Association of Severity of Autism Spectrum Disorder with Cardiac Autonomic Indices in Children

Remya Bharath[1], Shailaja S. Moodithaya[2], Ashwini Kishan[3], Shrinivasa Bhat U[4], Suchetha Kumari N[5], C. H. Krishna Bhat[6]

[1]Research Scholar, [2]Additional Professor, [3]Associate Professor, *Department of Physiology, [4]Professor, Department of Psychiatry, [5]Professor, Department of Biochemistry,* [6]Professor, *Department of Biostatistics, K. S. Hegde Medical Academy, Nitte (Deemed to be University), Deralakatte, Mangalore, Karnataka*

Abstract

Background & Objectives: Autism Spectrum Disorder (ASD) being a complex neuro-developmental disorder is found to be associated with Autonomic Nervous System (ANS) dysfunction. The sympatho-vagal continual dynamic excitatory- inhibitory interactions leads to Heart Rate Variability (HRV) which is an index of cardiac autonomic regulation**.** Aim of the study was to evaluate cardiac autonomic regulation in children with ASD at rest using short-term HRV analysis and to correlate it with severity of autism.

Methods: A total of 30 subjects were evaluated in the study comprising of 15 ASD children and 15 healthy controls. A five minutes recording of resting ECG was carried out from which R-R intervals were procured and HRV indices were analysed. Frequency domain analysis of HRV was carried out and the following parameters were evaluated: Spectral powers in low frequency (LF) bands, High frequency (HF) bands, total power (TP), LF/HF ratio and average heart rate (HR) were evaluated. HRV indices between the groups were compared using Student's t test. Severity of autism was correlated with the evaluated HRV indices using Pearson correlation test.

Results: Cardiac sympathetic activity as assessed by low frequency power spectrum ('p' value 0.034) and total power ('p' value 0.023) of the HRV spectrum was significantly higher in autistic children compared to that of normal controls. However, the association between severity of ASDs and HRV indices were not statistically significant.

Conclusion: Study concludes that here was no significant association between HRV indices and severity of autism.

Keywords- *Autonomic nervous system, Autism spectrum disorders, Heart rate variability, High frequency, Low frequency.*

Introduction

Autonomic nervous system (ANS) incorporates two opposing branches, the sympathetic and parasympathetic systems that maintain body homeostasis.[1] Functionally, the sympathetic system is activated during "fight-or- flight" situations and is associated with catabolic processes while the parasympathetic system is concerned with the vegetative functions of routine living and mediates anabolic processes of the body.[2] The parasympathetic division usually opposes or balances the actions of sympathetic division. ANS plays an important role in a wide range of visceral-somatic and mental diseases.

A network of brain areas like prefrontal cortex, amygdala and hypothalamus controls the ANS as

Corresponding Author:
Dr. Shailaja S. Moodithaya, Additional Professor,
Department of Physiology, K. S. Hegde Medical Academy, Nitte (Deemed to be University), Deralakatte, Mangalore, Karnataka- 575018.
Email id: shailaja.moodithaya@nitte.edu.in,
Mobile number: 9845516116

well as socio-emotional and cognitive processes. The central autonomic network has tonic, reflexive and adaptive control over autonomic functions and monitors cognitive, emotional and behavioural responses and its dysregulation is noted in various neuro-psychological ailments.[1] Rising evidence portrays the association of Autism spectrum disorders (ASDs) with the dysfunction of ANS.

ASD is a complex neurological and developmental disorder categorized by impaired social communication, limiting interests, and conventional repetitive behaviors.[1] Differences in development in 3 main areas: communication (verbal and non-verbal), social interactions and imagination. This is stated to as the triad of impairments. It is known as a 'spectrum disorder' because the severity of symptoms may range from a mild learning and social disability, to more complex needs with multiple complications and often very unusual behaviour. The Diagnostic and statistical manual for mental disorders -V (DSM-V) in May 2013 established the use of unique term 'Autism Spectrum Disorders (ASDs)'.[3] At least one comorbid mental disorder is associated with about 70% of ASDs and 40% may have two or more comorbid mental disorders.[4] The incidence of Autism has revealed a swift increase over the last few years. Current international studies show that about 1 in 68 people have autism and its incidence is believed to be steady around the world.[3] Males are more often affected with autism than females, at a ratio of 4:1 (males: females).[5] The onset of symptoms of ASDs are gradual for most children; although they develop before the age of 3 years.

