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Assessment of Autonomic Nervous System with Analysis of Heart Rate Variability in Children with Spastic Cerebral Palsy

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The purpose of this study was to investigate the function of the autonomic nervous system in children with spastic cerebral palsy (CP) through an analysis of heart rate variability (HRV) occurring with orthostatic stress. Twelve children with spastic CP and twelve normal children participated in this study. The echocardiogram (ECG) signals were recorded for 3 minutes in both the supine and 70° head-up tilt positions, and then the HRV signals underwent power spectrum analysis at each position. Two components were measured; a low-frequency (LF) component (0.05 - 0.15Hz) primarily reflecting sympathetic activity during orthostatic stress and a high-frequency (HF) component (0.15 - 0.4Hz) reflecting parasympathetic activity. In the supine position, there was no significant difference between any of the HRV components of the two groups. In the head-up tilt position, absolute and normalized LF were significantly increased and absolute HF was significantly decreased in the normal children ($p < 0.05$), but not in the children with spastic CP. The results of this study suggest that cardiac autonomic functions, such as vagal withdrawal and sympathetic activation which occur during head-up tilt position, are not sufficient to overcome the orthostatic stress arising in spastic CP children.

Key Words: Spastic cerebral palsy, heart rate variability, cardiac autonomic function

INTRODUCTION

The autonomic nervous system has been mainly attributed to the maintenance of homeostasis in the human body when it is exposed to environmental factors. Recently, autonomic dysfunctions in patients with central nervous system lesions such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, cerebrovascular accident and spinal cord injury victims have been noted.[1-7]

Heart rate variability (HRV) is caused by beat-to-beat fluctuations of instantaneous ECG R-R intervals, which change to maintain homeostasis.[8,9] The analysis of HRV is a form of measuring autonomic balance, which is principally controlled by the sympathetic and parasympathetic nervous systems.[10] The assessment of HRV is a very reliable, quantitative and non-invasive tool to evaluate autonomic function and sympathovagal balance, and has been widely used until now.[8-13]

Cerebral palsy (CP) can be defined as a syndrome showing abnormal movement and posture caused by non-progressive lesion in the immature brain. Besides motor deficits, many associated problems have also been noted. The symptoms of autonomic dysfunction can be suspected in cases of bowel and bladder dysfunction, excessive sweating and also tachycardia during walking, all of which have been noted frequently in patients with CP.[14-17] The studies of autonomic function in CP children have been limited and controversial because there has been mainly focused on abnormal gait pattern or early diagnosis.[18-20] Yang and co-workers[17] reported that there were no significant differences of sympathetic skin response and mean R-R interval between CP children and normal controls. But, one report has shown spe-

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cific patterns of HRV in brain-injured pre-term infants.[21] Furthermore, it was reported that heart rate was more variable in the athetoid group than in the spastic group of CP children when heart rate tracings were sampled at 10 second intervals to give 40 separate measures.[22] Time domain measurement of HRV was used in recordings of 1 min duration in the report by Yang et al.[17] and in 20 min-recordings in the report by Hanna et al.[21] However, there have been few reports on frequency domain measurement although it can provide more theoretical information on the interpretation of HRV in short term recordings and is easier to perform.[23]

The purpose of this study was to investigate the characteristics of HRV components with orthostatic stress using frequency domain analysis in children with spastic CP, as compared with those in normally developed children.

MATERIALS AND METHODS

Subjects

Twelve children with spastic CP (7 boys and 5 girls) aged from 6 to 11 years (mean age 8.58) participated in this study. The subjects who had previously taken medication and had a history of cardiovascular disease such as congenital heart disease and cardiac arrhythmia were excluded. Twelve normally developed children (7 boys and 5 girls) aged from 5 to 12 years (mean age 6.92) were also recruited as control subjects. There was no statistically significant difference of age or sex between the two groups.

The characteristics of the children with spastic CP are listed in Table 1. The spastic CP group included 5 quadriplegia, 4 diplegia and 3 hemiplegia cases/patients. It consisted of 3 non-ambulators and 9 ambulators; the latter comprising 2 exercise ambulators, 4 household ambulators and 3 community ambulators.

