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"Assessment Of Cardiac Autonomic Dysfunction In Children With Cerebral Palsy Using Heart Rate Variability"

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Abstract:
Background*: Cardiac autonomic imbalance in children with CP might be due to primary brain insult, vary with different levels of Gross Motor Functional Classification System or may alter with multimodal therapies in various types of cerebral palsy [(1,2)]. It is important to understand and to create awareness that autonomic impairment in children with CP is in part due to sedentary lifestyle [(3)].HRV(Heart Rate Variability) in cerebral palsy is recognized as an important tool for monitoring cardiovascular health, in which autonomic imbalance is characterized by reduced HRV (i.e. regarded as increased cardiac sympathetic activity and decreased vagal modulation) [(4,5)] . Of the research that does exist, each study discusses only very few parameters of the autonomic nervous system, thus providing opportunities for further research and hence the need for the study*.
Materials and Methods*: This is a cross-sectional case control study of 51 children with Cerebral Palsy (CP) and 51 normal children, conducted at District Early Intervention Centre (DEIC) in the Department of Paediatrics, Vani Vilas hospital. These 51 cases were assessed and classified based on their demographic features, etiology, type of CP, GMFCS scale and with the objectives of assessing the heart rate variability (HRV) in children with cerebral palsy and compare it with controls in both supine position and after a stress test, and also to correlate the obtained parameters with GMFCS level, type of CP using a systematically designed proforma.*
Results*: Results of the study showed that of the children with CP studied, 62% were male children, and majority of were between 6-8 years of age (58%), and it was found that the most common etiology for CP in our study was due to perinatal asphyxia (43%), and 80% of the children had history of NICU admission. Of the 51 cerebral palsy children studied 72% were in GMFCS levels 3 and 4, regarding the topographical classification majority had spastic quadriplegia (58.8%) followed by spastic diplegia (15.7%). Study revealed that cerebral palsy children had significantly lower HRV, higher sympathetic activity, autonomic response deficit to stress test, and higher autonomic dysfunction when compared to normal children. Among cases, HRV was lowest with spastic quadriplegia and triplegic CP, in functional classification HRV was lowest among GMFCS 4 and 3.*
Conclusion*: Cerebral palsy children had significantly higher sympathetic activity and less cardiac vagal modulation compared to normal children in supine position and there was existence of autonomic response deficit in cerebral palsy children after stress test, higher the motor impairment, higher was the sympathetic activity.*
Keyword: *Cerebral palsy, Heart rate variability, autonomic instability, spasticity, GMFCS levels*

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I. Introduction

Cerebral Palsy (CP) in children is the most common cause of severe physical disability, with an estimated prevalence of 2.4 per 1000 children. Disturbances in homeostatic functions due to autonomic dysfunction have been observed in these children. [(6)] Cardiac autonomic imbalance in children with CP might be due to primary brain insult, varies with different levels of Gross Motor Functional Classification System or may alter with multimodal therapies in various types of cerebral palsy [(1,2)]. It is important to understand and to create awareness that autonomic impairment in children with CP is in part due to sedentary lifestyle [(3)]. Heart rate variability (HRV) is characterized by significant beat-to-beat variability of the R-R intervals and its measure is considered an easy and non-invasive method of providing indirect assessment of the modulation of the sympathetic and parasympathetic branches on the sinoatrial node's intrinsic rhythm [(7,8)]. HRV in cerebral palsy

is recognized as an important tool for monitoring cardiovascular health, in which autonomic imbalance is characterized by reduced HRV (i.e. regarded as increased cardiac sympathetic activity and decreased vagal modulation) [4,5] . Performing physical activity is highly recommended for children with CP. Cardiac autonomic response to exercise is an essential component in achieving the desirable treatment effect, thus re-educating the cardiac autonomic system. [9,10]

Of the research that does exist, each study discusses only very few parameters of the autonomic nervous system in CP children thus providing opportunities for further research in this area. Hence this study was designed to assess the autonomic dysfunction in children with cerebral palsy, also to evaluate and compare the Heart rate variability in CP and normal children.