Autonomic imbalance, in which one branch of the ANS dominates over the other, is related to a lack of active flexibility and fitness. Clinical symptoms of these disorders are often non-characteristic and so to identify them it is vital to know the procedures of assessment of ANS function.[6] Autonomic activity dysfunctions may be related to social functioning in individuals with ASD. The mutual regions of the brain that are associated with both autonomic dysfunction and socio-emotional deregulations, make autonomic status a good biomarker for ASD.

Heart rate is complexly modified by the coordination of autonomic, respiratory, circulatory, endocrine and mechanical influences over time. It is an important parameter for the assessment of autonomic function and reflects the autonomic activity of sinoatrial node.[1] The sympatho-vagal continual dynamic excitatory-inhibitory interactions leads to heat rate instantaneous oscillations called Heart rate variability (HRV) which is assessed by computing R-R intervals.[3] HRV pattern variations provide an advanced indicator of health involvements. Higher HRV is a signal of good adaptation and symbolizes a healthy person with well-organized autonomic mechanisms, while lower HRV is frequently an indicator of abnormal and inadequate adaptation of the ANS. HRV is a useful non-invasive tool to study central processes involved in autonomic regulation, thereby emphasizing its relevance in various psychiatric conditions. As per literature, fluctuations in HRV reflects both the sympathetic and parasympathetic responses and the sympathovagal balance can also be assessed.[7] Various HRV indices are widely recognized as useful and powerful indicators of physiological and psychological interaction.[8]

As suggested by literature, the link between ASD symptoms and ANS dysfunction can be related to parasympathetic underactivity, sympathetic over-arousal, or an atypical interaction between these systems.[9-11] Some studies have reported no significant differences in resting autonomic activity in children with ASD compared to controls.[12,13] Both sympathetic and parasympathetic lower resting activity were revealed in studies done by Bujnakova et al. in 2016, indicating autonomic under arousal in ASD children.[14] Studies assessing orthostatic stress in ASD children have shown higher parasympathetic responses with the same sympathetic modulation, suggesting parasympathetic dominance in this population.[15] Thus, the inconsistencies in the existing literature on autonomic function in ASD propose a large heterogeneity in this population.

Many paediatric autonomic disorders occur as a result of developmental abnormalities caused by specific genetic mutations and others as a result of generalized central dysfunction. In addition to traditional neurodevelopmental symptoms, autism also produce symptoms attributable to other organ systems that suggest underlying autonomic dysfunction. Aim of the present study was to evaluate cardiac autonomic regulation in autistic children using HRV as an assessment tool and compare HRV indices between normal and autistic children. The study also correlated the severity of autism with the obtained HRV indices.

Materials and Method

Study population: The study was conducted on Children diagnosed with ASDs and age and gender matched controls. 40 children were recruited for the study including 24 autistic children and 16 controls. Excluding dropouts during ECG recording and HRV analysis reliable statistical data could be obtained only for 15 autistic and 15 normal children. Out of the autistic children 9 were boys and rest 6 were girls whereas normal group comprised of 8 boys and 7 girls. Children aged between 3 and 14 years were recruited for the study.

Selection Method: Children with ASDs were diagnosed by a Psychiatrist or clinical Psychologist using DSM-V criteria (APA, 2013).

Exclusion criteria: Children with diagnosis of disruptive behaviour disorders, severe and profound Intellectual disability, and with autonomic dysfunction were excluded as all these conditions affected HRV parameters evaluated in the study.

Study setting: Study was conducted in the research lab of Department of Physiology of K. S. Hegde Medical Academy, Mangalore. Subjects were recruited from Psychiatric, Paediatric & Speech language pathology departments of K.S Hegde Charitable Hospital.

Ethical clearance: Institutional and Central ethics committee approval was obtained from Nitte University for the study. Study procedure was explained in detail to the parents' of children recruited and written consent was procured from them.

Assessment of severity of autism: Diagnosis of ASD was made by experienced Psychiatrist or Clinical Psychologist according to DSM-5[5] criteria and based on previous psychiatric reports. Medical practitioner confirmed ASD diagnosis in autistic group and normal functioning in control group. Severity of autism was rated using Childhood Autism Rating Scale (CARS-2), which is a behaviour rating scale. It consists of two 15-item rating scales which is completed by a trained clinician and a Parent/Caregiver questionnaire. CARS-2 identifies children 2 years and older with ASD and distinguishes between mild to moderate and severe autism.

