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Topics: Low birth weight, Birth weight, Intrauterine growth restriction and Heart rate variability

Heart Rate Variability Analysis of Normal and Growth Restricted Children

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Abstract:- Intrauterine growth restriction (IUGR) has been associated with an increased risk of cardiovascular disease in later life. The regularity mechanism of cardiovascular system is under the control of autonomic nervous system (ANS). The non-optimal fetal growth may alter the development of the ANS and this appears to persist in later life. The aim of the present work is to analyse the synergic activity of the ANS in normal and growth restricted children. For that purpose, heart rate variability analysis from 24 hour ECG recordings of 70 children between 9 and 10 years old, normal and IUGR was performed using linear and non-linear time series analysis techniques. The HRV parameters showed no significant difference between normal and IUGR children. Low birth weight and its association with development of the cardiovascular system and its control have been extensively studied. In order to investigate the effect of low birth weight on HRV parameters, the IUGR children were further divided into two groups: IUGR-1 (birth weight < 2.50 kg) and IUGR-2 (birth weight ≥ 2.50 kg). The results demonstrated that most of the HRV measures showed significant differences between normal *Vs.* IUGR-1 as well as IUGR-1 *Vs.* IUGR-2 groups. The effect of gender on HRV measures were also examined and we noticed that girls had lower HRV than boys.

Keywords: Autonomic nervous system, Coronary heart disease, HRV analysis, IUGR, Low birth weight.

Introduction

Fetal growth restriction, also known as intrauterine growth restriction (IUGR), complicates 3% to 10% of all pregnancies. Low birth weight (LBW), premature birth and small for gestational age (SGA) are the markers to monitor intrauterine growth restriction (IUGR) and adverse prenatal outcomes [8]. A low birth weight infant is one born weighing < 2.5 kg [12, 30]. An infant born less than 37 weeks from first day of menstrual period

regardless of birth weight is preterm, whereas the growth retarded infants are characterized by their biometric dimension < 10^{th} percentile for a given gestational age[12]. IUGR children are reported to suffer from increased incidence of intrauterine fetal death (IUFD), sudden death in infancy, cognitive dysfunction during childhood, altered autonomic nervous system (ANS), increased incidence of obesity and cardiovascular morbidity during adulthood. Geva *et al.* (2006) evaluated the effect of late onset of intrauterine growth restriction on neuropsychological profile and academic achievements at 9 years of age [11]. They found that IUGR children had lower quotient of intelligence and more frequent neuropsychological difficulties.

During life in the uterus, the malfunction of the placenta is the major cause of the under nutrition of the developing fetus [28]. The reduced supply of nutrients to the fetus from the placenta prevents it from getting his/her complete growth potential [9]. Barker *et al.* (1989) proposed that the development of cardiovascular disease is initiated by unfavourable conditions during intrauterine fetal life and adverse environment during early childhood [3]. This hypothesis has been reinforced by epidemiological evidences of association between birth weight and risk of cardiovascular disease [15, 21]. The correlation between cardiovascular disease and low birth weight has been replicated among both males and females in Europe, North America and India [4, 7]. Banci *et al.* (2009) described negative correlation between birth weight and risk of coronary artery disease in non-diabetic females [2]. Andersen and co-workers described that higher BMI in children with very low birth weight is associated with higher cardiac risk [1].

The mechanism of cardiovascular system regulation is mainly dependent on autonomic control of the nervous system. The altered autonomic cardiovascular control, such as increased pulse, hypertension and heart rate variability have been described in low birth adults [19, 29]. Heart rate variability analysis is a well established non-invasive measure of synergic activity of the autonomic nervous system, which regulates the heartbeat dynamics [13]. Heart rate variability has been widely used to measure cardiac autonomic control both in physiologic and pathologic conditions during the last two decades [23]. In 1996, the Task Force of European Society of Cardiology (ESC) and North American Society of Pacing Electrophysiology (NASPE) published standards for HRV analysis proposing several time and frequency domain parameters for assessment of HRV [23].

