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AUTONOMIC DYSREGULATION AND LOW HEART RATE VARIABILITY IN SPINAL CORD INJURY (SCI): A MARKER FOR DEPRESSION

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ABSTRACT

Background: Spinal cord injury (SCI) results in physical, autonomic, and psychological consequences. Depression is among one the most common psychological effects of SCI, with an incidence of 22%. Depression is associated with reduced heart rate variability (HRV), but it remains unclear if autonomic dysregulation possesses depression risk in SCI. Thus, this study aims to explore the association between HRV and depression in SCI.

Methodology: Ninety-one spinal cord injured patients (eighty-eight males and three female) representing three levels of severity of injury (cervical, high thoracic, and low thoracic) were recruited. Basal/resting HRV was assessed using 1000Hz Polar Heart rate monitor RS800 CX and Kubios HRV software. PHQ-9 assessed the depression; a cut of 10 was used to divide the sample into patients with probable Major Depressive Disorder (MDD) and non-MDD.

Results: Non-parametric tests for between-group comparisons showed a significant difference in HRV variables ($p<0.05$) between the probable MDD and non-MDD SCI. Significant differences in HRV were observed between the low and high thoracic ($p<0.05$) and low thoracic and cervical group ($p<0.05$), suggesting that the functioning of the autonomic nervous system might differ with level of SCI.

Conclusion: Depression in SCI has been associated with injury-related factors; we use the neurovisceral theory to explain the role of the autonomic nervous system in depression in SCI.

Keywords: Autonomic nervous system, HRV, depression, spinal cord injury, PHQ-9, Neurovisceral Theory

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INTRODUCTION

Depression is linked with autonomic nervous system dysregulation; the parasympathetic nervous system fails to inhibit the sympathetic branch of the nervous system that continues to process affective states such as emotion arousal in an uninhibited manner [1]. This reduced inhibition by the parasympathetic nervous system reflects the monotonous functioning of the autonomic nervous system, possibly reflective of reduced social and emotional interactions. Depression reduces the physical activity of the body, and it is unclear whether the severing of the spinal cord and the resulting reduced physical activity impacts depression - the estimated prevalence of depression rate in spinal cord injured (SCI) patients is around 22% [2].

Further, depression in SCI is detrimental to rehabilitation outcomes, as it is associated with various physical and psychological consequences like reduced functional independence, secondary complications, reduced community and social integration, and lower motor score along with a reduction in quality of life [3-6]. Meta-analyses show that depression to be a risk factor for various somatic disorders like cardiovascular diseases, stroke, diabetes, and obesity. Depression has been identified as a significant risk factor for developing cardiovascular diseases [1,7,8]. Depression has been associated with the impaired cardiac autonomic activity. The most commonly studied index for the cardiac autonomic system is Heart rate variability (HRV). Reduced HRV is associated with depression [9,10], and it acts as a potential risk factor for cardiovascular disease in subjects with depression [10]. SCI has been associated with impairment in the cardiac autonomic nervous system [11], and HRV is reduced in SCI as well as is sensitive to the level of injury [11-14]. Studies also show that SCI and life-style factors increase the risk of cardiovascular diseases as compared to that of healthy counterparts [15]. The autonomic nervous system is common to depression and cardiovascular disease risk in SCI. A large population-based study suggests a higher risk of depression in SCI, and low-income was found as one of the risk factors [16]. It is unclear if autonomic dysregulation is linked with depression in SCI in low-income countries such as India. Therefore, the main aim of this study is to explore the association of autonomic dysregulation in the form of HRV with depression in spinal cord injury.

METHODOLOGY

Sample: A total of ninety-one participants with Spinal cord injury aged between 18-40 years were recruited for the study. The study had ethical clearance from the Institutional Ethical clearance board of Indian Spinal Injuries Center. SCI who were hemodynamically stable with the level of injury from the cervical vertebra C4 to Thoracic vertebra T12, were included for the study. Any participant with a clinical diagnosis of cardiovascular diseases, traumatic brain injury, and any other systemic illness were excluded from the study.

Procedure

The participants were recruited after obtaining informed consent. The participants of the study were briefed about the procedure of recording of Heart rate variability. The participants were instructed to tie the strap of Polar Heart rate monitor around the xiphisternum, and five minutes recording was done by Polar Heart rate monitor RS 800 CX in sitting position in the wheelchair [12,17]. During the recording procedure, the participants were instructed to do normal breathing and restrain from any activities, thus forming the baseline resting recording—following which the participants were asked to fill PHQ 9. The signal processing was done by Kubios Heart rate variability software standard version 2.1.