II. Material And Methods

Data was collected from children attending the District Early Intervention Centre (DEIC) in the Department of Paediatrics, Vani Vilas hospital, attached to Bangalore Medical College and Research Institute, between the period of Feb 2021 to Aug 2022.

Study Design: Cross-sectional case control study.

Study Location: This was a tertiary care teaching hospital based study done in Department of Paediatrics, at Vani Vilas Hospital, Bangalore Medical College and Research Institute, Bangalore.

Study Duration: Feb 2021 to Aug 2022

Sample size: 51 cases and 51 controls.

Sample size calculation: The sample size was calculated from the formula $n = \frac{(Z\alpha)2.(\sigma)2}{(d)2}$, where n=sample size, σ = 10.2 (pooled standard deviation of heart rate variability), Zα= z-value corresponding to the desired power (approx. 1.96), d= 2.8 (expected effect size/difference in means), computing all the parameters, the sample size was finalized to be 51 cases and 51 controls.

Subjects & selection method: The cases were selected from cerebral palsy children attending DEIC clinic at Vani Vilas Hospital,BMCRI. Accordingly, age and sex matched controls were chosen among siblings of patients attending the OPD and from the healthy children of healthcare workers working in the hospital.

Inclusion criteria:

1. Patients clinically diagnosed with CP
2. Children with CP attending DEIC whose parents have given written consent for the study.
3. Children, both boys and girls in the age group of 6-18 years, Control group includes age and sex matched normal children.

Exclusion criteria:

1. Children with cardiovascular and/ or respiratory disease
2. Recent surgeries (in the preceding 1 year)
3. Use of botulinum toxin within the six-month period prior to the study
4. Drugs influencing autonomic nervous system

Procedure methodology

Informed written consent was taken from all the study subjects, the anthropometric profile of the children including body weight (kg), height (cm), Head circumference and BMI were recorded. GMFCS staging was done according to Annexure 3 and type of CP was also analyzed, the demographic profile of the child was entered according to Annexure 2.

Measurement of HRV: All assessments were carried out in the afternoon in order to minimize circadian changes. Room temperature was maintained at 22-26ºC and relative air humidity at between 40 and 60%. One week and the day prior to the cardiac autonomic control assessment, the children and their parents or guardians received relevant instructions to ensure a safe and satisfactory performance. Instructions were given to avoid the consumption of stimulating beverages or foods (e.g., coffee, soda, energy drinks, chocolate, black or green tea etc.,) and to suspend any major physical activity at least 24h before the testing, to have a light meal before the testing and to have a good night's rest. Precautions were taken to obtain an artefact free recording. Subjects were rested comfortably in supine position for 5 minutes and then ECG of the subjects were recorded in Lead II

for 3 minutes using three electrodes placed in right infraclavicular region, left infraclavicular region and left iliac region, the same procedure repeated for the child in standing position. For children who are unable to perform the orthostatic test, ECG was recorded using ergometric exercises such as squeezing a sponge ball, pulling a pulley, the children who were unable to perform the ergometric exercises were made to sit at 70^0 position to the surface and then the ECG was recorded, children with GMFCS level V were excluded. HRV parameters, time and frequency domain both were measured according to the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology.

Time Domain: The following parameters were assessed:

SDNN- Standard deviation of Normal-to-Normal RR interval, recorded in milliseconds(ms), SDNN reflects all the cyclical components responsible for variability in the period of recording. Lower values of SDNN indicate higher sympathetic activity.