Methods

The clinical autonomic symptoms evaluated in children with spastic CP, were focused on bladder, bowel, thermoregulatory and vasomotor dysfunctions. Symptoms of bladder dysfunctions included urinary incontinence, urgency, frequency or voiding difficulty; of bowel dysfunctions included constipation, fecal incontinence or abdominal distention; of thermoregulatory abnormalities included mainly excessive sweating or anhidrosis; of cardiovascular and vasomotor abnormalities included facial flushing or dizziness during head-up tilt.

Measurements were carried out at about 3:00 PM after the subjects had a very light lunch in a quiet room at room temperature of 20-24℃.[17] They had taken a 10 min rest to adapt to the environment.[24] Then, ECG signals were collected for 3 minutes with subjects both in the supine

Table 1. Characteristics of the Children with Spastic Cerebral Palsy

	sex/age(yrs)	subtype	ambulation state	clinical autonomic symptoms
case 1	M/ 7	quadriplegia	exercise ambulator	constipation, facial flushing
case 2	M/ 9	quadriplegia	non-ambulator	excessive sweating, constipation, abdominal distension
case 3	M/ 6	diplegia	household ambulator	urinary and fecal incontinence, constipation
case 4	F/ 7	quadriplegia	household ambulator	constipation
case 5	F/ 7	hemiplegia	household ambulator	
case 6	F/ 9	diplegia	exercise ambulator	constipation, abdominal distension
case 7	F/ 7	diplegia	household ambulator	
case 8	F/ 8	diplegia	community ambulator	constipation
case 9	M/10	hemiplegia	community ambulator	
case 10	M/11	quadriplegia	non-ambulator	excessive sweating, constipation
case 11	M/11	quadriplegia	non-ambulator	excessive sweating, constipation, fecal incontinence
case 12	M/11	hemiplegia	community ambulator	excessive sweating on hemiplegic side

position and the 70° head-up tilt position for accelerating the sympathetic stress.[25-28] The 70° head-up tilt position was performed using a tilt table. The subjects were introduced to breathe in synchrony with a metronome set at 15 beats/min (0.25Hz).[24]

A data acquisition system, specially designed for this study, was developed to obtain cardiovascular signals such as ECG for evaluation of the cardiac event series. ECG signals were derived using standard lead II electrodes. To eliminate unwanted noise signals, the signals were passed through a band pass filter of 0.1-150Hz. Then, ECG was quantized at a sampling rate of 1 kHz/sec. For patient safety, this quantized signal was isolated by photo-coupler, and transmitted to personal computer using Direct Memory Access methods for the rapid transfer of a large quantity of information. A data acquisition program running on personal computer transferred ECG and other signals together for visual monitoring and simultaneously detected the QRS complex of the ECG signals and saved the raw data to hard disk for off-line processing of HRV analysis.

For HRV signal analysis, ECG QRS peaks were first detected by the modified spatial velocity algorithm,[29] and cardiac event series were reconstructed from the digitalized ECG signals. However, as these cardiac event series are not temporally regular, conventional power spectral analysis algorithms such as fast Fourier transform (FFT) cannot be applied to HRV signal analysis and therefore in this study, the cubic spline interpolation method was used to obtain evenly spaced HRV.[30] Then, the power spectrum was estimated by autoregressive model power spectrum estimation using the Burgs maximum entropy method.[31] (Fig. 1)

$$P_{xx}(f) = \frac{s^{2}T}{\left[1+\sum_{k=1}^{p} a_k e^{-j2pkT}\right]^2}$$

Where ó is the standard deviation of the signals. From the estimated power spectrum of the HRV signals, we could compare the spectral band power of any frequency of interest. For the autonomic nervous system, we accepted the LF (0.05-0.15Hz) and HF (0.15-0.4Hz) bands as indexes of sympathetic and parasympathetic activities, respectively, as described in the previous study.[30] The normalized power is defined as,

$$NP(f) = \frac{P(f)}{P_{Total} - P_{VLF}}$$

where P_{Total} and P_{VLF} are power over 0-0.5Hz and 0-0.05Hz respectively. LF_N, the index of sympathetic activity and HF_N, the index of parasympathetic activity, were defined as,

$$LF_N = \int_{0.05}^{0.15} NP(f)df, \qquad HF_N = \int_{0.15}^{0.4} NP(f)df$$

The powers of LF and HF spectral components were expressed as both absolute values (ms^2) and normalized units (0-100). The latter represented the relative value of each power in proportion to the total power minus the VLF component, and this emphasized the controlled measure of both

