**Full Title: Heart Rate Variability in Low Birth Weight Growth Restricted Children
During Sleep and Wake Stages**

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Short Title: HRV Analysis of Growth Restricted Children

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Abstract

Intrauterine growth restricted (IUGR) individuals have greater predisposition to develop a metabolic syndrome in later life manifesting itself as obesity, hypertension, type 2 diabetes or cardiovascular disease. Poor fetal growth may alter the regularity mechanism of cardiac autonomic system that is involved in the development of these diseases. The malfunctioning of the cardiac autonomic system assessed by decrease in heart rate variability (HRV) is associated with negative cardiovascular outcomes. This study is aimed at investigating the risk of development of coronary heart disease in IUGR children in later life. For that purpose HRV analysis of normal and growth restricted children was performed during sleep and wake stages. The study group consisted of 9 to 10 years old, 32 normal, 20 low birth weight IUGR children. The standard time domain HRV metrics (mean RR, SDNN, RMSSD, NN50 and pNN50) and Poincaré indices (SD1 and SD2) were used to analyse and compare the RR-interval time series of these groups. The IUGR children showed lower HRV as compared with normal children during both sleep and wake stages. The significantly decreased HRV during sleep provide an evidence of autonomic derangement that may be associated with higher risk of lethal arrhythmias in the IUGR children in later life.

Keywords: Autonomic function, Biological Signals, HRV analysis, IUGR.

Introduction

Intrauterine growth restriction is the failure of the fetus to achieve his/her essential growth potential due to anatomical and/or functional disorders of the fetoplacental-maternal unit [8]. The growth restricted fetus often has an estimated fetal weight less than the 10th percentile for its gestational age. The incidence of IUGR is estimated to be approximately 5 - 7% [6]. Recent research evidences suggested that several later life diseases including hypertension, type 2 diabetes and coronary artery disease are initiated by adverse fetal growth and development [4, 7, 18]

Studies in animals have shown that adverse fetal growth programmes persisting changes in a range of metabolic, physiological and structural parameters [27]. An increased

rate of coronary heart disease has been found in men and women who had low birth weight, who were short or thin at birth or who were small as compared with placental size [4]. The correlation between cardiovascular disease and low birth weight has been replicated among both males and females in Europe, North America and India [5]. The link of low birth weight to coronary heart disease in men has been verified in Helsinki [18]. In a number of studies, low birth weight has been shown to predict altered glucose tolerance [19]. Andersen and co-workers explored combined association of birth weight and childhood body mass index (BMI) at the age of seven with risk of coronary heart disease in adult life [2]. They found that both birth weight and BMI at the age of seven were independently associated with the risk of coronary heart disease.

The malfunctioning of the autonomic nervous system and its relation with cardiovascular mortality has been widely investigated during the last two decades [1, 29, 30]. In our previous study, we found reduced heart rate variability in low birth weight IUGR children with birth weight <2.5 kg as compared to normal and IUGR children having birth weight ≥ 2.5 kg [3]. The reduced HRV in low birth weight IUGR may be associated with negative outcome of the cardiovascular system. This study is aimed to examine the cardiac autonomic activity of 9 to 10 years old normal and intrauterine growth restricted children by analysing the HRV during sleep and wake periods. The investigations showed a decrease in HRV for low birth weight IUGR children during both sleep and wake stages, however, most of the HRV parameters showed significant difference between the normal Vs. low birth weight IUGR children during sleep stage.

Materials and Methods

Data Sets

This study is a collaborative research work of Child Health Department of The Leicester Royal infirmary and the Bio-Engineering group of the Department of Engineering,

University of Leicester, to investigate the effect of intrauterine growth restriction (IUGR) on postnatal developmental physiology. In the original study, the researchers from Royal Infirmary Leicester UK developed a database of 69 IUGR and 127 normal children without IUGR for investigating the development of circadian rhythm in deep body temperature, heart rate and cortisol excretion [15, 16]. The IUGR infants were identified either by serial ultrasound or by birth weight [15, 16]. The infants whose serial abdominal girth was more than two standard deviations or birth weight below the 2nd centile were considered IUGR.

After 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 children were advised to perform normal daily routines during recording and parents were asked to keep a diary of all activities including sleep and wake timings, which were subsequently collected from them. The recordings of less than 23 hours, with more than 1 % of ectopic beats or with presence of heart block were excluded from the study. The ECG recording of all subjects were extracted by Pathfinder 700 series analysis system and examined for artefacts. Thirty two normal and thirty six growth restricted children participated in the current study.