RMSSD- It is square root of the mean squared difference of successive Normal to Normal RR interval, measured in milliseconds (ms), denotes vagal modulation of heart rate, lower values indicate lower parasympathetic activity

Frequency Domain: Power spectral analysis is used to determine the frequency domain parameters. Power Spectral Density analysis (PSD) extrapolates the heart rate signal into its frequency components and then it is quantified in term of their relative intensity, which is termed as power. Low Frequency (LF)- Normal range is (0.04-0.15 Hz) is influenced by both parasympathetic and sympathetic activity. High Frequency (HF) - Normal range is (0.15-0.4 Hz) influenced by parasympathetic activity. LF/HF ratio - indicates sympatho-vagal balance. Power Spectral Density analysis was plotted in ms^2 /Hz against preset frequency.

The artefact free recording was analysed using RMS Power Lab 26T device (4 channel, 16-bit resolution polygraph) from AD instruments. Lab chart 8 software from AD instruments was used for analysis, Frequency of acquisition was 500 Hz.

Assessment Tools: Heart Rate Variability- Frequency domain and Time domain parameters

Statistical analysis

Data was entered into Microsoft Excel and statistical analysis was carried out in SPSS software version 17.0. Qualitative variables like consanguinity, cry at birth, NICU admission, ante-natal and post-natal risk factors, developmental quotient, microcephaly, BMI, co-morbid conditions, type of CP and functional classification within the groups were presented as frequency and percentages. A comparison of age and birth weight between the cases and controls was done using independent t test. Distribution of gender between the groups was done using a chi squared test. Quantitative variables like HR, GMFCS 3, SDNN, RMSSD, LF, HF, LF/HF ratio between the cases and controls were done with an independent t test. Difference between these parameters in supine and stress between cases and controls was done with an independent t test. Difference in mean LF/HF ratio across the functional classification and type of CP was done using one-way ANOVA. Spearman correlation was performed to find out the linear relationship between the difference in LF/ HF ratio with PASS scores separately in cases and controls. Data was presented as mean (standard deviation). Bar diagrams, scatter plots and pie charts were used for graphicalrepresentation of data. A p value of less than 0.001 was considered statistically significant.

III. Result

Age and gender distribution: The mean (SD) age among the cases was 8.7 (3) years and the controls was 9 (2.9) years. There was no significant difference in age between the cases and controls. Among both cases and controls majority of the children belonged to the age group of 6y to 8y (58% in cases, 51% in controls), followed by the age group of 9y-11y (23.5%in cases, 31.3% in controls), Age group of 12y-14y and more than 14y having 6 children and 3 children respectively in both cases and controls. About 62% of the cases were males and 37% were females. Among controls, 55% were males and the remaining 45% were females. There was no difference in the distribution of gender between the cases and controls (p=0.421).

Birth weight in cases and controls: Among the cases, half of them delivered baby of >2.5kgs, 20 (39%) delivered 1.5-2.5 kgs. Among controls, nearly 60% babies had a birth weight of 2.5 kgs, 39% had birthweight of 1.5-2.5 kgs. No baby had a weight of less than 1.5kg among the controls butthe same was nearly 8% among cases but this was not significant. Out of all the 51babies delivered, 29 (56.9%) cried at birth and 22 (43%) did not and had a diagnosis of perinatal asphyxia.

