

Heart rate variability study of childhood anxiety disorders

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ABSTRACT

Background: The current study aims at assessment of heart rate variability among children and adolescents with childhood anxiety disorder, using the case-control design. **Materials and Methods:** The study was carried out at a tertiary care multispecialty hospital. It included 34 children and adolescents with diagnosis of childhood anxiety disorder, in the age range of eight to eighteen years, and 30 age- and sex-matched healthy controls. Heart-rate variability was studied using the standard protocol. **Results:** Significantly reduced variability of the heart rate was observed in both the time as well as frequency domains in the disorder group as compared to the control group. These findings indicate decreases in the sympathetic and parasympathetic activity in the disorder group, thus representing diminished physiological variability at rest. **Conclusions:** The notion of autonomic inflexibility, as seen in the current study, has important implications for stability in biological systems. The loss of variability in the physiological systems in general, and in the cardiovascular system in particular, has an association with a number of diseases and dysfunctions.

Key words: Adolescents, anxiety disorders, childhood, heart rate variability

INTRODUCTION

Rubric anxiety disorders comprise of some of the most prevalent psychiatric disorders in children and adolescents. The point prevalence of these disorders has ranged from 3 to 13% across studies.^[1-3]

Behavioral inhibition, possibly a childhood precursor to adult anxiety disorders, has been associated with high heart rate [HR] stability.^[4] Thus, diminished variability in HR, skin conductance, and possibly other measures of peripheral physiological activity may be common to clinical anxiety

and the related psychopathologies. Furthermore, low vagal tone has been found to be associated with increased distractibility in infants and adults.^[5]

Noninvasive assessment of the intrinsic sources of HR variability is an area of great interest in psychophysiology.^[6,7] Spectral analysis of HR variability is a method widely recommended and employed in deriving indices that reflect sympathetic and parasympathetic cardiovascular influences.^[8]

The role of the parasympathetic activity in HR regulation remains debatable.^[9] Even as some studies^[10,11] have demonstrated a direct relationship between HR variability and parasympathetic effect, others have failed to do so.^[12,13] Moreover the impact of parasympathetic regulation of HR variability among patients with anxiety disorders remains understudied. The literature is limited to a few studies for childhood anxiety disorders.^[14,15]

The notion of autonomic inflexibility has important

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implications with regard to recent conceptualizations of stability and instability in biological systems. Contemporary models of nonlinear dynamical systems view flexibility in response to changing environmental demands as a marker of system integrity, and interpret reduced high frequency variability as being pathological.^[16] The loss of complexity and variability in physiological systems in general and cardiovascular system in particular, has recently been linked with a number of diseases and dysfunctions.^[17] Reduced HR variability reflects a shift away from the parasympathetic control of the heart.

The current study aims at assessing the HR variability among children and adolescents with anxiety disorders as compared to healthy controls. We have used a comparative analysis of children and adolescents with anxiety disorders and matched healthy controls for this purpose.

MATERIALS AND METHODS

The study was carried out at a multispecialty tertiary level hospital. The subjects were recruited from the child guidance clinic of the institute and the assessments were carried out at the Autonomic Functions Laboratory in the Department of Physiology at the same institute. The sample consisted of two groups, which were drawn from those seeking treatment at the Outpatient Child Guidance Clinic. The subjects meeting the inclusion and exclusion criteria and providing valid informed consent were included in the study. Age and sex-matched healthy control children and adolescents were used as a control group. The disorder group comprised of 34 subjects [children and adolescents] with a diagnosis of childhood anxiety disorder [Diagnostic and Statistical Manual of Mental Disorders - IV — Text Revision (DSM IV TR)], in the age range of eight-to-eighteen years. The control group consisted of 30 age- and sex-matched subjects recruited from a nearby primary school. The subjects with co-morbid diagnosis of other psychiatric disorders were excluded.

The clinical assessment of the psychiatric disorders was carried out using a semi-structured interview,

- K-SADS [Schedule for affective disorders and Schizophrenia for children and adolescents]
- STAIC [State and trait anxiety inventory for children]
- CDRS [Childhood depression rating scales]
- SCARED [Self-report for childhood anxiety-related disorders]

After inclusion in the study, a complete psychiatric and medical history was taken and a mental status examination

was performed on the subjects. This was followed by a general physical examination. The diagnosis was reached using DSM-IV TR. The findings, including the diagnosis were discussed and confirmed with the consultant psychiatrist. This was followed by the application of the semi-structured proforma. The semi-structured proforma included details about the education, birth, and developmental history, family history, and past history of psychiatric and medical illness.

