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Antenatal Hemodynamic Findings and Heart Rate Variability in Early School -Age Children Born with Fetal Growth Restriction

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Abstract

Background According to epidemiological studies impaired intrauterine growth increases the risk for cardiovascular morbidity and mortality in adulthood. Heart rate variability (HRV), which reflects the autonomic nervous system function, has been used for risk assessment in adults while its dysfunction has been linked to poor cardiovascular outcome.

Objective We hypothesized that children who were born with fetal growth restriction (FGR) and antenatal blood flow redistribution have decreased HRV at early school age compared to their gestational age matched peers with normal intrauterine growth.

Study Design A prospectively collected cohort of children born with FGR (birth weight < 10^{th} percentile and/or abnormal umbilical artery flow, n=28) underwent a 24-hour Holter monitoring at the mean age of 9 years, and gestational age matched children with birth weight appropriate for gestational age (AGA, n=19) served as controls. Time- and frequency domain HRV indices were measured and their associations with antenatal hemodynamic changes were analyzed.

Results Time- and frequency domain HRV parameters (standard deviation of R-R intervals, SDNN; low frequency, LF; high frequency, HF; LF/HF; very low frequency, VLF) did not differ significantly between FGR and AGA groups born between 24 and 40 weeks. Neither did they differ between children born with FGR and normal umbilical artery pulsatility or increased umbilical artery pulsatility. In total, 56 % of the FGR children demonstrated blood flow redistribution (cerebroplacental ratio, CPR < -2 SD) during fetal life, and their SDNN (p=0.01), HF (p=0.03) and VLF (p=0.03) values were significantly lower than in FGR children with CPR ≥ -2SD.

Conclusions Early school-age children born with FGR and intrauterine blood flow redistribution demonstrated altered heart rate variability. These prenatal and postnatal findings may be helpful in targeting preventive cardiovascular measures in FGR.

Keywords

placental insufficiency;

umbilical artery;

cerebroplacental ratio;

heart rate variability;

catch-up growth

Abbreviations

AGA appropriate growth for gestational age

CPR cerebroplacental ratio

FGR fetal growth restriction

HF high frequency

HRV heart rate variability

LF low frequency

LF/HF low frequency/high frequency ratio

PI pulsatility index

SDNN standard deviation of R-R interval

UA umbilical artery

VLF very low frequency

Introduction

Low birth weight is associated with an increased risk of cardiovascular disease, obesity, dyslipidemia and type 2 diabetes in adulthood independently of gestational age, underlining the importance of normal fetal growth on later outcomes [1−4]. Placental dysfunction, the main cause of fetal growth restriction (FGR), causes redistribution of blood flow in favor of vital organs − the heart and the brain, thus enabling the fetus to survive compromised circumstances in utero. These physiologic adaptations are thought to re-program the development of key fetal organs, but the exact underlying mechanisms of fetal programming are still unclear. A relationship between placental insufficiency and adverse short-term outcomes as well as later cardiovascular changes in children and young adults has been reported [5-10]. However, catch-up growth during the early years of life seems also to play a role in later cardiovascular health [11,12].

Heart rate variability (HRV) reflects the control of the autonomic nervous system over the cardiovascular system in physiologic and pathologic conditions and describes the heart`s ability to adapt to changing circumstances. Abnormal autonomic nervous system function is associated with cardiovascular mortality. Even among subjects without cardiovascular disease, higher general mortality rates have been reported in the presence of reduced HRV [13,14]. Furthermore, HRV can predict adverse cardiovascular events after ischemic cardiac and cerebral insults [15-17]. In children, the delayed maturation of the autonomic nervous system has been described in preterm born children [18,19], and an association between low birth weight and abnormal autonomic nervous system function has been suggested [20-22].

In this study, we hypothesized that HRV in 8-10-year-old children born with FGR is reduced compared to children with appropriate growth in utero (AGA). Specifically, we wanted to evaluate

whether significant placental insufficiency and prenatal blood flow redistribution are associated with reduced HRV measures in FGR children at early school age.