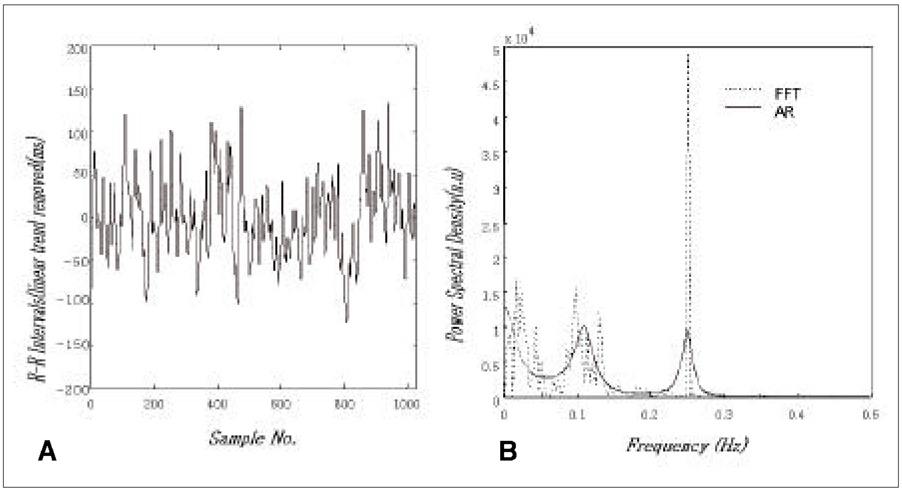

Fig. 1. Schematic outline of frequency domain analysis of HRV. (A) tachogram, (B) autoregressive power spectrum analysis

sympathetic and parasympathetic nervous systems.[23,32,33] Furthermore, the ratio of LF/HF, absolute LF power divided by absolute HF power, was expressed as the sympathovagal balance of the autonomic function.

Statistical analysis

The Wilcoxon signed ranks test was used for statistical analysis to compare the values of HRV components between supine and 70° head-up tilt positions in children with spastic CP and normal controls, and to compare them according to ambulatory status and autonomic symptoms in children with spastic CP. In addition, the Mann-Whitney U test was used to compare the HRV components between the children with spastic CP and normal controls in supine and 70° head-up tilt positions. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Supine position

There were no significant differences in mean HR, absolute LF, absolute HF, total power, normalized LF and normalized HF of the HRV components between the CP children and the controls. However, the LF/HF ratio, indicating sympathovagal balance, in the CP children was significantly greater than in the controls ($p < 0.05$) (Table 2).

70° head-up tilt position

While the subjects were moved from supine to 70° head-up tilt position which stimulated the sympathetic nervous system, the mean HR was significantly increased in the controls ($p < 0.05$), but not in the CP children. There was a significant increase in absolute LF and a significant decrease in absolute HF in this position for the controls ($p < 0.05$). However, there were no such significant differences in the CP children. In contrary to the controls, absolute and normalized HF were rather increased in the CP children. As well, normalized LF and LF/HF ratio were significantly increased in the controls ($p < 0.05$), but not in the CP children (Table 2).

Difference from 70° head-up tilt to supine position (Δ)

Although the mean HR and absolute LF were increased in both groups during orthostatic stress, their differences from 70° head-up tilt to supine position tended to be lower in the CP children than in the controls. As the increase of normalized

Table 2. Heart Rate Variability in Spastic CP and Normal Children during Head-up Tilt

	Spastic CP (n=12)			Control (n=12)		
	0°	70°	Δ	0°	70°	Δ
Heart rate (beats/min)	97.67±8.32	99.42±10.48	1.75±4.09	95.47±12.33	100.08±12.83*	4.62±2.25
Absolute LF (msec^2)	1739.80±1241.74	1901.26±1371.88	161.34±1304.30	1015.39±700.38	1358.01±1175.56*	342.62±518.67
Absolute HF (msec^2)	416.67±595.04	634.59±663.84	216.97±933.89	501.32±472.02	298.04±208.51*	-212.36±301.92
Total power (msec^2)	2148.81±1691.11	2554.83±1872.56	81.60±2051.32	1953.34±1822.67	1913.79±1668.79	-122.90±500.44
Normalized LF (nu)	51.08±14.80	51.25±17.45	0.50±10.31†	41.70±13.51	52.79±15.67*	11.09±5.44
Normalized HF (nu)	10.42±8.65	15.75±10.24	6.17±11.91†	17.02±11.37	13.33±8.29	-3.68±7.06
LF/HF ratio	6.22±3.69†	5.03±3.99	-1.24±3.97†	2.97±1.98	5.49±3.14*	2.52±1.99