Experimental procedure: Subjects suitable for our study criteria were screened. The time required for recording varied from subject to subject depending on their psychological status during the procedure. For normal children the study procedure went for approximately 20-25 minutes, including the initial time taken for subjects to adapt to the study setting. Basal Blood pressure (BP) and anthropometric characteristics like height, weight and body mass index (BMI) were evaluated.

Assessment of HRV: Lead II Electrocardiogram (ECG) was recorded using a computerised 4- channel data acquisition unit (Power lab 26-T, AD instruments, Australia) in sitting position for 5 minutes. From the ECG recording a sequential series of successive R-R intervals were obtained which was validated before analysis using a standardised procedure as recommended by the Task Force of European Society of Cardiology.[7] The data so gathered was then subjected to spectral analysis of HRV using Fast Fourier Transform (FFT) and indices were calculated. Two main spectral components were retained to quantify the power spectral density: low frequency (LF; 0.04 to 0.15 Hz); high frequency (HF; 0.15 to 0.40 Hz) bands and total power (TP: variance of all RR intervals). LF components represent both parasympathetic and sympathetic modulations[16] whereas HF is associated to parasympathetic modulation[7]. Additional calculation included LF/HF ratio which constitutes evaluation of the ANS balance (sympathetic/parasympathetic). If this ratio is <1, there is a parasympathetic predominance, whereas a ratio above 1 reflects a sympathetic predominance.[7,17] These data formed a tachogram and were exported. From the report obtained total power (TP in ms^2), absolute & normalized units of HF and LF HRV indices and LF/HF ratio were considered for statistical analysis.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0. (SPSS- Inc., 233 South Wacker Drive, Chicago) software package.HRV indices recorded were expressed in terms of Mean + Standard error. Comparison of HRV indices between autistic and control group was performed using Student't' test. Probability value $p < 0.05$ was considered as statistically significant. The strength of association of severity of autism with HRV indices was assessed using Pearson correlation for parametric variables.

Results

Subject characteristics

The general subject characteristics are summarized in Table 1. The results suggest that autistic children exhibited a significantly higher weight (p= 0.020) and BMI kg/m^2 (p= 0.041) compared to their non-autistic

counterparts. All other characteristics like age, height, SBP, DBP, and basal heart rate did not show any significant difference between the groups.

Table 1- Subject characteristics

Characteristics	ASD	Control
Age (years)	10.1 ± 1.01	8 ± 1.03
Weight (kg)	32.7 ± 4.36*	20 ± 1.9
Height (m)	1.3 ± 0.07	1.2 ± 0.05
BMI (kg/m2)	18.8 ± 2.07*	13.9 ± 0.46
SBP (mm Hg)	97.7 ± 5.3	98.3 ± 2.84
DBP (mm Hg)	70.7 ± 5.09	67 ± 2.4
Heart rate (bpm)	94.42 ± 3.47	98.02 ± 3.19

Abbreviations: BMI- Body Mass Index, calculated as Weight (kg)/Height (m^2), SBP- Systolic blood pressure, DBP- Diastolic blood pressure, *p < 0.05

Table 2 shows comparison of HRV indices between the study groups. The LF absolute units were found to be significantly higher in the ASD group than the control group ($p = 0.034$); on the contrary, the HF absolute indices, despite exhibiting a lower range in ASD, was not significantly higher ($p = 0.008$) compared to their non-autistic counterparts. The HF and LF nu did not show statistical significance between the groups. . The TP values ($p = 0.023$) on the other side exhibited a significantly higher value in ASD group compared to controls.

Table 2- Heart Rate Variability Indices

HRV INDICES	ASD	Control
HF absolute (ms2)	651.57 ± 123.3	1262.62 ± 295.90
HF normalized	37.47 ± 3.6	43.1 ± 5.09
LF absolute (ms2)	1028.32 ± 138.46*	552.26 ± 59.3
LF normalized	40.55 ± 3.7	36.51 ± 4.32
TP (ms2)	4097.00 ± 877.2*	2180.78 ± 364.8
LF/HF ratio	1.12 ± 0.241	0.85 ± 0.25

Abbreviations: HF- High frequency, LF- Low frequency, TP- Total power, * p< 0.05

Table 3 shows the results of assessment of strength of association of severity of autism with cardiac autonomic parameter using Spearman rank correlation for non-parametric variables and Pearson correlation for parametric variables.