Materials and methods

The subjects of this study belong to a prospectively collected cohort (n=72) of growth-restricted fetuses (birth weight < 10th percentile and/or umbilical artery pulsatility index, UA PI > 2 SD in a normal population [23,24]). Recruited between 1998 and 2001 from our high-risk prenatal unit, the mothers were followed up serially until delivery. In all cases, gestational age was confirmed with ultrasound before 20 gestational weeks. Women whose pregnancies were complicated with major structural and chromosomal abnormalities, chorioamnionitis and/or ruptured membranes were excluded. Later, the families were contacted to book a follow-up visit for their 8-10-year−old children for this protocol: 39 children born with FGR participated in the follow-up studies and successful Holter recordings were obtained from 28 children born with FGR. AGA controls were collected from the delivery room records from the same period by selecting the following AGA peer matched for gestational age and gender for the index FGR neonate. The research protocol was approved by the local ethics committee (permission number 8/2008) and written informed parental consent was a prerequisite to participation in the study.

Prenatal assessment

Maternal characteristics and obstetric data were collected during the prenatal and delivery visits. Maternal hypertensive disorders were categorized according to the guidelines of the American College of Obstetrics and Gynecology [25]. Antenatal steroid therapy included two 12 mg betamethasone doses given 24 hours apart.

Detailed information concerning placental and fetal hemodynamic assessments by a single investigator within a week (median of 2.9 days) prior to delivery was described earlier [26]. Acuson Sequoia 512 (Acuson, Mountain View, CA, United States) with 4-8 MHz transducers was used for scanning, and the angle of insonation was kept at <15 degrees in all examinations. Three consecutive cardiac cycles were obtained and the mean values were used in the analyses. The UA PI was measured from the free loop of the umbilical cord and further categorized as normal or increased (UA PI > 2 SD) flow [24,27]. The middle cerebral artery (MCA) PI was assessed, and the cerebroplacental ratio (CPR) was calculated as the MCA PI/UA PI [28]. Significant placental insufficiency (UA PI > 2SD) and redistribution of blood flow (CPR < - 2 SD) were determined according to earlier published longitudinal data [29,30].

Clinical management was based on surveillance tests performed by the managing obstetricians, who were blinded to the data collected by the investigators. During the period between 1998 and 2001, the indications for delivery were 1) worsening maternal condition, 2) abnormal non-stress test in fetal heart rate monitoring, and 3) abnormal ductus venosus pulsatility.

Postnatal assessment

At birth the mode of delivery, antenatal cardiotocographic evaluation, UA blood gas values, Apgar scores and neonatal morphometric measurements were recorded.

The follow-up studies were performed at a median age of 9 years. Weight and height were measured by a single investigator. Upper arm blood pressure was measured bilaterally 1 to 3 times (Dinamap ProCare, GE Helthcare, United States) and its mean value was used for the analyses.

Heart rate variability analysis

Twenty-four-hour ambulatory ECG recordings were performed with a portable two-channel tape recorder (Oxford Medilog, Oxford, United Kingdom). The monitoring was started in morning, and the children were advised to do their normal daily activities during the monitoring. The data was sampled digitally and transferred from the Oxford Medilog scanner to a microcomputer for HRV analysis. All data were first edited automatically, and then subjected to detailed manual editing by visual inspection. Linear trends were abolished from RR interval data segments of 512 samples to make data more stationary. This was done by fitting a straight line to a segment by a standard least-squares method and then subtracting it from the sample value. The standard deviation of all R-R intervals (SDNN) and the mean heart rate were chosen as the time domain indices of HRV. After editing, a fast Fourier transform method was used to estimate the power spectrum densities of HRV. The power spectra were quantified by measuring the areas in the following frequency power bands: (1) <0.0033 Hz: ultra-low frequency; (2) 0.0033 to <0.04 Hz: very low frequency; (3) 0.04 to < 0.15 Hz: low frequency; (4) 0.15 to < 0.40 Hz: high frequency; as recommended by the Task Force [13]. Recordings with <16 hour of data or <85% of qualified sinus beats were excluded.