CP, cerebral palsy; Control, neurologically normal children; Δ, difference from 70° head-up tilt to supine position; LF, low frequency (0.05 - 0.15Hz); HF, high frequency (0.15 - 0.4Hz); nu, normalized unit; Values are mean ± standard deviation.
*$p < 0.05$, compared between 0 and 70 degree by Wilcoxon signed ranks test.
†$p < 0.05$, compared between spastic CP and control by Mann-Whitney U test.

LF was blunt in the CP children during orthostatic stress compared with the controls, and as the normalized HF was increased in the CP children after 70° head-up tilt in contrary to the decrease that occurred in the controls, ⊿normalized LF, ⊿normalized HF and ⊿LF/HF ratio were significantly different between the two groups ($p < 0.05$) (Table 2).

HRV according to ambulatory status in the CP children

When the differences of HRV components from 70° head-up tilt to supine position were compared according to ambulatory status, ⊿normalized LF were mean -2.00 nu in non-ambulators of the CP children, mean 1.33 nu in ambulators of the CP children and mean 11.09 nu in the controls. In addition, ⊿normalized HF were mean 15.67 nu, 3.00 nu and -3.68 nu, and ⊿LF/ HF ratio were mean -5.02, 0.03 and 2.52 respectively. Therefore, ⊿normalized LF and ⊿LF/HF were lower and ⊿normalized HF were higher in the order of poor ambulatory status among three groups (Fig. 2).

HRV according to autonomic symptoms in the CP children

Nine (75%) of the 12 CP children had one or more clinical autonomic symptoms, 8 children (67%) had bowel dysfunction and 4 children (33.3%) had excessive sweating. However, HRV components did not show any significant relationship with the presence of autonomic dysfunction symptoms.

DISCUSSION

The measurement of HRV can be classified into time domain analysis and frequency domain analysis. The former is a general measure of autonomic nervous system balance, whereas the latter allows not only some degree of separation of parasympathetic and sympathetic contributions of autonomic control, but is also more appropriate in short term recordings[10,23] The LF component is a quantitative marker of sympathetic modulation or reflects both sympathetic and parasympathetic activities, whereas the HF component mainly contributes only to vagal activity.[23,34]

The HRV components are dependent on age with a basic pattern of LF, HF and total power exhibiting an increase from 0 to 6 years, followed by a decrease until 24 years.[35] Especially between 5 and 12 years, a significant decrease in LF amplitude and a lesser decrease in HF amplitude were observed.[25] It is suggested that the sympathetic activity is predominantly decreased during this age period. The age dependency of HRV components was not evaluated in our study

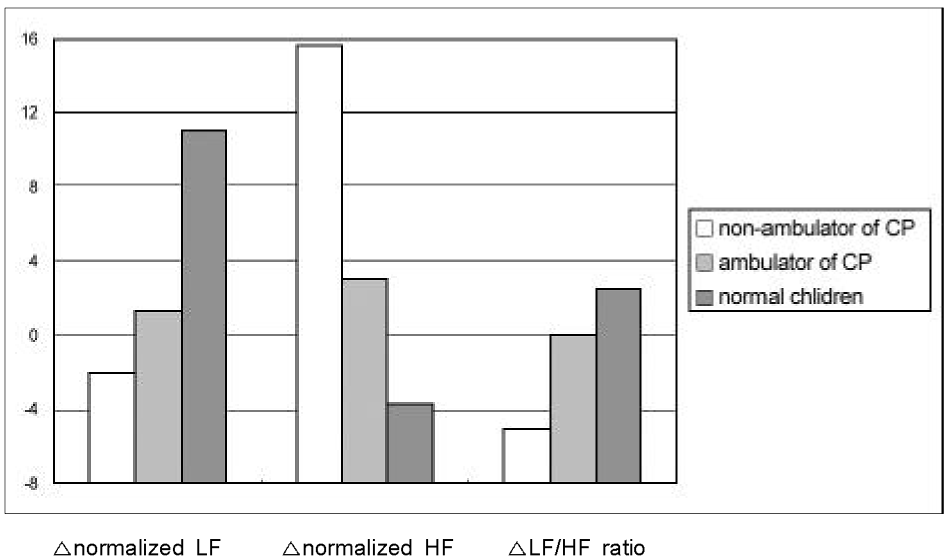

Fig. 2. △normalized LF, △mormalized HF and △LF/HF ratio from 70° head-up tilt to supine position according to ambulatory status. LF: low-frequency (0.05 - 0.15Hz), HF: high-frequency (0.15 - 0.4Hz)