The normal group comprised of 32 children (20 male and 12 female), current age 8.96 ± 0.72 years (mean $\pm$ standard deviation), birth weight 3.56 ± 0.45 kg, current weight 32.87 ± 6.13 kg, weight gain 32.87 ± 6.13 kg, current height 133.86 ± 0.86 cm and current BMI 18.21 ± 2.52 kg/m². The IUGR children having birth weight < 2.5 kg (World Health Organization, 1993; Goldenberg and Culhane, 2007) were included the study. The choice was motivated by the fact that birth weight is inversely related to hypertension, pulse rate and hence the risk of cardiovascular disease in adulthood. The low birth weight (LBW) IUGR group comprised of 20 children, 8 male and 12 female having birth weight 2.29 ± 0.19 kg,

Figure 1: The representative interbeat interval time series of normal child
(a) Sleeping period (b) Waking Period.

current weight 28.13 ± 4.74 kg, weight gain 25.83 ± 4.75 , current height 131.00 ± 5.84 cm and BMI $16.38 \pm 2.55 \text{ kg/m}^2$. Using the heartbeat interval time series of normal, In our study cohort, there was more illness in IUGR children (50%) as compared to 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. IUGR-1 children, 30,000 data points from sleep and wake period were then obtained. The representative interbeat interval time series from a normal child during sleep and wake periods is shown figure 1.

Statistical Analysis

The significant difference between the groups was analysed using rank sum test and results were considered to be statistically significant at $p < 0.05$. The Wilcoxon rank sum test is a non-parametric analogue of unpaired sample t-test [21, 32].

HRV Techniques

Heart rate variability analysis during sleep and wake stage of the normal and IUGR children was performed using standard time and frequency domain methods and Poincaré plot indices [17, 29].

Time Domain HRV measures

The time domain analysis represents the simplest way of evaluating the variability by identifying the measures of variation over time. The time domain measures used in this study included: Mean RR, SDNN, RMSSD, NN50 and pNN50. SDNN, the standard deviation of normal to normal RR intervals is a global index of HRV that reflects all long term components and circadian rhythms responsible for variability in the recording period. RMSSD (Square root the mean of the sum of the squares of differences between adjacent NN intervals) and NN50 (number NN intervals that are greater than 50 ms) are the most common parameters based on the interval differences. The pNN50 is the percentage of difference between NN intervals that are greater than 50 ms.

Poincaré Plot

A Poincaré plot is a quantitative visual tool that represents correlation between successive RR intervals [17]. In this scatter plot each RR-interval is plotted against the previous RR interval. A common approach to quantitatively summarize the shape is to fit an ellipse to the plot [17, 22]. The ellipse is oriented according to the line of identity. SD1 measures dispersion of points perpendicular to the line of identity and is related to the fast beat to beat variability in the data. SD2 measures dispersion of points along the line of identity and describes long term variability of the data. For unit lag, Poincaré plot descriptors SD1 and SD2 are related to the basic statistical measures SDNN (standard deviation of normal to normal RR interval) and SDSD (standard deviation of successive difference of RR interval), given by following relations.

$$SD_1 = \sqrt{\frac{1}{2}SDSD^2}$$

$$SD_2 = \sqrt{2SDNN^2 - \frac{1}{2}SDSD^2}$$

Results

Heart rate variability (HRV) parameters during sleep and wake stages were calculated using RR-interval time series extracted from the ECG signals of normal, low birth weight IUGR children. In table 1, the results of HRV measures (mean $\pm$ standard deviation) during sleep and wake stages for normal, IUGR children and their corresponding p-values are presented. The heart rate variability was lower for IUGR as compared to normal children during both sleep and wake stages. The HRV time domain parameters SDNN, RMSSD, NN50, pNN50 and Poincaré plot indices SD1 and SD2 showed a significant difference between normal Vs. IUGR during sleep stage, however, none of the HRV measures showed significant difference between two groups during wake stage.

The behaviour of HRV parameters during sleep and wake stages was also investigated on gender basis. In table 2, results of the HRV measures for normal and IUGR children on gender basis during sleep stage are presented. The HRV indices were significantly smaller for normal female as compared to male children and none of the HRV measure showed significant difference between IUGR male and female children.

The results of the HRV parameters for male and female normal and IUGR children during wake are given in table 3. None of the HRV parameters of both normal and IUGR children showed significant difference on gender basis during wake stage on gender basis.