Statistical analysis

The data were analyzed using the SPSS 22.0 for Windows software package (SPSS Inc., Chicago, IL, United States). For between-group comparisons, the Student`s t-test was used if the data were normally distributed, otherwise the Mann-Whitney U test was chosen. Categorical data were compared with Chi-square analysis and Fisher`s exact test. Data are presented as mean (SD) and median (range). A two-tailed p-value of <0.05 was selected as the level of statistical significance.

Results

Maternal and perinatal data are shown in Table 1. Maternal characteristics did not differ between the studied groups, except for higher incidence of hypertensive pregnancies in the FGR group. As expected, FGR children were delivered with lower birth weights than the AGA controls. At the time of the follow-up visit, when the children were between 8 and 10 years of age, there were no significant differences in weight or height between the FGR children and AGA controls.

Successful Holter recordings were available for 28 FGR children and 19 AGA children. Holter recordings were unsuccessful in 11 FGR children and 5 AGA children in the initially recruited groups due to technical reasons. Table 2 shows that there were no significant differences in time and frequency domain HRV measures between FGR and AGA groups at the age of 8-10 years.

To evaluate the effects of significant placental insufficiency (UA PI > 2 SD) and the redistribution of fetal blood flow (CPR < -2 SD) on HRV at the age of 8-10 years, subgroup analyses in the FGR population were performed. HRV measures did not differ significantly between FGR children with increased UA PI and those with normal UA PI (Table 3). In this FGR cohort, 14 fetuses demonstrated significant prenatal blood flow redistribution (CPR < -2SD). At the mean age of 9 years, they demonstrated significantly lower SDNN, HF and VLF values compared with FGR children with normal CPR (Table 4).

Discussion

At an early school age, children born with FGR demonstrated no significant differences in HRV measures compared to children with appropriate intrauterine growth (AGA). A subgroup of FGR children with significant blood flow redistribution to vital organs during fetal life showed lower SDNN, HF and VLF values, indicating lower vagal and increased sympathetic activity compared to

FGR children with no Doppler-detectable blood flow redistribution during fetal life. This suggests that fetal hemodynamic changes are associated with later autonomic nervous system regulation.

The redistribution of fetal cardiac output during chronic hypoxemia is speculated to be either dependent on the increase in fetal sympathetic activity, or cerebral blood flow could be possibly maintained by a precise relationship between the prevailing arterial oxygen tension and plasma noradrenaline concentrations in growth-restricted fetuses. Animal experiments support the latter choice, while placental embolization doubled fetal noradrenaline concentrations in a 10-day period in a near-term sheep [31]. The precise timing of the autonomic nervous system development during fetal life is not known. For decades, heart rate variability has been used for antenatal fetal surveillance and fetal monitoring during delivery. According to non-invasive human observations, changes in fetal HRV measures show significant maturation of the autonomic nervous system beyond 30 gestational weeks [32]. The sympathetic nervous system matures earlier than the parasympathetic system, whereas there is a significant increase in parasympathetic actions after 30 to 32 weeks of gestation [33, 34]. Prematurity has been suggested to possibly prevent the physiological maturation of parasympathetic activity [33]. Previous studies have also demonstrated a higher sympathetic tone and lower vagal tone also in growth-restricted newborns [35], and increased sympathetic activity is recognized as a risk factor for cardiovascular disease [36]. Due to these facts and conflicting results of previous studies, probably due to various FGR etiologies, we wanted to target our study to early school- aged FGR children, who had suffered from ultrasonographically detected placental dysfunction and hemodynamic stress during their intrauterine development.