Evaluation of heart rate variability

The subjects were advised to refrain from food, tea, coffee or any other beverages two hours prior to the test. The entire range of tests was carried out in an air-conditioned laboratory environment [$22 \pm 2^\circ\text{C}$] in supine and sitting positions, between 9 am and 4 pm.

Heart rate variability [HRV] and resting blood pressure were taken as measures of autonomic activity [tone]. HR VARIABILITY was measured according to the Guidelines laid down by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.^[18]

Methods for HRV analysis

The study subject was asked to lie down comfortably. After a gap of 15 minutes, an ECG was recorded under standardized conditions. The ECG recording was taken in the Lead II configuration, using the Nevrokard ECG data acquisition system [Nevrokard v 6.0, Slovenia]. This consisted of a PCI 20450P DASport A/D converter hardware apparatus that acquired and recorded the ECG. A signal sequence was recorded for 300 seconds. A 50 Hz notch filter was used to remove the power line noise, while electromagnetic interferences were also minimized, as the laboratory was optimally shielded from electromagnetic influences. The signal was amplified for optimal detection of the QRS peaks and the amplification depended on the amplitude of the input signal, which differed for each subject. As per the standard recommendation, the sampling rate was kept at 500 Hz. The signal was processed using the Nevrokard HR VARIABILITY analysis software. The recorded ECG signal was stored on a personal computer, which was later analyzed offline.

A careful manual editing was then performed by visual inspection, to mark the peaks. This was done to remove artifacts as well as insert missing peaks or delete false peaks and artifacts. Abnormal beats were identified and dealt with adequately, while recordings with a high number of ectopic

beats were discarded from the analysis. The analysis of the detected RR waveform (form of R waves in the ECG record) was carried out in two domains: Time domain and Frequency domain.

Time domain analysis

- In the Time Domain, the following values were selected for statistical analysis:
- Minimum: The shortest duration of the RR interval, in the recording period
- Maximum: The longest duration of the RR interval, in the recording period
- Max. /Min.: The ratio between the maximum duration of the RR interval [in minutes] and the shortest duration of the RR interval, in the recording period

Coefficient of variance of successive RR intervals

- SDNN: Standard deviation of the RR interval [SDNN], that is, the square root of variance, is mathematically equal to the total power of the spectral analysis, and reflects all the cyclic components responsible for variability in the period of recording
- SDSD: Standard deviation of differences between the adjacent RR intervals
- RMSSD: The square root of the mean of the sum of the squares of differences between the adjacent RR intervals, estimates the short-term components of HR VARIABILITY
- NN50 Count: The number of interval differences of successive RR intervals greater than 50 ms of RR intervals
- pNN50 Count: The proportion derived by dividing NN50 by the total number of RR intervals
- All these measurements of short-term variation estimate high frequency variations in the heart rate and are thus highly correlated with parasympathetic influences.

Frequency domain analysis

The spectral power density of the different component frequencies in the heart rate was carried out by Fast Fourier

Transform [FFT]. The FFT algorithm is based on the non-parametric method. A Hamming window was used and the power spectrum was subsequently divided into three frequency bands: VLF – [0.001 to 0.04] Hz, LF – [0.040 to 0.15] Hz, and HF – [0.15 to 0.4] Hz. The FFT was calculated in three preset frequencies and the power spectral densities were plotted in ms² and also in normalized units; for example, in the case of LF it was calculated by the formula: $LF / [total\ power - VLF] \times 100$.^[18] These frequencies of the heart rhythm are as enumerated in Table 1.

Analysis

Data analysis was done using the SPSS (ver 10, 1983) software. Descriptive statistical measures were performed. In between, group comparisons were made for the two study groups using the chi square test [categorical variables] and two sample *t* tests for different sociodemographic and clinical variables. Phi test and Cramer's V were used for categorical variables with 2*3, 2*4, and 2*6 contingency tables.