The purpose of this study was to investigate systematically the autonomic balance in 9-10 years old normal and IUGR children using linear techniques (traditional time and frequency domain HRV measures) and also methods derived from nonlinear dynamics. We

have examined the effect of birth weight and gender on HRV of normal and IUGR children. Most of the HRV measures for IUGR-1 children (birth weight < 2.5 kg) were significantly different from both normal and IUGR-2 children (birth weight ≥ 2.5 kg). We also noticed that girls had lower HRV than boys.

Material and Methods

Data Sets

This work is part of a study that started at Leicester Royal Infirmary (LRI) for investigating the long term effects of intrauterine growth retardation on the autonomic nervous system. In the original study, infants who were identified as IUGR either by serial ultrasound scans, which identified infants who had fetal abdominal girth two or more standard deviation below the mean, or who, by birth weight, were on or below the 2nd centile for gestational age [17]. Only the recordings fulfilling inclusion criteria (Caucasian, Gestation age ≥ 37 weeks, no Congenital and chromosomal problem, no epilepsy or diabetes in mother, evidence of IUGR) were used for subsequent analysis. After a complete medical examination, the 24 hour ECG of IUGR and normal children were recorded with a Lifecard CF ambulatory ECG recorder (Delmar-Reynolds Medical Limited, Hertford, UK). The subjects were advised to perform normal daily routines during recording and to keep a diary of all activities including sleep and wake timings. The ECG recording of all subjects were extracted by Pathfinder 700 series analysis system and examined for artefacts. Characteristics of the study population are described in table 1. The normal group consisted of 33 subjects, 21 male and 12 female, current age 8.96±0.72 years (mean ± standard deviation), birth weight 3.53±0.48 kg, current weight 32.87±6.13kg, and gestational age 39.15±0.91 weeks. The IUGR groups consisted of 37 subjects (16 male and 21 female), current age (9.31±0.62 years), birth weight (2.58±0.42 kg), current weight (28.82±5.90 kg) and gestational age (38.95±1.37 weeks). There was no significant difference between the gestational ages of normal and IUGR groups, so we divided IUGR children into two groups on the basis of their birth weights. The low birth weight group IUGR-1comprising of children having birth weight less than 2.5 kg and IUGR-2 having birth weight greater than 2.50 kg. It is clear from table 1 that, by any criterion, IUGR children do not catch up with normal children in height or weight in the first decade of their life. IUGR-1 children gain weight at a faster rate (weight gain centile 37.37±25.21) than both IUGR-2 (32.09±28.48) and normal children (16.11±33.69). The

children in the normal group have higher tendency to towards obesity, with 50% of them above the 85th percentile for BMI. In our study there were more illness in IUGR-1 children (50%) as compared to IUGR-2 (29%) and normal children (12%). The commonest medical condition was mild asthma, but there were two cases with autism, one child with epilepsy and two children with moderately delayed development.

HRV Parameters

There are many ways of assessing HRV and a comprehensive list of measures investigated since 1960 are explained in detail by the Task Force for European Society of Cardiology the North American Society of Pacing Electrophysiology [23]. In this study, both linear (time and frequency domains) and nonlinear HRV parameters were analysed.

Linear HRV Techniques

Linear time domain parameters included those measures derived from direct measurement of RR intervals (SDNN and SDANN) and from RR-intervals differences (RMSSD, NN50 and pNN50). Standard deviation of all normal to normal RR intervals (SDNN) is the most commonly used index for HRV analysis. SDNN can be calculated for short periods between 30 s and 5 min duration (short term variability) or for long periods (24 hours) as a measure of long term variation [23]. In practice it is inappropriate to compare SDNN measures of recordings of different duration and standardized durations of recordings have been suggested [23]. Other commonly used statistical index SDANN (standard deviation of average NN intervals calculated over 5-min intervals within the entire period of recording) is a measure of long term variation. The most commonly used measures of short term variation derived from interval differences include RMSSD (square root of mean squared differences of consecutive NN intervals), NN50 (number of pairs of NN intervals differing by more than 50 ms) and pNN50 (proportion derived by dividing NN50 by total number of NN intervals).