because of the small sample size. However, the wide variation of HRV component values of our study might have originated from the age range as mentioned in previous studies.[25,35]

No HRV components, except the LF/HF ratio in the supine position of the CP children, differed significantly from the controls. These findings are compatible with the report of Yang et al.[17] However, a higher LF/HF ratio was noted in the CP children than in the controls, and it was also higher than that previously reported in the same age range.[35] Although the LF and HF components showed wide variation in this age group, the LF/HF ratio had been found to be similar in all age groups except for infants.[35] Thus, the higher LF/HF ratio in the CP children might suggest some difference of sympathovagal balance in the initial supine position from that of the controls, but further research into other possibilities is required.

The use of passive tilt has been considered the most appropriate stimulus to induce graded changes in sympathovagal balance.[12] In our study, we selected the 70° head-up tilt because this position was found to be the maximal tolerable upright position capable of provoking sympathetic activation in physically disabled people in previous studies.[36,37]

The LF power increased progressively, while the HF power decreased progressively, as the tilt angle increased in young healthy males.[8,27] The results of our study on orthostatic stress in normal children were quite similar to these findings. But these significant changes were not observed in the report by Finley et al.[25] probably due to the wide variation of HRV in this age range group as mentioned in their report. However, increased LF/HF ratio with standing was the constant pattern in all age groups,[13,25] as it was in the controls of our study. Thus, the change of LF/HF ratio during orthostatic stress can be considered to be a reliable marker in the assessment of sympathovagal balance in these young children.

In contrary to the normal controls, the CP children showed different and blunt responses to orthostatic stress. The normalized LF and LF/HF ratio were not significantly increased in these children during orthostatic stress, and the HF components were rather increased in the CP children, unlike normal vagal withdrawal during head-up tilt. Therefore, ⊿normalized LF, ⊿normalized HF and ⊿LF/HF ratio from 70° head-up tilt to supine position were significantly different from the normal controls (Table 2). These findings indicate some diminution of the adaptive reservoir of cardiac autonomic regulation in these children. There were no significant differences of absolute LF and normalized LF in the supine position between the CP children and the normal children, but the relatively higher values of these components in the CP children might have partly caused the lack of any significant increase of HRV components during orthostatic stress in these children.

When the differences of HRV components from 70° head-up tilt to supine position were investigated according to ambulatory status, ⊿LF/HF ratio was much lower in non-ambulators of the CP children than other groups because this parameter tended to be decreased during orthostatic stress in non-ambulators, while remaining unchanged in ambulators (Fig. 2). In other words, it suggests a lesser reservoir of sympathovagal adaptation in non-ambulators than ambulators of the CP children. But we could not compare the results statistically according to ambulatory status because of the small sample size.

Although clinical symptoms of autonomic dysfunction found in the CP children of our study has also been commonly reported in previous studies,[14-17] we could not identify any significant difference of HRV components between the CP children with and without clinical symptoms of autonomic dysfunction in this study.

Several possible limitations in our study may have prevented the demonstration of any significant difference. Firstly, the number of cases was not enough for the statistical analysis. Secondly, the 70° head-up tilt was not as stressful as the 90° head-up tilt in this young age group. Thirdly, the objective assessment of clinical autonomic symptoms might provide a better analysis of the relationship with HRV components than the subjective symptoms.

In conclusion, we could identify a difference in the responses to orthostatic stress in children with spastic CP. This finding suggests that the CP children had some difficulties in adjusting their sympathovagal balance to this stimulus. Thorefore, we conclude that cardiac autonomic responses, such as vagal withdrawal and sympathetic activation during head-up tilt position, are not sufficient to overcome the orthostatic stress in the CP children.

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