The Nevrokard HR VARIABILITY analysis System (v 6.4, Medistar Slovenia), Biopac system MP150 / Acquknowledge 3.5, and MatLab (v 6.5, MathWorks Inc. Japan), were used for analysis of the heart rate variability. To quantify the association between the two variables, Pearson's Correlation coefficient was used for normally distributed measures. The level of statistical significance was kept at $P < .05$ for all analyses.

RESULTS

A total of 64 children and adolescents were recruited in the study of which 34 were in the disorder group and 30 were in the control group.

The disorder group comprised of subjects with a diagnosis of childhood anxiety disorder [DSM IV TR]. The control group included age- and sex-matched healthy children and adolescents.

The socio-demographic profile of the subjects in the disorder group and the control group are described in

Table 1: Frequency bands for measurement of heart rate variability and their physiological correlates

Frequency bands	Frequency	Mediated by
Very low frequency (VLF)	≤ 0.04 Hz	Possible neurohumoral mechanisms (circulating catecholamines and the renin-angiotensin system). However, its physiological explanation in short-term recordings is not well-defined
Low frequency (LF)	0.04 – 0.15 Hz	Parasympathetic and sympathetic influences
Frequency (HF)	0.15 – 0.4 Hz	Parasympathetic influences

Reference: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996

Table 2. Apart for the place of residence no significant differences were observed between the study and the control groups in terms of the socio-demographic profile. The study group comprised of 15 [44%] subjects from the rural back ground, while the control group had all subjects [100%] from the urban backgrounds [$P < .05$]. The two groups were comparable on the education, birth order, and number of siblings [Table 2].

The diagnoses of subjects in the disorder group are shown in the Figure 1. The diagnoses of the subjects included generalized anxiety disorder [GAD], separation anxiety disorder [SAD], social phobia [SP] and combination thereof. The distribution of the disorders among male and female subjects was comparable [$P = .47$].

Heart rate variability exhibited significant differences between the disorder and control groups for both time and frequency domains. Time and frequency domain measures of HR VARIABILITY in the disorder and control groups are depicted in Tables 3 and 4, and Figures 2 and 3, respectively. In the time domain, the anxiety group had shorter minimum R-R interval [RRI], maximum RRI, maximum RRI / minimum RRI ratio, coefficient of variance, standard deviation of RRI's [SDNN], standard deviation of successive RRI's [SDSD], root mean of squared successive RRI's [RMSSD], a number of interval

differences of successive RR intervals greater than 50 ms of RR intervals [NN50], and percentage of NN50 Frequency [PNN50]. All these values were smaller compared to the control group values and all were statistically significant [$P < .05$], except the minimum RRI.

In the frequency domain, the disorder group patients had significantly lower LF [Low Frequency], HF [High Frequency], and total spectral power when compared to the control group [$P < .05$]. The other variables also had smaller values than the control group. LF maximum frequencies, although none, were significant. These findings signify decreases in sympathetic and parasympathetic activities in the disorder group, thus representing diminished physiological variability at rest.

DISCUSSION

The current study is aimed at finding the differences in HR variability among children and adolescents with anxiety

Table 2: Socio-demographic profile of the study and control groups

Variable	Study Group (n = 34)	Control Group (n = 30)	P-value
Age (years)	12.12 ± 2.76	11.66 ± 2.50	
Sex			P = .814
Male	16 (47.1)	15 (50.0)	
Female	18 (52.9)	15 (50.0)	
Residence			P < .05
Urban	29 (85.3)	30 (100)	
Rural	5 (14.7)	0 (0)	
Education			P = .82
Primary School	17 (50)	16 (53.3)	
Middle	8 (23.5)	7 (23.3)	
High	8 (23.5)	7 (23.3)	
Undergraduate	1 (2.9)	0 (0)	
Family type			P = .814
Nuclear	27 (79.4)	26 (86.3)	
Joint	7 (20.6)	4 (13.3)	
No. of siblings			P = .44
No sibling	4 (11.8)	6 (20)	
1 – 2	25 (73.6)	22 (73.3)	
> 3	5 (14.7)	2 (6.7)	
Order of siblings			P = .15
Only child	4 (11.8)	6 (20)	
1	21 (61.8)	19 (63.3)	
2	4 (11.8)	3 (10)	
> 3	5 (14.7)	2 (6.7)	