The linear frequency domain measures used for HRV analysis included low frequency (LF, 0.04-0.15 Hz), high frequency (HF, 0.15-0.4Hz) and the ratio of LF to HF power (LF/HR). The power spectral density was calculated using fast Fourier transform-based Welch periodogram method. Prior to the spectrum estimation the interbeat interval time series was converted into equidistantly sampled time series using cubic spline interpolation and resampling. The resampling frequency was 4 Hz, which works well for human data. The sampled data was divided into overlapping segments, and the Fourier transform was

calculated for each segment. The power spectrum was obtained by averaging the spectra of these segments. The number samples in each segment was 256 with 50% overlapping. This decreases the variance of the spectral estimate.

Nonlinear HRV Techniques

The nonlinear behaviour of HRV was investigated using Poincaré plots, Approximate Entropy and Sample Entropy [20, 26, 27]. A Poincaré plot is a quantitative visual tool that represents correlation between successive RR intervals [20]. A common approach to quantitatively summarize the shape is to fit an ellipse to the plot [14, 22]. The ellipse is oriented according to the line of identity. A standard Poincaré plot and its two basic two basic descriptors SD1 and SD2 are shown in the figure 1. SD1 measures dispersion of points perpendicular to the line of identity, describes short term variability. SD2 measures dispersion of points along the line of identity, describes long term variability.

Approximated Entropy (ApEn) analysis is a measure of irregularity or randomness of the signal that quantifies the predictability of the fluctuations in the signal [26]. Large values of ApEn indicate high complexity and smaller values of ApEn indicate a more regular signal. The values of ApEn depend on two factors, the length of the vectors (m), and the tolerance (r), that is, ApEn can be written as ApEn(m, r). The tolerance r is the percentage of standard deviation (SD) of the original time series (for HRV 10%-25% of standard deviation). Two patterns are similar if the difference between any pair of corresponding measurements in the pattern is less than r. The sample entropy (SamEn) is a modification of the ApEn algorithm in which self matches are excluded [27]. The SamEn is less dependent on the time series length and provides reliable and reproducible results. In this study the parameters used for the computation and ApEn and SamEn were m=2 and r=0.2. These values of m and r were chosen based on the results of previous studies by Pincus indicating good statistical validity for approximate entropy [26].

Results

The linear and nonlinear time series analysis techniques have been applied to interbeat interval time series of 33 normal and 37 IUGR 9 to 10 years old children. Wilcoxon rank sum test was used to find the significant difference between the groups with Bonferroni correction for repeated tests. In table 2, the results of HRV measures for normal and IUGR subjects are shown. The HRV decreased for IUGR subjects, but no significant difference was found

between normal and IUGR subjects. The influences of birth weight and gender on HRV measures were also examined.

The results of linear and nonlinear HRV measures after dividing the IUGR cases according to birth weight are summarized in table 3. The time domain parameter of overall HRV, SDNN showed a significant difference between normal *Vs.* IUGR-1 (p=0.0129) and IUGR-1 *Vs.* IUGR-2 children (p=0.0019), however, SDNN was not statistically significant in Normal *Vs.* IUGR-2 (p=0.138). SDANN was statistically smaller in IUGR-1 children than both normal and IUGR-2children (p= 0.0322 and 0.0008 p=respectively). Similar results were obtained for RMSSD for IUGR-1 *Vs.* normal and IUGR-1 and IUGR-2 (p=0.0010 and p=0.0016 respectively). NN50 and pNN50 were significantly different between IUGR-1 *Vs.* IUGR-2, but revealed no significant difference between normal *Vs.* IUGR-1 and normal *Vs.* IUGR-2. The frequency domain HRV measures LF, HF and LF/HF were significantly smaller in IUGR-I than both normal (p=0.0217, p=0.0321 and p=0.0384 respectively) but LF and HF were significantly smaller between IUGR-1 *Vs.* IUGR (p=0.0012 and 0.0046). None of the linear HRV measures showed significant difference between normal and IUGR-2 children.