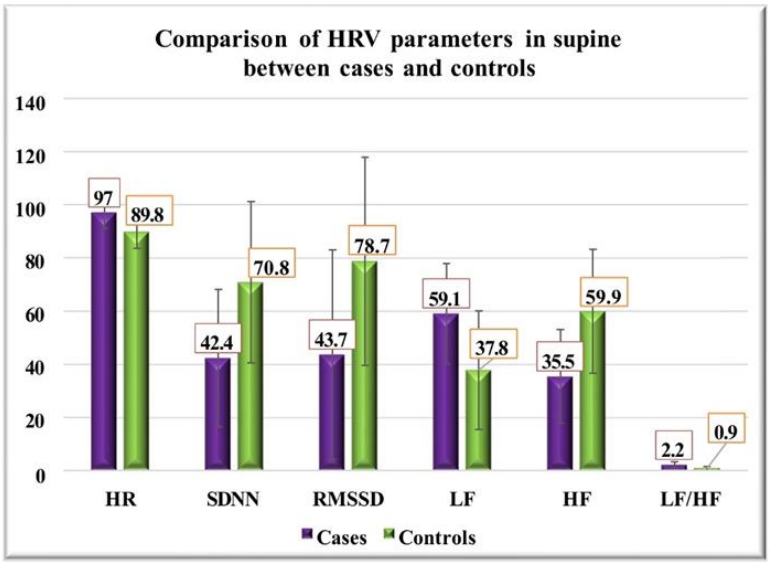
Topographical classification (Type of CP): Of all 51 participants, 30 (58.8%) had Spastic quadriplegia, 8(15.7%) had Spastic diplegia, 7 (13.8%) had Spastic hemiplegia. Similarly, 2 participants had dyskinetic CP, 2 had mixed and 2 had triplegic CP.

Functional classification: About 19 (37.3%) of the participants came under the functional classification of GMFCS 3, 18 (35.3%) were under GMFCS 4, 13 (25.5%) under GMFCS 2 and one patient under GMFCS 1 classification.

Comparison of HRV parameters in supine between cases and controls

Parameter in supine	Cases		Controls		P value
	Mean	SD	Mean	SD	
HR	97.0	6	89.8	6.3	<0.001
SDNN	42.4	25.8	70.8	30.3	<0.001
RMSSD	43.7	39.3	78.7	39.2	<0.001
LF	59.1	18.9	37.8	22.2	<0.001
HF	35.5	17.7	59.9	23.3	<0.001
LF/HF	2.2	1.1	0.9	0.8	<0.001

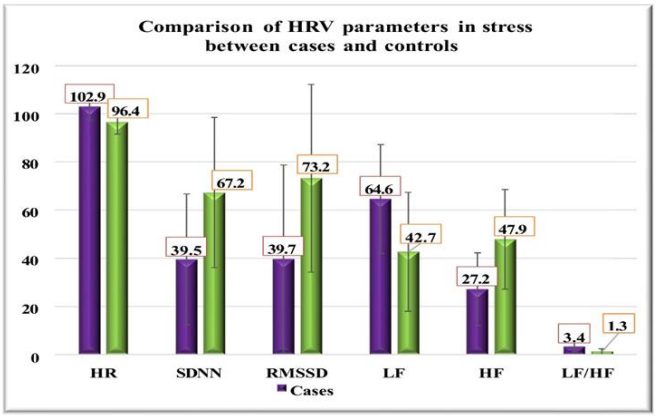
The mean (SD) HR was 97.0 (6) among cases, 89.8 (6.3) among controls. The mean (SD) SDNN was 42.4 (25.8) among cases and 70.8 (30.3) among controls. Similarly, the mean RMSSD, LF, HF and LF/HF were 43.7, 59.1, 35.5 and 2.2 among cases and 78.7, 37.8, 59.9 and 0.9 among controls respectively. The difference in the above-mentioned parameters between the cases and controls in supine was significant (p=<0.001). Cases had lower values of SDNN, RMSSD, HF and higher values of LF, LF/HF ratio when compared to controls in supine position.



Comparison of HRV parameters in stress between cases and controls

Parameter in stress	Cases		Controls		P value
	Mean	SD	Mean	SD	
HR	102.9	5.6	96.4	4.9	<0.001
SDNN	39.5	27.2	67.2	31.2	<0.001
RMSSD	39.7	39	73.2	38.9	<0.001
LF	64.6	22.6	42.7	24.7	<0.001
HF	27.2	15.1	47.9	20.7	<0.001
LF/HF	3.4	2.2	1.3	1.2	<0.001