Table 3: Time domain measures of HRV in the disorder and control groups

Parameters	Disorder group (n = 34)	Control group (n = 30)	P-value
Min.	560.75 ± 80.82	570.27 ± 72.79	0.639
Max.	821.51 ± 156.79	925.03 ± 152.68	0.014
Max / min	1.46 ± 0.16	1.62 ± 0.21	0.00
Coefficient of variance	5.99 ± 1.9	8.81 ± 3.19	< .0001
SDNN	40.6 ± 16.87	63.67 ± 29.91	0.001
SDSD	40.28 ± 26.99	67.26 ± 42.28	0.006
RMSSD	40.23 ± 26.95	67.17 ± 42.22	0.006
NN50	37.00 ± 36.39	68.00 ± 42.13	0.004
PNN50	896.33 ± 982.59	1634.84 ± 1066.03	0.009

Values are expressed in Mean ± Standard deviation. HRV — Heart rate variability, Min — Minimum interval of RRI, Max — Maximum interval RRI, Max. / min. ratio between the maximum and minimum RRI, cost of variance of RRI, SDNN — standard deviation of RRI's, SDSD — standard deviation of successive RRI's, RMSSD — root mean of squared successive RRI's, NN50 — number of interval differences of successive RR intervals greater than 50 ms of RR intervals, PNN50 — percentage of the NN50 Frequency domain measures of HRV in anxiety and control groups

Table 4: Frequency domain measures of HRV in study and control groups

Frequency domain	Disorder group (n = 34)	Control group (n = 30)	P values
LF / HF	1.11 ± 0.88	1.12 ± 1.10	0.965
LF max. freq.	0.1085 ± 0.1258	0.0962 ± 0.0324	0.614
LF Power MS2	435.84 ± 398.17	1453 ± 1856.79	0.006
LF Power n.u.	37.6837.68 ± 15.53	37.4166 ± 18.1314	0.952
HF max. freq.	0.2938 ± 0.810	0.3005 ± 0.759	0.744
HF power MS2	813.39 ± 998.28	2389.44 ± 2919.42	0.008
HF power n.u.	47.09 ± 18.70	47.6701 ± 19.46	0.908
Total power	1682.74 ± 1561.17	4774.04 ± 5182.37	0.004

Values are expressed in Mean ± Standard deviation. Abbreviations: HRV — Heart rate variability, LF — Low frequency, HF — High frequency

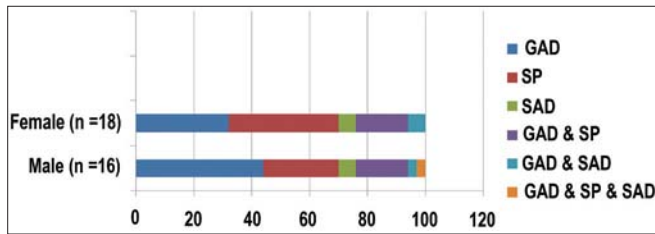


Figure 1: Diagnosis break-up of the disorder group ($n = 34$) (disorders represented as percentage of total)*. GAD-Generalised anxiety disorder; SP-Social Phobia; SAD-Separation anxiety disorder, * Male and Female sub-groups did not differ significantly with regards to the diagnosis ($\Phi = .37$, $P = .47$)