The nonlinear measures used for quantifying the dynamics of heart rate signals of normal and IUGR groups include Poincaré plots, approximate entropy and sample entropy. Two Poincaré plot indices SD1 (dispersion of points perpendicular to the line of identity) and SD2 (dispersion of points along the line of identity) were computed. The value of SD1 was significantly smaller between IUGR-1 *Vs.* IUGR-2 (p=0.0011) but not between normal *Vs.* IUGR-1 (p=0.1442). SD2 revealed significant difference between normal *Vs.* IUGR-1 (p=0.0209) and within IUGR groups (p=0.0033) but not for normal *Vs.* IUGR-2.

The nonlinear complexity measures, approximate entropy and sample entropy were computed by setting length of vector m=2, tolerance r=20% of standard deviation of the time series. ApEn was not statistically significant between any of the groups (p=0.4423 normal *Vs.* IUGR-1, p=0.1198 IUGR-1 *Vs.* IUGR-2 and p=0.5003 normal *Vs.* IUGR-2). Sample entropy showed significant difference normal *Vs.* IUGR-1 and within IUGR groups (p=0.0209 and 0.0328 respectively), but not for normal *Vs.* IUGR-2.

The HRV parameters for studying gender related differences in normal and IUGR children are presented in table 4. A decrease in heart rate variability was found in both normal and IUGR female children. SDNN, LF and SD2 were significantly smaller in female subjects (p=0.0360, p=0.04 and p=0.0369 respectively), however no other HRV parameter reached statistically significant level in normal children based on gender.

Discussion

During intrauterine life, malfunctioning of fetal supply, which includes placenta, is the major cause of fetus under nutrition [28]. The fetus survives by metabolic and cardiovascular adaptations. The control mechanism of cardiovascular system depends on the autonomic nervous system involving mediation of both sympathetic and parasympathetic branches. In growth restricted children, altered cardiovascular control such as increased pulse rate [25] altered blood pressure and heart rate fluctuations [19, 29] have been observed. Numerous animal studies support the connection of unfavourable prenatal environment and alterations in the sympathetic autonomic balance [18, 24]. Flanagan and co-workers found inverse correlation between adult resting pulse rate (sympathetic activity index) and birth weight [10]. In IUGR adolescents, an increased cardiac sympathetic nerve activity was observed [16].

The adverse environment during fetal life may alter the development of the autonomic nervous system, which appears to persist in postnatal life. Heart rate variability (HRV) analysis is a valuable non-invasive measure of autonomic control, which regulates heart rate dynamics. During last three decades a large number of studies both in physiological and pathological condition show the power of HRV as quantitative marker of the activity of the cardiovascular control system [23]. This study was carried out to find the association between intrauterine growth retardation and cardiovascular disease, as well as the early identification and possible prevention of illness in later life. The cardiac autonomic activity was assessed using linear and nonlinear heart rate variability from 24 hour ECG recordings of IUGR and normal 9 to 10 years old children. We found no significant alteration in HRV measures of normal and IUGR (combined IUGR-1 and IUGR-2) children.

The birth weight of only one normal child was less than 2.5 kg and more than 50% IUGR subjects have birth weight less than 2.5 kg. In order to examine the effect of birth weight on HRV parameters, we divided IUGR subjects into IUGR-1 and IUGR-2. SDNN, SDANN, RMSSD, LF, HF, SD2 and SamEn showed significant differences between IUGR-1 *Vs.* Normal as well as IUGR-1 and IUGR-2. NN50, pNN50 and SD1 ratio were statistically significant within IUGR groups but not in normal *Vs.* IUGR-1 children. None of the HRV measures except SD1 revealed significant difference between IUGR-2 and normal children. Table 3 shows that HRV parameters are similar for normal and IUGR-2 subjects and are significantly different for IUGR-1. Our results demonstrate significantly altered autonomic control of low birth weight IUGR children (IUGR-1). The altered autonomic control of low

birth weight IUGR children is in accordance with Baker's hypothesis of fetal origin of adult disease [3]. The epidemiological evidence of this hypothesis has been provided in various studies [6, 15, 21]. In different studies among male and female in Europe, North America and India, the association of low birth weight and cardiovascular disease has been described [4].