In the present study, no differences in HRV measures were detected between the AGA and FGR group with or without increased umbilical artery pulsatility at early school age, although negative insults during fetal life have been suggested to impact autonomic nervous system function postnatally. In a sheep model, chronic hypoxemia due to placental insufficiency was shown to result

in a suppression of fetal adrenaline synthetic capacity and impaired adrenaline secretory responses to acute hypoxia immediately after birth [37]. In humans, the impact of antenatal stress on later autonomic nervous system function has been evaluated by the means of HRV. Associations between low birth weight and various HRV measures have been reported [20,21,35, 38] but negative results have also been found [22, 39]. We suspect that this is due to the differences in study designs and cohorts. In the studies with positive correlations between birth weight and HRV measures, the age of the monitored children varied between 1 day and 14 years of age; and the monitoring period varied between 3 to 40 minutes and 24 hours. Aziz et al. [22] found no HRV differences between term-born FGR and AGA 9-10-year-old children with a 24-hour HRV monitoring, which is in line with our findings. However, in their subgroup analyses, time and frequency domain HRV differences were detected between lighter born FGR children (< 2500g at delivery) and FGR children with a heavier birth weight (> 2500g at delivery) and AGA controls, but no ultrasonographic data on fetal circulation were available. In Aziz et al.`s study, the AGA controls and lighter FGR children showed body mass index (BMI) centiles of 73 and 43 at the age of 9-10 years. In our study, however, the difference in postnatal growth between FGR and AGA groups was small, with the BMI centiles being 54 and 52, respectively.

In the present study, 56 % of the FGR group showed a significant redistribution of blood flow during fetal development according to abnormally low ratio between cerebral and placental pulsatility. Compared with FGR children with normal CPR, this subgroup demonstrated lower SDNN, HF and VLF values reflecting lower overall HRV and altered autonomic nervous system regulation of HRV, but they were also born with a lower gestational age. Low birth weight can result from preterm delivery, as well as from fetal growth restriction. Prematurity, *per se*, can affect the function of the autonomic nervous system later in life. Gestational age at delivery has varied in earlier studies. Rakow et al. [21] compared heart rate variability at 9 years of age in children born preterm with children born at term with either low or normal birth weight, and found that preterm

born children and term children with low birth weight had significantly lower time and frequency domain parameters compared to the controls. On the other hand, in a small follow-up study, preterm born infants revealed a delayed autonomic nervous system development at term age, but in re-investigations at 2-3 years and 6-7 years of age, no differences were found when compared to term born controls [18]. De Rogalski Landrot et al. [18] reported that, in preterm infants, the autonomic nervous system maturation reached the control group at 2 years of age, and parasympathetic activity showed marked long-term maturation up to 6-7 years of age, and according to Cohen et al. [38] preterm FGR neonates displayed compromised HRV compared to preterm AGA neonates immediately after delivery with no differences at the age of 1 and 6 months. Interestingly, Yiallourou et al. [39] found no differences in HRV parameters of 5-12-year-old children born preterm with severe FGR with umbilical artery blood flow abnormalities, when compared to term born, normally grown controls, whereas preterm born, appropriately grown children demonstrated altered HRV. They speculated the possibility that FGR may protect the autonomic nervous system from the effects of prematurity [39]. In our study, the FGR and AGA groups were gestational age-matched in order to control the impact of gestational age on the results. However, in our subgroup analyses, we were unable to explore the impact of the gestational age on the HRV outcome. Furthermore, we suspect that the variability of HRV measures in the AGA control group in our study may partly reflect the effect of gestational age on HRV assessment as earlier studies have shown that prematurity impacts HRV [18, 21,39].

We recognize that the rather small size of the study group is a limitation of our study. Unfortunately, Holter recordings were unsuccessful in some cases due to technical reasons. While the results of some previous studies have been reached from 3-minute recordings, we used 24-hour Holter monitoring, the golden standard, for our analyses. In addition, we think that the strength of our study lies in the precise prenatal cardiovascular assessments of placental and fetal circulation.