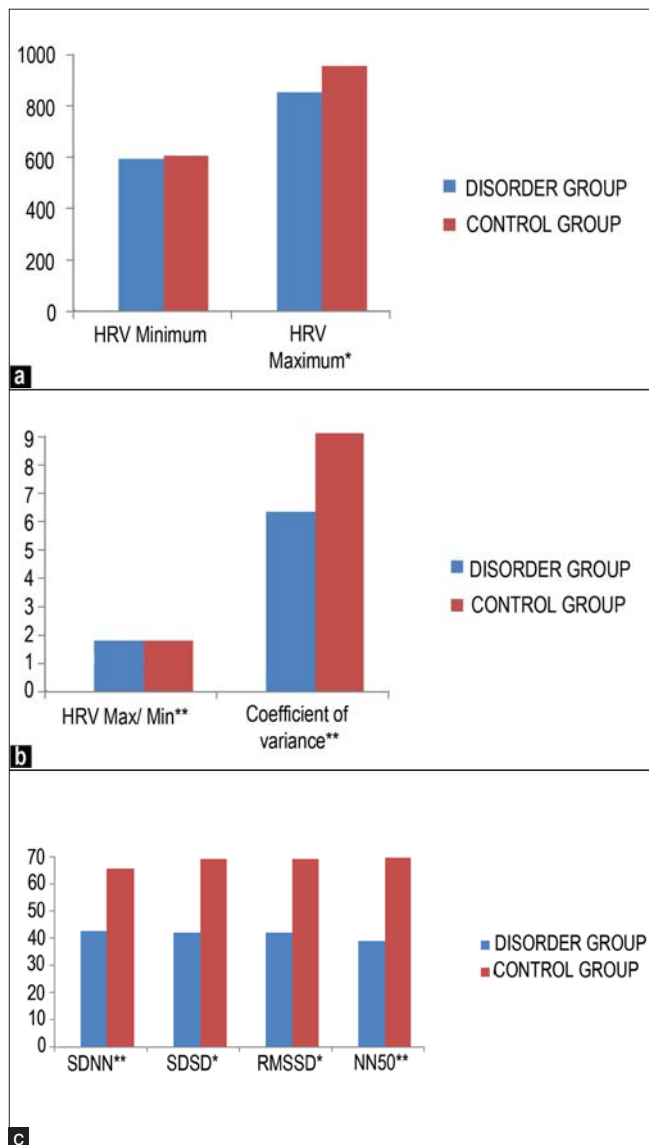


Figure 2: Time domain measures of Heart Rate Variability (HRV) in disorder and control groups. (a) HRV- heart rate variability-maximum and minimum; (b) Heart rate variability max/ Min ratio, Coefficient of variance; (c) SDNN-standard deviation of RRI's, SDSD -Standard deviation of successive RRI's, RMSSD-root means of squared successive RRI's RRIS, NN50- number of interval difference of successive RR intervals greater than 50 ms of rr INTERNAL. *Statistically significant at $P < .05$, **Statically significant at $P < .005$