The effect of gender on HRV indices was studied and we noticed a decrease in HRV in both normal and IUGR female children. In normal children, SDNN, LF and SD1 showed significant sex difference but no HRV measure reached to significant level on gender basis in IUGR children. The decrease in HRV parameters for female children is consistent with the study of [5], who found that the female population presents lower overall HRV compared with the male population.

Our finds indicate that disturbances in ANS function reflected by reduced heart rate variability may represent one of the pathways to negative outcome of the cardiovascular system and hence the risk of coronary heart disease in low birth weight IUGR children. Andersen *et al.* (2010), found that birth weight and BMI at the age of seven appears to exercise mutually independent effects on the risk of cardiovascular disease [1]. They described that children with a combination of low birth weight and relatively high BMI had a cardiac risk of 44%. The present study showed an inverse relation of birth weight and negative outcome of the cardiovascular system in growth retarded children, however, as the BMI of low birth weight IUGR children is small, we did not study the relation of BMI and risk of coronary heart disease.

The established cardiovascular risk in low birth weight IUGR children, concerns the underlying physiological mechanisms. The hypothesis that this is driven by a stress/autonomic response has been made before. The differences between normal and low birth weight IUGR Children provide further evidence for this at an age in which clinical manifestation of disease are not yet apparent. Our findings implicate further follow-up study as the child progresses to second decade of his life.

Conclusions

The association of fetal growth retardation and development of cardiovascular disease has been extensively replicated. The cardiovascular system regulation strongly depends on the autonomic control of the nervous system. Heart rate variability is a valuable non-invasive marker of cardiac autonomic balance. In this study, linear and non-linear HRV parameters were computed for seventy 9 to 10 year old normal and IUGR children. The direct comparison of HRV parameters between normal and IUGR children showed no significant

difference between the two groups. We also examined the effect of birth weight and gender on HRV parameters. The findings revealed that most of HRV measures showed significant difference between Normal and low birth weight IUGR children and also within IUGR groups. The decrease in HRV depicts the altered autonomic control in low birth weight IUGR children as compared with normal and IUGR-2 children. Three HRV measures (SDNN, LF and SD1) showed significant gender specific differences in the normal cohort. It is suggested that low birth weight in IUGR children can have adverse implications for the autonomic nervous system.

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Table 1

	Normal	**IUGR-1**	**IUGR-2**
Recordings	33	20	17
Birth Weight (kg)	3.53 ± 0.48	2.29 ± 0.19	2.92 ± 0.36
Gender (Male/Female)	21/12	8/12	8/9
Current Weight (kg)	32.87 ± 6.13	28.13 ± 4.74	29.64 ± 6.89
Weight Gain (kg)	29.34 ± 6.13	25.83 ± 4.75	26.72 ± 6.88
Weight Gain Centile	16.11 ± 33.69	37.37 ±25.21	32.09 ± 28.48
Current Height (cm)	133.86 ± 5.00	131.00 ± 5.84	132.18 ± 7.01
Current Height Centile	57.91 ± 25.75	34.17 ± 25.04	33.25 ± 25.18
Current BMI (kg/m^2)	81.21 ± 2.52	16.38 ± 2.55	16.77 ± 2.58
Current BMI Centile	72.72 ± 28.40	42.75 ± 29.29	50.25±29.30