Discussion

Intrauterine growth restriction is a condition in which nutrient delivery to the baby is

Table 1: HRV Measures (Mean $\pm$ Std) for normal Vs IUGR during sleep and wake stages.
*p-value<0.05 and ** p-value<0.005

HRV Measures	Sleep Stage			Wake Stage		
	Normal	IUGR	p-value	Normal	IUGR	p-value
RR (ms)	844.07 $\pm$ 74.90	812.31 $\pm$ 59.80	ns	583.14 $\pm$ 58.26	593.74 $\pm$ 72.54	ns
SDNN (ms)	123.02 $\pm$ 29.92	100.80 $\pm$ 18.06	*	106.60 $\pm$ 24.79	99.49 $\pm$ 16.53	ns
RMSSD (ms)	100.58 $\pm$ 43.16	75.41 $\pm$ 31.56	*	45.07 $\pm$ 22.02	38.17 $\pm$ 10.47	ns
NN50 (ms)	12876 $\pm$ 4818	10454 $\pm$ 4327	*	4547 $\pm$ 2948	4064 $\pm$ 2160	ns
pNN50	42.92 $\pm$ 16.06	34.85 $\pm$ 14.42	*	15.16 $\pm$ 9.83	13.55 $\pm$ 7.20	ns
SD1 (ms)	71.12 $\pm$ 30.52	53.32 $\pm$ 22.32	*	31.87 $\pm$ 15.57	26.99 $\pm$ 7.40	ns
SD2 (ms)	157.87 $\pm$ 34.00	131.30 $\pm$ 20.18	**	146.89 $\pm$ 33.52	137.95 $\pm$ 23.06	ns

Table 2. HRV Measures (Mean $\pm$ Std) during Sleep for Normal and IUGR male and female children. *p-value<0.05 and ** p-value<0.005 and ns for non significant

HRV Measures	Normal Sleep			IUGR Sleep		
	Male	Female	p-value	Male	Female	p-value
RR (ms)	872.16 $\pm$ 75.48	797.24 $\pm$ 46.31	**	809.71 $\pm$ 65.42	814.05 $\pm$ 58.70	ns
SDNN (ms)	134.03 $\pm$ 29.81	104.66 $\pm$ 20.01	**	97.41 $\pm$ 17.13	103.07 $\pm$ 19.04	ns
RMSSD (ms)	112.14 $\pm$ 46.21	81.31 $\pm$ 30.24	*	62.21 $\pm$ 21.74	84.20 $\pm$ 34.77	n.s.
NN50 (ms)	14231 $\pm$ 4680	10617 $\pm$ 4320	*	9075 $\pm$ 4102	11373 $\pm$ 4396	n.s.
pNN50	47.44 $\pm$ 15.60	35.39 $\pm$ 14.40	*	30.25 $\pm$ 13.67	37.91 $\pm$ 14.65	n.s.
SD1 (ms)	79.30 $\pm$ 32.68	57.50 $\pm$ 21.38	*	43.99 $\pm$ 15.37	59.54 $\pm$ 24.59	n.s.
SD2 (ms)	171.12 $\pm$ 32.99	135.78 $\pm$ 22.94	**	130.20 $\pm$ 21.23	132.03 $\pm$ 20.37	ns

Table 3. HRV Measures (Mean $\pm$ Std) during wake stage for Normal and IUGR male and female children.

HRV Measures	Normal wake			IUGR Wake		
	Male	Female	p-value	Male	Female	p-value
Mean RR (ms)	593.08 $\pm$ 62.70	566.58 $\pm$ 44.02	n.s.	603.18 $\pm$ 75.32	587.45 $\pm$ 73.29	n.s.
SDNN (ms)	111.74 $\pm$ 26.08	98.03 $\pm$ 19.16	n.s.	101.16 $\pm$ 16.60	98.37 $\pm$ 17.12	n.s.
RMSSD (ms)	106.23 $\pm$ 10.70	109.90 $\pm$ 8.47	n.s.	36.07 $\pm$ 10.90	39.57 $\pm$ 10.41	n.s.
NN50 (ms)	4866 $\pm$ 3281	4014 $\pm$ 2104	n.s.	3795 $\pm$ 2362	4243 $\pm$ 2102	n.s.
pNN50	16.22 $\pm$ 10.94	13.38 $\pm$ 07.01	n.s.	12.65 $\pm$ 7.87	14.14 $\pm$ 7.01	n.s.
SD1 (ms)	34.34 $\pm$ 17.76	27.76 $\pm$ 8.94	n.s.	25.51 $\pm$ 7.71	27.98 $\pm$ 7.36	n.s.
SD2 (ms)	153.67 $\pm$ 34.95	135.60 $\pm$ 26.87	n.s.	140.62 $\pm$ 23.22	136.16 $\pm$ 23.81	n.s.

not sufficient to allow it to thrive in the womb. The intrauterine malnutrition causes a spectrum of prenatal complications including fetal morbidity and mortality, fetal compromise, the need for induction labour and caesarean delivery. The adverse fetal growth programmes persisting changes in the normal fetal physiology. As a result of these alterations in the normal fetal physiology, these individuals have greater predisposition to development of metabolic syndromes in later life, manifesting themselves as obesity, hypertension, and

coronary artery disease and type 2 diabetes. Numerous animal studies support the connection of unfavourable prenatal environment and alterations in the sympathetic autonomic balance [16, 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 [13].