Tools used

Depression - PHQ-9

PHQ- 9 was used to screen depression in subjects with spinal cord injury. Patient Health questionnaire – 9 is a self-administered nine-item depression questionnaire devised to identify probable major depressive disorder (MDD). Items are rated in terms of how persistent the symptoms have been in the past 2 weeks: 0 – not at all, 1 – several days, 2 – more than half of the days, 3 – nearly every day. The total score of the questionnaire ranges from 0-27. A cut-off =10 was used to divide the sample into probable major depressive disorder (MDD) and non-MDD [18,19]. Internal consistency for the overall PHQ-9 scale was reported to be high; Cronbach's alpha = 0.89 [20].

Heart rate variability- Kubios Heart rate variability software (standard version 2.1)

Polar RS 800 CX was used to record the RR variability of the participant. Kubios Heart rate variability software (standard version 2.1) was used to calculate the heart rate variability. The sampling rate was at 1000Hz. An average of five minutes recording using Polar RS 800 CX was done. The Heart rate monitor (hrm) files obtained from the polar heart monitor was uploaded to the Kubios Heart rate variability software (standard version 2.1) for further analysis. Both time domain and frequency domain analysis was used for the study. The RR-time series were automatically detected using the Kubios QRS detection algorithm, which used band-pass filtering and moving average filtering. The RR-time series were then processed using automatic artifact detection and detrending. The pre-processed RR-time series was then subjected to time and frequency domain analysis [21].The time-domain methods used statistical analysis of series of successive RR intervals and applied directly to the series of successive RR interval values. Mean value of heart rate HR(Mean HR), a mean value of RR interval (Mean RR), SDNN, RMSSD, NN50, and PNN50 were calculated. SDNN is the standard deviation of normal-to-normal(NN), RR intervals and requires long duration recording [21], thus not considered for the current study. NN50 is the number of successive intervals differing more than 50 ms, and pNN50 is the relative percentage of NN50 overall NN interval. RMSSD

is the square root of the mean of the sum of the squares of differences between adjacent NN intervals. Thus, among the time - domain Mean HR, RMSSD, NN50, and pNN50 were considered for analysis.

For the frequency domain analysis, the RR time series was equidistantly sampled at the sampling rate of 4 Hz (default in Kubios 2.1) for further spectral analysis. Using Welch's periodogram method, the RR-time series was divided into overlapping segments (50% overlap), which were windowed (256s width). Both time domain and frequency domain analysis were performed. Fast Fourier transformation method was used to average these windows was averaged to yield spectrum estimates. The spectrum estimates are then divided into very low frequency (VLF), low frequency (LF), and high frequency (HF) bands. The limits for these bands are 0–0.04 Hz (VLF), 0.04–0.15 Hz (LF), and 0.15–0.4 (HF)(22). As the interpretation of VLF should be done with the recording of longer duration [22], thus for the study, the absolute values of LF, HF, and the ratio has been analyzed.

Data analysis

The statistical package SPSS 21 was used for data analysis. Among the HRV parameters, both time domain and frequency domain parameters were taken for analysis. The SCI participants were divided into two groups based on the PHQ-9 scores. Group 1(Non- Major Depressive Disorder) had PHQ-9 scoreless than equal to 10, and Group 2(Major Depressive Disorder) had PHQ-9 score greater than 10. Both HRV parameters, and PHQ-9 scores were not normally distributed, thus nonparametric tests were done for analysis.

RESULTS

Demographics

A total of ninety-one participants were recruited for the study after meeting the inclusion and exclusion criteria. The sample characteristics of Group 1 (Non- Major Depressive Disorder) and Group 2 (Major Depressive Disorder) are in Table 1. The two groups were comparable in age (t= -0.20, p=0.83) and duration of injury (t= 0.62, p=0.11)