Table 2

HRV Measures	Normal	IUGR	p-value
SDNN (ms)	156.82±28.24	152.82±35.21	0.6053
SDANN (ms)	77.65±20.46	76.87±21.33	0.8766
RMSSD (ms)	70.32±28.86	69.58±33.62	0.9226
NN50 (ms)	28290±11179	29870±12830	0.5867
pNN50 (%)	23.55±10.51	24.64±11.99	0.6893
LF (ms^2)	1966±969	1840±907	0.5742
HF (ms^2)	2704±2177	2678±2724	0.9647
LF/HF	0.92±0.38	1.16±0.78	0.1542
SD1 (ms)	49.72±20.41	54.81±28.28	0.3962
SD2 (ms)	215.63±37.42	205.16±53.32	0.3507
ApEn	1.14±0.08	1.16±0.09	0.1908
SamEn	1.07±0.08	1.10±0.13	0.1269

Table 3

HRV Measures	Normal	IUGR-1	IUGR-2	p-value		
				Normal Vs. IUGR-1	IUGR-1 Vs. IUGR-2	Normal *Vs.* IUGR-2
SDNN (ms)	156.81±28.24	136.99±25.22	171.45±36.78	0.0129	0.0019	0.138
SDANN (ms)	77.65±20.46	66.66±11.27	88.87±24.28	0.0322	0.0008	0.091
RMSSD (ms)	70.32±28.86	53.72±18.78	86.25±37.93	0.0262	0.001	0.0681
NN50 (ms)	28290±11179	25139±10115	35435±13712	0.308	0.0128	0.0534
pNN50 (%)	23.55±10.51	19.83±8.87	30.30±12.93	0.1916	0.0063	0.0525
LF (ms^2)	1966±2214	1418±456	2336±1057	0.0217	0.0012	0.2207
HF (ms^2)	2704±2178	1548±1102	4007±3433	0.0321	0.0046	0.1078
LF/HF	0.92±0.38	1.23±0.66	1.03±0.88	0.0384	0.4379	0.5602
SD1 (ms)	49.72±20.41	41.56±17.64	70.41±30.85	0.1440	0.0011	0.0066
SD2 (ms)	215.63±37.42	182.37±39.32	231.97±56.11	0.0209	0.0033	0.2249
ApEn	1.14±0.08	1.17±0.09	1.15±0.08	0.4423	0.1198	0.5003
SamEn	1.07±0.08	1.13±0.13	1.07±0.12	0.0209	0.0328	0.8684

Table 4

HRV Measures	Normal Children			IUGR Children		
	Male	Female	p-value	Male	Female	p-value
SDNN (ms)	164.52±30.14	143.34±18.87	0.0360	158.84±36.96	148.24±32.98	0.3721
SDANN (ms)	82.39±23.13	69.35±11.27	0.0778	79.92±23.40	74.54±19.18	0.4557
RMSSD (ms)	76.12±32.32	60.18±18.64	0.1289	69.95±32.69	69.30±34.34	0.9544
NN50 (ms)	29502±12899	26169±7303	0.4187	30555±12723	29348±12890	0.7813
pNN50 (%)	24.97±11.51	21.07±8.37	0.3136	25.90±12.48	23.68±11.49	0.5848
LF (ms^2)	2225±1095	1513±449	0.0400	2079±1081	1658±682	0.1642
HF (ms^2)	3086±2474	2036±1380	0.1873	2753±2677	2620±2760	0.8855
LF/HF	0.88±0.35	0.99±0.44	0.4444	1.11±0.58	1.16±0.89	0.8604
SD1 (ms)	53.82±22.86	42.55±13.18	0.1289	54.65±27.16	54.94±29.14	0.9760
SD2 (ms)	225.79±39.52	197.85±26.33	0.0369	213.49±54.89	198.82±51.09	0.4148
ApEn	1.13±0.08	1.14±0.07	0.7209	1.18±0.08	1.15±0.09	0.3318
SamEn	1.05±0.09	1.09±0.08	0.2497	1.13±0.12	1.08±0.13	0.2339