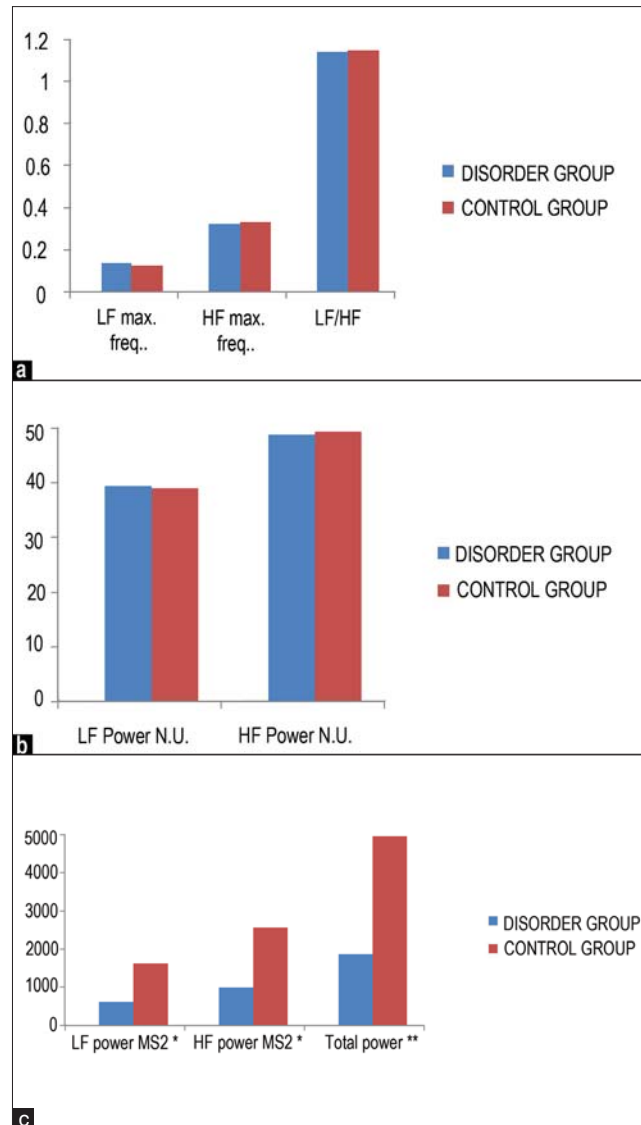


Figure 3: Frequency domain measures of Heart Rate Variability (HRV) in disorder and control groups. (a) LF- Max freq- Low Frequency maximum frequency, HF -max freq-high frequency maximum frequency, LF/ HF ratio; (b) LF power N.U. -Low Frequency Power, HF power N.U. - High Frequency; (c) Lf Power MS2 - Low Frequency Power, HF power MS2- High Frequency Power, Total Power *Statistically significant at $P < .05$ **Statistically significant at $P < .005$

disorders as compared to healthy controls. Additionally, the study explores the correlation between clinical parameters and autonomic dysfunction among children and adolescents with anxiety disorders. We have included an age- and sex-matched control group.

Both study groups were comparable on different socio-demographic parameters. A majority of the subjects [73.6%] had one or two siblings and were first in the birth order [61.8%]. It was found that a majority of the study subjects [85.3% in the disease group and 100% in control group] were from an urban setting, which could be due to the fact that the study was conducted in an

urban setting. Another reason might be that patients in the urban settings had more awareness and accessibility to treatment centers and thus sought treatment. Moreover, the available epidemiological studies from India have reported comparable rates of psychiatric disorders among children and adolescents from the rural and urban settings.^[6]

Generalized anxiety disorder [GAD] was the most common diagnosis [44.1%] followed by social phobia [SP] [26.5%], and separation anxiety disorder [SAD] [5.9%]. In the present study, the gender differences with regard to the type of anxiety disorder were not significant. Comparable rates of anxiety disorders have been reported among male and female children and adolescents.^[19]

Literature reveals that anxiety disorders in the youth are receiving increasing attention. Such attention is understandable considering that an estimated 10 – 20% of the youngsters suffer from anxiety and anxiety-related symptoms. Anxiety disorders comprise the most prevalent set of psychiatric disorders in children and adolescents.^[1-3] This can affect the developmental process, school performance, and result in a strained relationship with peers and family members.

Anxiety is often accompanied by somatic manifestations that suggest morbid changes in the autonomic nervous system [ANS] activity, such as rapid heart rate [HR], shortness of breath, and sweating. The autonomic characteristics of depression and panic disorder have been studied extensively.^[19] However, relatively few studies have examined the autonomic characteristics of anxiety disorder, especially in the case of children and adolescents.

Heart Rate [HR] variability, a measure of both sympathetic and parasympathetic activity exhibited significant differences between the disorder group and control group for both the time and frequency domains in the current study.

Although heart rate variability has been addressed among adult populations it has been given little attention among children and adolescents with anxiety disorders. A recent study done among children with ADHD has found that these children have lower HR reactivity immediately after a stress task.^[20] Dietrich *et al.*, found that while externalizing problems (e.g. conduct disorder, oppositional defiant disorder) were associated with lower HR, internalizing problems (e.g. depression) were associated with higher HR among pre-adolescents.^[14]

The HR variability has been postulated to have a heritable effect. Srinivasan *et al.*, compared children of parents with

panic disorders with healthy controls. Children of patients with panic disorder had a significantly lower Lyapunov exponent [LLE] of heart rate time series in the supine posture. It suggested a relative decrease of cardiac vagal function in this group of children.^[15]

The finding of decreased sympathetic activity in the present study are in contrast to a previous study by Thayer *et al.*^[19] A similar spectral analysis of HR variability has been used in this study. This method has been widely recommended and employed in deriving indices that reflect sympathetic and parasympathetic cardiovascular influences. Shorter interbeat intervals and lower high-frequency spectral power has been observed among adult patients of GAD as compared to controls. These findings indicate a tonically weak vagal autonomic control, which is in-keeping with our reported findings. However, strong sympathetic autonomic control has been observed in this study, which is in contrast to our findings of decreased sympathetic activity. This could be explained due to the age difference between the two patient groups or by the difference in the socio-cultural background and ethnicity. Cultures instill beliefs about how emotions should be experienced and expressed, which can translate into cultural group differences in actual emotional responses.^[21]

The sympathetic inhibition found in the anxiety disorder group was similar to that of a previous study on GAD patients in the adult population, which also reported sympathetic inhibition.^[22] The study assessed skin conductance and interbeat intervals in 40 GAD patients and 20 controls.