This is particularly relevant because no prenatal hemodynamic data was available in previous studies. In the present study, the weight and height of the Holter-recorded FGR and AGA groups did not differ significantly at 8-10 years of age. At early school age, the FGR children with unsuccessful Holter recordings were lighter than those with successful recordings. However, excessive postnatal catch-up growth rather than low body weight in childhood has been associated with later cardiovascular morbidity. Previous studies show that excessive postnatal growth and childhood obesity reduce cardiac parasympathetic activity and increase sympathetic activity, although the underlying mechanisms are unclear [40].

Conclusions

According to this study with detailed prenatal hemodynamic data, no significant HRV differences were detected between FGR and AGA children at early school age. However, a subgroup of FGR children with significant blood flow redistribution during fetal life showed signs of impaired autonomic nervous system regulation, which may indicate an increased risk for cardiovascular morbidities in later life.

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The authors declare no conflicts of interest.

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Table 1. Perinatal, morphometric and cardiovascular characteristics in 8-10-year-old children born with fetal growth restriction (FGR) and control children with appropriate fetal growth (AGA). The values given are mean (SD), median (range) and % (n).

	FGR (n = 28)	**AGA (n =19)**	**p-value**
Perinatal characteristics			
Maternal age at delivery (years)	30 (17 - 40)	31(21 - 39)	0.81
Preeclampsia	43 (12/28)	5 (1/19)	0.004
Mild	21 (6/28)	0	
Severe	21 (6/28)	6 (1/19)	
Pregnancy induced hypertension	11 (3/28)	6 (1/29)	
Cesarean delivery	71 (20/28)	84 (16/19)	0.49
Maternal indication	11 (3/28)	26 (5/19)	
Fetal indication	69 (17/28)	53 (10/19)	
Gestational age at delivery (weeks)	35 (24 - 40)	37 (27 - 40)	0.35
Birth weight (g)	1738 (370-2940)	2990 (985-5190)	0.001
Birth weight percentile	2.4 (0.1-41.6)	56.6 (20.0-96.9)	<0.001
Apgar – 5 minutes	9 (3 - 10)	9 (6 - 10)	0.48
Umbilical artery pH	7.29 (0.06)	7.26 (0.05)	0.16
Male	46 (13/28)	47 (9/19)	1.00
Antenatal steroids	57 (12/21)	60 (6/10)	1.00
Non-stress CTG Abnormal* Normal	 29 (7/24) 71 (17/24)	 8 (1/13) 92 (12/13)	 0.22

UA PI ≥ 2 SD	71 (20/28)	0	
MCA PI < -2 SD	32 (8/25)	0	
CPR < -2SD	56 (14/25)	0	
Morphometric and cardiovascular characteristics at early school-age			
Blood pressure (mmHg)			
Systolic	105 (4)	106 (11)	0.69
Z-score	0.04 (0.56)	0.21 (1.45)	0.69
Diastolic	61 (4)	61 (6)	0.80
Z-score	-0.02 (0.77)	0.07 (1.18)	0.81
Weight (kg)	29 (6)	30 (5)	0.57
Height (cm)	133 (7)	135 (7)	0.34
Body mass index (kg/m2)	16 (2)	16 (2)	0.91
Z-score	-0.16 (0.71)	-0.14 (0.52)	0.91

*Late decelerations, bradycardia

CPR, cerebroplacental ratio; CTG, cardiotocography; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery

Table 2. Heart rate variability (HRV) measures in 8-10-year-old children born with fetal growth restriction (FGR) and control children with appropriate fetal growth (AGA). The values given are mean (SD) and median (range).