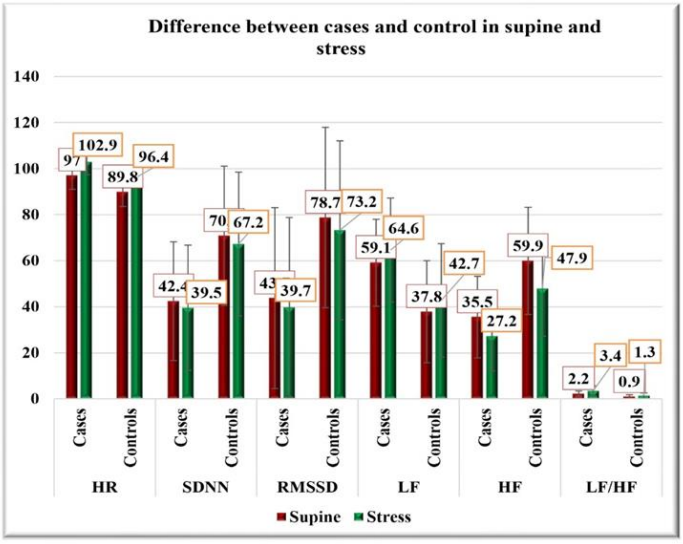
The mean (SD) HR was 102.9 (5.6) among cases, 96.4 (4.9) among controls. The mean (SD) SDNN was 42.4 (25.8) 39.5 (27.2) among cases and 67.2 (31.2) among controls. Similarly, the mean RMSSD, LF, HF and LF/HF were 39.7, 64.6, 27.2 and 3.4 among cases and 73.2, 38.9, 24.7, 20.7 and 1.2 among controls respectively. The difference in the above-mentioned parameters between the cases and controls in stress was significant (p=<0.001). Cases had lower values of SDNN, RMSSD, HF and higher values of LF,LF/HF ratio when compared to controls during the stress test.



Difference between all the parameters between supine and stress among cases and controls

Parameter	Group	Supine		Stress		Difference		P value
		Mean	SD	Mean	SD	Mean	SD	
HR	Cases	97.0	6.0	102.9	5.6	6.0	3.3	
	Controls	89.8	6.3	96.4	4.9	6.6	3.6	0.337
SDNN	Cases	42.4	25.8	39.5	27.2	-2.9	4.2	
	Controls	70.8	30.3	67.2	31.2	-3.6	4.4	0.431
RMSSD	Cases	43.7	39.3	39.7	39	-4.0	4.9	
	Controls	78.7	39.2	73.2	38.9	-5.5	4.1	0.102
LF	Cases	59.1	18.9	64.6	22.6	5.5	9.6	
	Controls	37.8	22.2	42.7	24.7	4.9	5.1	0.706
HF	Cases	35.5	17.7	27.2	15.1	-8.3	7.3	
	Controls	59.9	23.3	47.9	20.7	-11.9	9.1	0.028
LF/HF	Cases	2.2	1.1	3.4	2.2	1.2	1.3	
	Controls	0.9	0.8	1.3	1.2	0.4	0.5	<0.001

The mean difference in HR between supine and in stress between cases and controls was not significant. Similarly, we could not find significance in mean SDNN, RMSSD, LF, HF in supine and in stress between cases and controls. The mean difference in LF/HF ratio between supine and stress among the cases was 1.2 and the controls was 0.4. This difference in difference of LF/HF ratio between supine and stress in cases and controls was highly significant with the p value of <0.001.



Comparison of LF/HF ratio of cases in supine position with the type of cerebral palsy

Spastic quadriplegia	2.45
Spastic diplegia	1.09
Dyskinetic CP	1.96
Mixed CP	1.78
Hemiplegic CP	2.17
Triplegic CP	2.8

The LF/HF ratio in children with cerebral palsy in supine position was found to be highest among the triplegic type of CP, although there was a limitation that this particular group had only 2 children. This was followed by spastic quadriplegia (2.45), Hemiplegic CP (2.17), Dyskinetic CP (1.96), Mixed CP (1.78) and spastic diplegia (1.09).