Our findings show a pattern of decreased parasympathetic activity in the disorder group. This was similar to a previous study done on adults aged 23 – 40 years.^[21] This study postulated that anxiety was related to a reduced vagal control [parasympathetic activity] of the heart. Furthermore, a stepwise increase in trait anxiety scores were associated with reduction in vagal tone. BRC [Baroreflex control of heart rate] and RSA [Respiratory sinus arrhythmia] were used to assess the vagal tone in this study. Licht *et al.*, reported a lower HR variability among adults with anxiety disorders [including GAD and social phobia]. However, after controlling for potential confounders it was found to be related to the use of tricyclic antidepressants.^[23] The current study had recruited drug-free subjects, and hence, the findings were free of likely confounding by their effect.

In the current study, there were significant differences in the parasympathetic reactivity between the control and anxiety groups, thus implying that children and adolescents with anxiety disorder had their parasympathetic reactivity [heart rate response to given perturbation] outside the normal

range. Two other studies with a similar methodology had findings, which were in contrast to the findings of the present study.^[25,26] This disparity could be explained on the basis of methodological differences. In the current study, a detailed analysis of the interbeat intervals could only be done after plotting Fast Fourier Transform [FFT], in contrast to the aforementioned studies. However, the findings from a similar study among adults with GAD showed that no differences were observed in vagal tone (parasympathetic reactivity).^[19]

Our findings are suggestive of autonomic rigidity or diminished physiological flexibility in children and adolescents with anxiety disorder. This loss of variability in the autonomic control system, in general, has been linked with a number of diseases and dysfunctions. Reduced heart rate variability is a prognostic factor for cardiac mortality.^[27] A decrease in cardiac vagal function, as suggested by a decrease in heart rate [HR] variability, has been linked to sudden death.^[28] HR variability measurement is useful in investigating the pathophysiology of various psychiatric disorders.^[29]

Anxiety disorders during childhood and adolescence are associated with significant morbidity. Findings of studies exploring the role of childhood anxiety disorders as future predictors of adult psychiatric disorders have come up variable findings.^[30,31] The current study has shown reduced variability of the heart rate in both the time and frequency domains, as compared to the control population. These findings signify decreases in sympathetic and parasympathetic activity in the disorder group, thus representing diminished physiological variability at rest. The presence of a high vagal tone seems to be a marker of physiological and psychological flexibility. Alternatively, reductions in the complexity of responding in a wide range of physiological channels are associated with poor health outcomes and a lack of adaptive variability in behavioral and cognitive functioning.

The notion of autonomic inflexibility has important implications for recent conceptualizations of stability and instability in biological systems. Contemporary models of nonlinear dynamical systems view flexibility in response to changing environmental demands as a marker of system integrity, and interpret reduced high frequency variability as being pathological.^[16]

Reduced HR power reflects a shift away from the parasympathetic control of the heart. The loss of complexity and variability in the physiological systems in general, and in the cardiovascular system in particular,

has recently been linked with a number of diseases and dysfunctions. Several behavioral and psychological states, such as, acute and chronic smoking, acute and chronic alcohol ingestion, sedentary lifestyle, depression, panic disorder, and aging have all been associated with a loss of heart rate variability and complexity.^[32-36] Additionally physiological disorders such as fetal distress syndrome, sudden cardiac death, ventricular fibrillation, hypertension, diabetes mellitus, and coronary atherosclerosis have been associated with reduced HR variability.^[37-39]

The current study is one of the limited studies, exploring the role of the parasympathetic system on HR variability among childhood anxiety disorders. Although studies exist on adult anxiety disorders, literature is limited on children and adolescents. We have made use of a widely accepted technique to study HR variability and followed the standardized protocol.^[8]

Limitations

We made only cross-sectional observations. A prospective cohort study of these subjects, following remission of clinical symptoms, would further add to the understanding on the issue.

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