	FGR (n = 28)	**AGA (n = 19)**	**p-value**
HRV measures			
Time domain measures			
HHR	83.3 (7.5)	86.6 (8.9)	0.18
SDNN	166.6 (37.0)	157.3 (40.2)	0.42
Frequency domain measures			
LF	1625.0 (439.0-4494.0)	1362.0 (578.0-4549.0)	0.22
HF	1683.5 (308.0-12552.0)	1395.0 (474.0-7694.0)	0.45
LF/HF	1.08 (0.56)	1.04 (0.48)	0.77
VLF	2208.0 (1146.5)	1946.1 (1003.5)	0.42

HHR, Holter heart rate; HF, high frequency; LF, low frequency; SDNN, standard deviation of normal to normal RR intervals; VLF, very low frequency

Table 3. Heart rate variability (HRV) measures in 8-10-year-old children born with fetal growth restriction (FGR) and either increased UA pulsatility (UA PI ≥ 2 SD) or normal umbilical artery (UA) pulsatility (UA PI < 2 SD. The values are given in % (n), mean (SD) and median (range).

	FGR Increased UA pulsatility (n = 20)	**FGR Normal UA pulsatility (n = 8)**	**p-value**
Gestational age at birth (weeks)	34 (26-38)	38 (24-40)	0.14
Birth weight (grams)	1565 (370-2940)	2160 (538-2765)	0.12
Apgar 5 min	9 (1)	9 (1)	0.67
Apgar 5 min <7	11 (2/18)	13 (1/8)	1.00
UA pH at birth	7.27 (0.06)	7.31 (0.07)	0.20
Prenatal Doppler measures			
MCA PI < - 2 SD	39 (7/18)	14 (1/7)	0.36
CPR < -2SD	72 (13/18)	14 (1/7)	0.02
HRV measures			
Time domain measures			
HHR	84.1 (7.3)	81.5 (8.2)	0.43
SDNN	161.4 (38.4)	179.6 (31.8)	0.25
Frequency domain measures			
LF	1597.5 (439.0-4494.0)	2068.5 (764.0-3540.0)	0.53
HF	1519.5 (308.0-12552.0)	2591.5 (624.0-5910.0)	0.44
LF/HF	1.14 (0.62)	0.94 (0.35)	0.40

VLF	2142.8 (1077.2)	2371.1 (1370.3)	0.64

CPR, cerebroplacental ratio; HHR, Holter heart rate; HF, high frequency; LF, low frequency; MCA, middle cerebral artery; PI, pulsatility index; SDNN, standard deviation of normal to normal RR intervals; UA, umbilical artery; VLF, very low frequency

Table 4. Heart rate variability (HRV) measures in 8-10-year-old children born with fetal growth restriction (FGR) and either decreased cerebroplacental ratio (CPR < -2SD), showing significant blood flow redistribution or normal CPR (CPR ≥ -2SD). The values given are % (n), mean (SD) and median (range).

	FGR Decreased CPR (n=14)	**FGR Normal CPR (n=11)**	**p-value**
Gestational age at birth	33 (26-38)	38 (32-40)	0.007
Birth weight (grams)	1248 (370-2310)	2300 (2050-2765)	0.001
Apgar 5 min	9 (1)	9 (1)	0.23
Apgar 5 min <7	14 (2/14)	0	0.49
UA pH at birth	7.26 (0.06)	7.30 (0.06)	0.14
Prenatal Doppler measures			
UA PI > 2 SD	93 (13/14)	46 (5/11)	0.02
MCA PI < -2 SD	57 (8/14)	0 (0/11)	0.003
HRV measures			
Time domain measures			
HHR	85.4 (8.2)	80.5 (5.8)	0.11
SDNN	151.6 (34.5)	188.9 (31.6)	0.01
LF	1510.5 (439-3093)	2246.0 (1020-4494)	0.09
HF	1375.0 (308-8845)	2228.0 (624-12552)	0.03
LF/HF	1.27 (0.63)	0.87 (0.38)	0.07

VLF	1767.2 (848.9)	2808.6 (1359.6)	0.03

HHR, Holter heart rate; HF, high frequency; LF, low frequency; MCA, middle cerebral artery; PI, pulsatility index; SDNN, standard deviation of normal to normal RR intervals; UA, umbilical artery; VLF, very low frequency