Table 1: Demographic details of the groups

	Group 1 N=44 Mean(SD)	Median	Group 2 N=47 Mean(SD)	Median
Age(years)	26.47(7.61)	25	26.48(6.65)	26
Level of injury	Cervical = 10 High thoracic = 08 Low Thoracic = 26		Cervical = 26 High thoracic = 21	
Gender	Male = 43 Female = 01		Male = 45 Female = 02	
Duration of injury (months)	8.02(3.12)	8	7.00(3.49)	7
PHQ-9 score	6.13(4.24)	9	13.65(1.86)	14
Mean RR (ms)	535.53(73.93)	524.00	514.37(95.53)	522.60
Mean HR(bpm)	114.83(14.96)	114.74	115.25(25.06)	112.93
RMSSD(ms)	17.60(13.26)	11.80	11.77(11.61)	7.60
NN50 (count)	19.77(53.44)	2.00	2.76(4.04)	0.00
PNN50 (%)	3.56(8.55)	0.40	0.94(1.79)	0.01
LF(ms^2)	275.29(402.88)	138	171.32(244.33)	47
HF(ms^2)	105.93(185.58)	32	39.41(66.49)	10
LF/HF	4.57(3.51)	3.93	5.07(4.52)	3.93

Group 1-Non- Major Depressive Disorder

Group 2-Major Depressive Disorder

HR- Heart rate, RR-RR interval, RMSSD- square root of the mean of the sum of the squares of differences between adjacent NN intervals, NN50- Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, pNN50%- NN50 count divided by the total number of all NN intervals, LF- low frequency, HF- High Frequency

Difference of HRV between depressed and non-depressed SCI

Among the time- domain parameters RMSSD, NN50 count showed a significant difference between the groups. In the frequency domain parameters, Low frequency (LF) and High frequency (HF) showed a significant difference between the two groups. Still, the ratio had no significant difference (Table 2) though the mean value of the ratio was higher in Group 2 (Major Depressive Disorder).

Table 2: Comparison of HRV values between depressed and Non-depressed SCI at baseline

	Group 1 N=44 Mean rank	Group 2 N=47 Mean rank	Mann-Whitney U	p
Mean RR(ms)	45.21	41.79	851	0.52
Mean HR(bpm)	42.84	44.16	953.00	0.80
RMSSD(ms)	50.97	36.03	603.50	0.01
NN50 (count)	49.63	37.37	661.00	0.02
PNN50 (%)	48.42	38.58	713.00	0.06
LF(ms^2)	49.70	38.16	695	0.03
HF(ms^2)	50.89	36.95	643	0.01
Ratio	46.34	45.68	1019	0.90

Level of significance $p<0.05$, Group 1-Non- Major Depressive Disorder Group 2-Major Depressive Disorder HR- Heart rate, RR-RR interval, RMSSD- square root of the mean of the sum of the squares of differences between adjacent NN intervals, NN50- Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, pNN50%- NN50 count divided by the total number of all NN intervals, LF- low frequency, HF- High Frequency.

Difference in HRV and depression score within the level of injury

For analysis, the SCI participants were divided into 3 groups- Cervical(C4-C7), High Thoracic(T1- T5), and Low Thoracic (below T-6). The division is based on the vertebral level- Cervical(C) and Thoracic (T) [14,23]. There was a significant difference observed for RMSSD, NN50, pNN50, LF, and HF parameters. PHQ-9 also showed similar results with the level of injury (Table 3). The pair-

wise comparison between each level of injury was done for the significant parameters (Table 4).

Table 3: Comparison of depression score and HRV across the levels of injury

	Kruskal Wallis Test parameter	p
PHQ - 9	53.22	0.01
Mean RR(ms)	2.77	0.25
Mean HR(bpm)	1.62	0.44
RMSSD(ms)	8.83	0.01
NN50 (count)	8.38	0.01
PNN50 (%)	7.63	0.02
LF(ms^2)	11.61	0.003
HF(ms^2)	14.15	0.001
Ratio	0.03	0.97

Level of significance p<0.05, HR- Heart rate, RR-RR interval, RMSSD- square root of the mean of the sum of the squares of differences between adjacent NN intervals, NN50- Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, pNN50%- NN50 count divided by the total number of all NN intervals, LF- low frequency, HF- High Frequency.

Table 4: Pair-wise comparison between levels of injury

	Cervical(1) mean rank	High thoracic(2) mean rank	Low thoracic(3) mean rank	1/2	1/3	2/3
PHQ - 9	59.46	57.78	14.23	NS	0.01	0.01
RMSSD (ms)	39.09	37.24	55.6	NS	0.03	0.02
NN50 (count)	38.44	38.76	54.85	NS	0.03	0.04
PNN50 (%)	38.73	38.91	54.33	NS	0.04	0.06
LF(ms^2)	40.61	35.27	57.71	NS	0.03	0.003
HF(ms^2)	38.55	36.05	59.48	NS	0.005	0.002

Level of significance p<0.05, RMSSD- square root of the mean of the sum of the squares of differences between adjacent NN intervals, NN50- Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, pNN50%- NN50 count divided by the total number of all NN intervals, LF- low frequency, HF- High Frequency, NS- non – significant

DISCUSSION

The results suggest that autonomic dysregulation in the form of HRV might be linked with depression in SCI.