Table 3: Correlation of autonomic indices with severity of ASD.

Autonomic Indices	ASD severity	
	R	P
HF absolute (ms2)	0.034	0.83
HF normalized (nu)	0.06	0.71
LF absolute (ms2)	0.17	0.29
LF normalized (nu)	0.08	0.63
TP (ms2)	0.04	0.81
LF/HF ratio	0.02	0.89

Abbreviations: [R- Pearsons correlation coefficient, P- statistical significance,HF- High frequency, LF- Low frequency, TP- Total power]

Table 3 shows the results of assessment of strength of association of severity of autism with cardiac autonomic parameter using Pearson correlation for parametric variables.

Discussion

Cardiac autonomic regulation has emerged as one of the important psycho-physiological measures of various behavioral features in children and adults. Children with autism spectrum disorder are known to exhibit altered behavioral aspects. Since HRV is a validated indicator of the function of cardiac autonomic regulation, this study attempted to compare the short-term HRV power spectrums between children with and without autism spectrum disorders.

Findings of our study indicate that children with autism spectrum disorders are associated with cardiac autonomic dysfunction. This is reflected by a significantly higher absolute low frequency spectral band, the surrogate of cardiac sympathetic nervous activity, among autistic children compared to that of healthy controls. Further, the total power of HRV was also significantly higher in autistic children indicating that they have an overall greater cardiac autonomic modulation. However, the indices like absolute power of HF band and normalized HF and LF powers did not exhibit any statistical difference between the groups.

Measures of HRV are being increasingly applied in investigations of the central autonomic state and to study the fundamental links between various psychological processes and physiological functions.[8] It has been reported earlier that there is low baseline cardiac vagal tone with elevated sympathetic activity in autistic children.[11] Another study reported that autistic children are associated with lower resting cardiac vagal activity with no significant difference in sympathetic function.[18] Studies also have shown that elevated sympathetic activity is linked with several cardiovascular diseases. LF spectrum is a parameter that includes both sympathetic and parasympathetic activities[16, 19] and the presence of a significant difference of LF values, and TP between our two groups confirms that ASD and control groups have an altered cardiac autonomic function. Studies in children with ASD compared to TD controls under resting conditions as well as during mental stress have frequently reported increased heart rate suggesting an increased sympathetic activity. [20, 9]

Autism severity of the study subjects were evaluated by administering the Childhood Autism Rating Scale (CARS). Based on the obtained scores, we assessed the strength of association of severity of autism with HRV indices using Spearman rank correlation for non-parametric variables and Pearson correlation for parametric variables. However, there was no statistically significant correlation of severity with any of the variables (Table 3). This could be due to the relatively lesser number of autistic children in the severe grade in our study.

Findings of the present study indicate that children with autism are associated with elevated cardiac sympathetic activity with no difference in resting cardiac vagal tone indicating that autistic children have an early risk for cardiovascular disease. Further, higher total power observed in children with autism in this study is

contributed by their greater LF power spectrum of HRV. The behavioral response in ASD could be associated with their impaired sympathetic nervous activity. Our finding is based on relatively smaller sample size; therefore, evaluation including larger study population and using sensitive psycho-physiological measures like sympathetic skin response would help in better understanding of autonomic neural activity in autism spectrum disorders. The study of autonomic regulation in childhood psychiatric disorders may provide a better understanding of the etiology and aids in the prevention of cardiovascular diseases in adults.[21]

Conclusion

Study concludes that severity of autism was not associated with cardiac autonomic indices. ASD children exhibit altered cardiac sympathetic nervous activity. The altered behavioral responses in ASDs could be associated with their impaired sympathetic nervous activity. The core autistic symptoms which include impaired social interaction, repetitive and stereotypical behaviour could be a result of the differences in baseline arousal or stress which may be associated with impaired autonomic nervous activity. Future studies are needed to examine the association of this deregulation of ANS with symptoms and co-morbidity of ASDs.