Comparison of difference in LF/HF ratio with type of CP

Type of CP	Difference in LF/HFratio		P value
	Mean	SD	
Spastic quadriplegia	1.3	1.4	
Spastic diplegia	0.6	0.7	
Spastic hemiplegia	1.3	1.1	0.57
Dyskinetic CP	0.2	0.9	
Mixed CP	1.4	0.2	
Triplegic CP	2.6	.	
One-way ANOVA			

The mean of difference in LF/HF ratio across Spastic quadriplegia Spastic diplegia, Spastic hemiplegia, Dyskinetic CP, Mixed CP and triplegic CP was 1.3, 0.6, 1.3, 0.2, 1.4 and 2.6 respectively. One-way ANOVA was performed, and it revealed that the mean difference in LF/HF ratio across the CP groups was not significant with the p value of 0.57.

Correlation of LF/HF ratio in cases in supine position with GMFCS Levels

GMFCS LEVEL	LF/HF ratio
1	1.6
2	1.25
3	2.09
4	2.89

When LF/HF ratio in supine position of cases was compared with GMFCS levels, it was found that the LF/HF ratio was the highest in cerebral palsy children with GMFCS 4(2.89), followed by GMFCS 3(2.09). However, LF/HF ratio was found to be higher in GMFCS 1(1.6) when compared to GMFCS 2 (1.25).

Comparison of difference in LF/HF ratio with GMFCS levels

Functional classification	Difference in LF/HFratio		P value
	Mean	SD	
GMFCS 1	-0.4	.	
GMFCS 2	0.5	0.8	**0.012**
GMFCS 3	1.1	1.4	
GMFCS 4	1.8	1.1	
One-way ANOVA			

The mean of difference in LF/HF ratio in GMFCS 1, GMFCS 2, GMFCS 3 and GMFCS 4 was -0.4, 0.5, 1.1 and 1.8 respectively. One-way ANOVA was performed, and it revealed that the mean difference in LF/HF ratio across the GMFCS groups was significant with the p value of 0.012.

IV. Discussion

In the present study majority of the children had spastic quadriplegia 30 (58.8%), 8(15.7%) had Spastic diplegia, and 7 (13.8%) had Spastic hemiplegia. Similarly, 2 participants had dyskinetic CP, 2 had mixed, and 2 had triplegic CP. In a study conducted by *Mendlovic et al* (N=30), the topographical classification included 25 (83.3%) children with spastic quadriplegia and 5 children (16.6%) with spastic dyskinesia [(11)].

In the present study about 19 (37.3%) of the participants came under the functional classification of GMFCS 3, 18 (35.3%) were under GMFCS 4, 13 (25.5%) under GMFCS 2 and one patient under GMFCS 1 classification. Similar results were obtained from the studies as mentioned below

Study	GMFCS 4	GMFCS 3	GMFCS 2
Present study (n=51)	13 (25.5%)	18 (35.3%)	13 (25.5%)
Mendlovic et al. [(11)] (n=30)	17 (56.6%)	Not Reported	Not Reported
Katz-leurer et al [(12)] (n=110)	21 (20%)	17 (16%)	15(13.6%)
Suncica MartineC et al [(13)] (n=44)	Not Reported	5(11.4%)	11(25%)

Comparison of HRV parameters in supine position

The mean (SD) HR was 97.0 (6) among cases and 89.8 (6.3) among controls. Thedifference in both time domain and frequency domain parameters between the cases and controls in supine was significant (p=<0.001). Cases had lower SDNN, RMSSD, and HF values and higher LF and LF/HF ratios compared to controls in the supine position. In a study conducted by *katz-Leurer* which included 110 cerebral palsy children in theage group of 6-11 years, to compare the HRV parameters at rest and to compare itwith typically developed controls, it was found that there were significant differences in all HRV measures between the two groups. Children with cerebral palsy had significantly lower RR intervals, SDNN and RMSSD values, and higher low frequency/high frequency values when compared to typically developed controls. The results obtained in the present study were also similar thus indicating higher sympathetic and less cardiac vagal modulation in children with cerebral palsy [(12)].