Among the HRV parameters, RMSSD, NN50, pNN50, and High frequency (HF) represents the parasympathetic activity. Low frequency (LF) represents both sympathetic and parasympathetic influences. The LF/HF ratio indicates the sympathovagal balance (Guidelines for Heart rate variability 1996, Shaffer and Ginsberg 2017, Shaffer, Mc Carty, and Zerr 2014). A recent meta-analysis by Koch et al. 2019 has shown that among the HRV parameter, RMSSD, LF, and HF are reduced in major depressive disorder with an increase in the LF/HF ratio [10]. The current study results showed a similar difference in HRV esp in HF and LF between MDD and non-MDD SCI participants, except for the sympathovagal balance (LF/HF ratio), which failed to show the difference. The spinal cord injury causes an impairment of the sympathetic activity until the thoracic level T6 (Sorenson et al. 2017) [11] and therefore the ratio must have failed to show a difference between the group. Further, the results of the current work suggest that the sympathovagal balance is disrupted in SCI; that is, the parasympathetic activity fails to regulate the sympathetic activity (Serro Ano et al. 2015, Malmquist et al. 2015) [12,14]. In line with the meta-analysis by Koch et al. 2019 [10], the NN50 showed a significant difference between the groups, and pNN50 showed significant difference at p=0.06 level, with mean rank values reduced in MDD group (Table 2). The NN50 parameter represents the parasympathetic system as per Guidelines for Heart rate variability 1996 [22], and further suggests that reduced parasympathetic activity in depression.

Similar to other populations (Kemp et al. 2013, Kemp et al. 2010, Koenig et al. 2016) [9,24,25] even spinal cord injured participants of the current study showed reduced HRV in a major depressive group. The possible explanation of the role of cardiac autonomic regulation in depression roots from the Neuro-visceral Integration model (NVI) that suggests that depression might have a neurophysiological basis. High frequency (HF) HRV is reflecting cardiac autonomic regulation and is mandatory for goal-oriented behavior, absence of which is associated with clinical depression(Thayer and Lane 2000, Thayer et al. 2009, Beauchaine et al. 2015) [26–28]. The results also imply the co-morbidity of depression and cardiovascular problems in SCI. The current guidelines by Nash et al. 2018 evaluating the cardio-metabolic risk in SCI consider glucose levels, lipid level, obesity, physical activity level, and hypertension as possible risk factors [15]. According to Vaccarino et al. 2019, depression is an important risk factor for coronary heart disease has not been considered in SCI [8]. The results of this study indicate the cardiac autonomic dysregulation in SCI should prompt screening of depression and cardiovascular diseases in SCI.

Another aspect the study explored how HRV parameters and depression scores differed along with the level of injury. The results show that both depression and HRV parameters change with the level of injury. Pair-wise comparisons showed that both PHQ-9 and HRV parameters showed a similar trend; that is, both failed to differ significantly between the cervical and high thoracic but differed within the thoracic levels (Table 3 and 4). According to Biering-sørensen 2017, HRV is mainly affected by the T-6 level [11], which was reflective in the severity of PHQ-9. The results further offer motivation to examine the neurophysiological aspect of depression as per the severity of depression in SCI.

CONCLUSION

As expected, we found reduced inhibition of a parasympathetic nervous system reflected in low HRV to be a critical marker of depression in SCI. Further, the extent of autonomic dysregulation in the form of low HRV differed with severity in SCI. To the best of our knowledge, this is the first of its kind study, which offers insights into the neurophysiological aspect of depression in SCI. The HRV measures might be useful in predicting depression, and depression should be regularly screened and treated for better management of spinal cord injury.

Limitations and future recommendations:

This current study confirmed that cardiac autonomic dysregulation indicated in reduced HRV might be a marker for depression in SCI, and the severity of depression and HRV dysregulation might be inter-linked.

Since this study was cross-sectional, longitudinal studies could be undertaken for establishing the association of cardiac autonomic regulation and depression in spinal cord injury in the future. Adequate sample size, according to a different level of spinal cord injury, could be taken to strengthen the evidence further. The severity of depression, followed by the pattern of HRV dysregulation in SCI, could also be investigated for future studies.

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