Source of Funding: The study is a part of project funded by Department of Health Research (DHR), Indian Council of Medical Research (ICMR).

Conflicts of Interest: The authors have no conflict of interest to declare.

References

1. Song R, Liu J, Kong XJ. Autonomic Dysfunction and Autism Subtypes and Clinical Perspectives. N A J Med Sci,2016;9:172-180.
2. Sabyasachi Sircar. Principles of Medical Physiology. Second edition, Thieme Publishers Delhi. 2014;pp 642.
3. Iveta B, Igor O, Michal M, Ingrid T. Autonomic Nervous System in Children with Autism Spectrum Disorder. Cognitive Remediation Journal, 2015;4.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th edition.) Arlington, VA: American Psychiatric Publishing, 2013.
5. Tan YH, Xi CY, Jiang SP, Shi BX, Wang LB, Wang L. Auditory abnormalities in children with autism. Open Journal of Psychiatry, 2012;2:33-37.
6. Zygmunt A, Stanczyk J. Methods of evaluation of autonomic nervous system function. Arch Med Sci, 2010;6:11-18.
7. Task Force of the European Society of Cardiology. The North American Society of Pacing and Electrophysiology (Membership of the Task Force listed in the Appendix), Heart rate variability Standards of measurement, physiological interpretation, and clinical use. Eur. Heart J, 1996, 17, 354–381.
8. Berntson G.G, Thomas Bigger J., Jr, Eckberg D.L, Grossman P, Kaufmann P.G, Malik M, Nagaraja H.N, Porges S.W, Saul J.P, Stone P.H, et al. Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology, 1997: 34: 623–648.
9. Porges, S.W. The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. Clevel. Clin. J. Med, 2009: 76: S86–S90.
10. Bal, P.M, Jansen, P.G, Van Der Velde, M.E, de Lange, A.H, Rousseau, D.M. The role of future time perspective in psychological contracts: A study among older workers. J. Vocat. Beha, 2010;76:474–486.
11. Ming X, Julu P, Brimacombe M, Connor S, Daniels M. Reduced cardiac parasympathetic activity in children with autism. Brain Dev, 2005; 27:509-516.
12. Daluwatte C, Miles J.H, Christ S.E, Beversdo D.Q, Takahashi T.N, Yao G. Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder. J. Autism Dev. Disord, 2013; 43: 1910–1925.
13. Levine T.P, Sheinkopf S.J, Pescosolido M, Rodino A, Elia G, Lester B. Physiologic arousal to social stress in children with autism spectrum disorders: A pilot study. Res. Autism Spectr. Disord, 2012; 6: 177–183.
14. Bujnakova I, Ondrejka I, Mestanik M, Visnovcova Z, Mestanikova A, Hrtanek I, Fleskova D, Calkovska A, Tonhajzerova I. Autism spectrum disorder is associated with autonomic underarousal. Physiol. Res, 2016; 65: S673–S682.
15. Bricout, V.A, Pace, M, Dumortier, L, Favre-Juvin, A, Guinot M. Autonomic responses to head-up tilt test in children with autism spectrum disorders. J. Abnorm. Child. Psychol, 201; 46: 1121–1128.

16. Pomeranz B, Macaulay R.J, Caudill M. A, Kutz I, Adam D, Gordon D, et al., Assessment of autonomic function in humans by heart rate spectral analysis, Am. J. Phys, 1985; 248:H151–H153.
17. Malliani A. The pattern of sympathovagal balance explored in the frequency domain, News Physiol. Sci, 1999; 14: 111–117.
18. Montoni T, Yoko K. Autistic adolescent autonomic response to mental load. Japanese Journal of Child and Adolescent Psychiatry. 1999;40:316-328.
19. Parati, G, Mancia, G, Di Rienzo, M, Castiglioni, P. Point: Cardiovascular variability is/is not an index of autonomic control of circulation. J. Appl. Physiol, 2006; 101: 676.
20. Kushki A, Brian J, Dupuis A, Anagnostou E. Functional autonomic nervous system profile in children with autism spectrum disorder. Mol. Autism, 2014.
21. Shrinivasan K. Childhood Psychopathology and Autonomic Dysregulation: Exploring the Links using Heart Rate Variability. J. Indian Assoc. Child Adolesc. Ment. Health, 2007: 3: 96–104.