Study	SDNN (ms)	RMSSD (ms)	LF/HF ratio
Present study (n=51)	42.4	43.7	2.2
Katz-Leurer et al [(12)] (n=110)	53	33	1.9
Yang et al [(14)] (n=30)	Not Reported	Not Reported	2.61

Difference between all the parameters between supine and stress

The difference in the LF/HF ratio between supine and stress in cases and controls was highly significant, with a p-value of <0.001. A study by *Park et al.* tried to document autonomic disorders in CP individuals using HRV analysis, there was a significant difference in response to stress in CP individuals presenting a smaller increase in the LF/HF ratio than that of the control groups, which might indicate the existence of an autonomic response deficit in the CPgroup [(15)].

Study	LF power(nu)		HF power(nu)		LF/HF ratio		P value for difference in LF/HF ratio for cases
	Supine	Stress	Supine	Stress	Supine	Stress	
Presentstudy (n=51)	59.1	64.6	35.5	27.2	1.1	2.2	<0.001
Park et al [(15)] (n=12)	51.08	51.25	10.42	15.75	6.22	5.03	<0.05
Yang et al [(14)] (n=30)	52.49	57.10	25.92	25.48	2.61	2.67	0.658

Comparison of LF/HF ratio in cerebral palsy children in supine position with type of cerebral palsy: The LF/HF ratio in children with cerebral palsy in supine position was found to be highest among the triplegic type of CP, although there was a limitation with occurrence of selection bias that this particular group had only 2 children. This was followed by spastic quadriplegia (2.45), Hemiplegic CP (2.17), Dyskinetic CP (1.96), Mixed CP (1.78) and spastic diplegia (1.09). In a study conducted by *Yang et al*, the authors reported that heart rate variability was greater in the group with athetoid cp than the group with spastic cp however the study did not show major differences in thesympatho-vagal balance [(14)]

Correlation of LF/HF ratio in children with cerebral palsy with GMFCS levels: When LF/HF ratio in supine position of cases was compared with GMFCS levels, it was found that the LF/HF ratio was the highest in cerebral palsy children with GMFCS 4(2.89), followed by GMFCS 3(2.09). However, LF/HF ratio was found to be higher in GMFCS 1(1.6) when compared to GMFCS 2 (1.25). According to the results of the study conducted by *Mendlovic et al*, higher values of LF/HF Ratio were seen with higher GMFCS levels, the higher the motor impairment is, the lower their capacity to perform autonomic adjustments through the neuro-cardiac system. These results were similar to the present study [(11)].

Study	LF/HF ratio in GMFCS 2	LF/HF ratio in GMFCS 3	LF/HF Ratio in GMFCS 4
Present study	1.25	2.09	2.89
Mendlovic et al [(11)]	Not reported	Not reported	2.2
Katz-Leurer at al [(12)]	1.6	1.8	3.4

Comparison of the difference in LF/HF ratio with GMFCS levels

The mean difference in LF/HF ratio in GMFCS 1, GMFCS 2, GMFCS 3 and GMFCS4 was -0.4, 0.5, 1.1 and 1.8, respectively.

Study	Sample size	Mean difference in LF/HF ratio in GMFCS 4	P value
Present study	51	1.8	0.012
Mendelovic et al [(11)]	30	3.8	0.03

V. Conclusion

Cerebral palsy children had significantly higher sympathetic activity and less cardiac vagal modulation compared to normal children in supine position. There was existence of autonomic response deficit in cerebral palsy children after stress test and analysis showed that higher the motor impairment, higher was the sympathetic activity.

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