagnosis and management. Journal of Cardiovascular Medicine 2015;16(2):75–81. doi:10.2459/01.jcm.0000446386.01100.35. [published Online First: 2014/06/17].
14 Krassioukov A, Warburton DE, Teasell R, *et al*. A systematic review of the management of autonomic dysreflexia after spinal cord injury. Arch Phys Med Rehabil 2009;90(4):682–695. doi:10.1016/j.apmr.2008.10.017. [published Online First: 2009/04/07].
15 Cruse JM, Keith JC, Bryant Jr. ML, *et al*. Immune system-neuroendocrine dysregulation in spinal cord injury. Immunol Res 1996;15(4):306–314. doi:10.1007/bf02935314. [published Online First: 1996/01/01].
16 Stampas A, Dominick E, Zhu L. Evaluation of functional outcomes in traumatic spinal cord injury with rehabilitation-acquired urinary tract infections: A retrospective study. J Spinal Cord Med 2019 Sep;42(5):579-585. doi:10.1080/10790268.2018.1452389.
17 de Mestral C, Nathens AB. Prevention, diagnosis, and management of surgical site infections: relevant considerations for critical care medicine. Crit Care Clin 2013;29(4):887–894. doi:10.1016/j.ccc.2013.06.009. [published Online First: 2013/10/08].
18 Lehmann KG, Lane JG, Piepmeier JM, *et al*. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: incidence, time course and severity. J Am Coll Cardiol 1987;10(1):46–52. doi:10.1016/s0735-1097(87)80158-4. [published Online First: 1987/07/01].
19 McKinley WO, Jackson AB, Cardenas DD, *et al*. Long-term medical complications after traumatic spinal cord injury: a regional model systems analysis. Arch Phys Med Rehabil 1999;80(11):1402–1410. doi:10.1016/s0003-9993(99)90251-4. [published Online First: 1999/11/24].
20 Chung WS, Lin CL, Chang SN, *et al*. Increased risk of deep vein thrombosis and pulmonary thromboembolism in patients with spinal cord injury: a nationwide cohort prospective study. Thromb Res 2014;133(4):579–584. doi:10.1016/j.thromres.2014.01.008. [published Online First: 2014/01/25].
21 Kim SW, Charallel JT, Park KW, *et al*. Prevalence of deep venous thrombosis in patients with chronic spinal cord injury. Arch Phys Med Rehabil 1994;75(9):965–968. [published Online First: 1994/09/01].
22 Hales M, Biros E, Reznik JE. Reliability and validity of the sensory component of the international standards for neurological classification of spinal cord injury (ISNCSCI): A systematic review. Top Spinal Cord Inj Rehabil 2015;21(3):241–249. doi:10.1310/sci2103-241. [published Online First: 2015/09/14].
23 Kopp MA, Watzlawick R, Martus P, *et al*. Long-term functional outcome in patients with acquired infections after acute spinal cord injury. Neurology 2017;88(9):892–900. doi:10.1212/wnl.0000000000003652. [published Online First: 2017/01/29].
24 Williams DP, Koenig J, Carnevali L, *et al*. Heart rate variability and inflammation: A meta-analysis of human studies. Brain Behav Immun 2019;80:219–226. doi:10.1016/j.bbi.2019.03.009. [published Online First: 2019/03/16].