Heart rate variability analysis provides a powerful non-invasive tool for observing the interaction between sympathetic and parasympathetic branches of the autonomic nervous system for controlling the heart rate. HRV is a dynamic variable that is influenced by the physiological and maturational factors. Maturation of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), result in an increase in HRV with gestational age and early postnatal life [25]. Sympathetic activity is high in infants and declines quickly between the age 5 and 10 years [9]. The influence of provocation of HRV is more obvious at the younger ages. HRV decreases with advancing age in healthy subjects [34].

The malfunctioning of the autonomic control of the cardiovascular system associating increased sympathetic and reduced parasympathetic activity plays an important role in the genesis of the coronary artery disease. This study was undertaken to investigate the risk of the coronary artery disease in the growth restricted children in later life by analysing the HRV during sleep and wake stages. The heart rate variations were examined in normal, low birth weight IUGR children during sleep and wake stages.

Our findings indicated that during sleep heart rate variability was higher in both groups compared to wake stage. This finding supports the evidence that vagal activity is dominant during sleep. During both sleep and wake periods, we found that HRV of the IUGR group is smaller than that for normal children. The depressed HRV of IUGR children

can be an indicator of the risk factors for the several negative cardiovascular outcomes in this group.

The comparison of the groups on the gender basis showed no significant difference during wake stage for both normal and IUGR children. During sleep HRV was significantly smaller in normal female children than that of male children.

HRV is a dynamic variable that varies with level of physical activity and dietary habits. All of the HRV measures showed significant difference between normal and IUGR, during sleep but none of the HRV measures showed significant difference between normal and IUGR children during wake stage. The difference in dietary habits and physical activity level of the children of this age during wake stage may be responsible for these contrary directions in the comparison. Sleep may be considered a condition in which autonomic control of the cardiovascular system can be investigated in the absence of factors such as physical activity and higher cortical functions and HRV can best identify the malfunctioning of the autonomic control [30].

Our findings are consistent with the study of Spassov *et al.* (1994), who found significantly decreased HRV in SGA neonates during sleep [28]. In contrast, our findings are not consistent with study of Schäffer *et al.* (2008) [27]. The difference in results may be due to the fact that they analysed overall HRV for a period of 24 hours and did not study sleep wake variation.

Anderson and co-workers described that birth weight and BMI at the age of seven were independent predictors of cardiovascular disease risk in later life [2]. They found a cardiac risk of 44% in children with a combination of low birth weight and relatively high BMI. Our study showed a negative relation of birth weight with the risk of cardiovascular in growth restricted children; however, we did not study the relation of BMI and risk of cardiovascular disease because BMI of low birth weight IUGR children is small.

Although this study provides an evidence of the altered autonomic function and hence the risk of coronary heart disease in the low birth weight IUGR children at an age in which clinical manifestation of disease are not yet apparent, various limitations are in order. The number of subject is modest; the examination with larger sample size may be performed for verification. We did not investigate the variations in the HRV during different sleep stages due to the unavailability of the electroencephalogram recording for identification of different sleep stages. The HRV analysis during different sleep stages may provide better insight to understand the autonomic derangement and risk of coronary artery disease in the low birth weight IUGR children.

Conclusions

The present study was carried out to investigate the risk of development of coronary heart disease in IUGR children in later life. Several studies have shown association between cardiovascular mortality and altered autonomic nervous system activity. Reduced heart rate variability indicates the derangement of the autonomic control of the heart. The analysis of heart rate variability of normal, IUGR was performed during sleep and wake stages. A reduction in heart rate variability was found for low birth weight growth retarded children as compared with normal children of same age group during sleep and wake stages. The comparison on the gender basis indicated that the difference between male and female is less marked in IUGR children than that of normal children. The significantly decreased HRV in the absence of external factors (during sleep) provide an evidence of autonomic derangement in the IUGR children that may be associated with higher risk of lethal arrhythmias in later life.

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