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Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by fetal growth restriction

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***Objective*: To study fetal heart rate (FHR), its short term variability (STV), average acceleration capacity (AAC), and average deceleration capacity (ADC) throughout uncomplicated gestation, and to perform a preliminary comparison of these FHR parameters between small-for dates (SFD) and control fetuses. *Methods*: Prospective observational study of 7 h FHR-recordings obtained with a fetal-ECG monitor in the second half of uncomplicated pregnancies ($n = 90$) and pregnancies complicated by fetal SFD ($n = 30$). FHR and STV were calculated according to established analysis. True beat-to-beat FHR, recorded at 1 ms accuracy, was used to calculate AAC and ADC using Phase Rectified Signal Averaging (PRSA). Mean values of FHR, STV, AAC, and ADC derived from recordings in SFD fetuses were compared with the reference curves. *Results*: Compared with the control group the mean z-scores for STV, AAC, and ADC in SFD fetuses were lower by 1.0 SD, 1.5 SD, and 1.7 SD, respectively ($p < 0.0001$ for all comparisons). In SFD fetuses, both the AAC and ADC z-scores were lower than the STV z-scores ($p < 0.02$ and $p < 0.002$, respectively). *Conclusions*: Analysis of the AAC and ADC as recorded with a high resolution fECG recorder may differentiate better between normal and SFD fetuses than STV.**

Keywords: Antenatal monitoring, growth restriction, fetal heart rate

Introduction

There are a number of antenatal assessment techniques which are suitable for the diagnosis, classification and monitoring of pregnancies complicated by intra uterine growth restriction (IUGR): assessment of fundal height, kick-charts, ultrasound biometry, pulsatility index of the umbilical artery (PI UA) and fetal heart rate (FHR) testing. With progressive deterioration of the fetal condition a certain rank order can be determined in which test results become abnormal [1–5]. While it is relatively easy to recognize the severely IUGR fetus in poor condition, difficulties are encountered with the vast majority of IUGR fetuses that may be constitutionally small (i.e. small for gestational age, SGA)or exhibit less severe degrees of compromise. Furthermore, the rank order of fetal assessment holds especially for the preterm period, as near term most Doppler indices are not particularly suitable [3,6,7].

Early studies of FHR monitoring in small for dates (SFD) fetuses have demonstrated that the presence and amplitude of accelerations in these fetuses after 30 weeks' gestation are comparable to those of healthy fetuses before 30 weeks' gestation [8]. This might indicate a delay in functional maturation of the sympathetic (cardio-acceleratory) nervous system due to chronic nutritional deprivation and hypoxemia [5,8]. FHR decelerations appear after a gradual decrease in FHR variability and are considered a late sign of fetal impairment [9,10]. In case of mild hypoxemia the presence and duration of decelerations are comparable to those in healthy fetuses. It has therefore been suggested that the parasympathetic (cardio-inhibitory) system is probably not affected to the same extent as is the sympathetic tone [8].

Differentiation between contributions of the sympathetic and parasympathetic branches of the nervous system on FHR regulation may offer a more specific assessment of the (term) SFD fetus. Such a differentiation is feasible using a signal processing technique called phase rectified signal averaging (PRSA). This technique provides separate characterizations of acceleratory (sympathetic) and inhibitory (parasympathetic) modulations in FHR, quantified by 'average acceleration capacity' (AAC) and 'average deceleration capacity' (ADC), respectively [11]. The PRSA methodology, proven to provide better prediction of survival in patients suffering myocardial infarction in adult cardiology, is currently gaining interest in fetal medicine [12,13]. Results from a recent study indicated that the AAC, calculated from FHR recorded with Doppler cardiotocography (CTG), has the potential to provide better differentiation between normal and compromised fetuses compared to the calculation of short term variability (STV [12,13]). Although this study demonstrated promising results, PRSA analysis of FHR recorded with CTG is not recommended, since conventional Doppler CTG devices have a low sample rate of 4 Hz and average FHR through a process of autocorrelation [14]. A preferable method for PSRA analysis of FHR is available using a high resolution fetal-ECG recorder, offering true beat-to-beat FHR with an accuracy of 1 ms due to a high sample rate of 1000 Hz. Since it is assumed that true beat-to-beat FHR provides a more accurate assessment of fetal cardiovascular (patho-) physiology compared to conventional Doppler FHR [15], PRSA analysis of true beat-to-beat FHR may offer an even better recognition of the compromised IUGR fetus.

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It was the objective of this investigation to study FHR, its short term variability, AAC and ADC throughout normal gestation as recorded with a high resolution fetal-ECG monitor, and to perform a preliminary comparison of these FHR parameters between small for dates and normal fetuses.

Methods

Study design and participants

A prospective observational study was performed from December 2006 until July 2008 at University Medical Centre Utrecht, The Netherlands. The study was approved by the local Institutional Review Board. Women with singleton pregnancies between 20 and 42 weeks' gestation were considered eligible for participation. Exclusion criteria were multiple gestation and pregnancies complicated by congenital malformations and/or chromosomal abnormalities.

The control group consisted of 90 healthy women at 20–40 weeks' gestation at study entry. These pregnancies remained uncomplicated and no medication was administered. Thirty women with pregnancies complicated by fetal growth restriction were approached to participate in the study. For all participants, the pregnancies were reliably dated using the last menstrual period and/or by early ultrasound scan. After informed consent was obtained a single overnight FHR recording (17:00–08:00 h) was performed, either at home (controls) or in hospital (IUGR). Maternal co-morbidities and treatment, fetal characteristics (ultrasound measurements) and neonatal characteristics were noted from the women's medical charts.

Small for dates fetuses

Fetuses were defined to be small for dates (SFD) if estimated fetal weight was measured ≤10th percentile and birth weight was found to be ≤10 percentile corrected for gestational age (GA), sex and parity [16]. Intrauterine growth restriction (IUGR), based on suspected uteroplacental insufficiency, was defined when the criteria as mentioned for SFD were accompanied by Doppler abnormalities of the umbilical artery (see below). In eleven women,fetal growth restriction was accompanied by hypertensive disorders treated with either Methyldopa following local protocol ($n = 9$) or Labetalol 100 mg twice daily ($n = 2$). All women with complicated pregnancy were admitted to the antenatal care unit. They received daily computerized FHR monitoring, twice weekly Doppler measurements (pulsatility index of the umbilical artery; PI UA), and every 2 weeks ultrasound measurements of fetal biometry.

Three subgroups of SFD fetuses were formed to distinguish between different degrees of fetal compromise based on PI UA. The PI UA measurements before and after study participation were retrieved from the woman's chart. The first group comprised SFD fetuses with normal PI UA both before and after participation in this study. The second group had normal PI UA before participation, but showed progressive deterioration with abnormal PI UA later in gestation. The third group consisted of SFD fetuses with abnormal PI UA (measurement > 2SD, adjusted for GA) both before and after participation (i.e. IUGR fetuses).

FHR analysis and parameters

FHR recordings were performed with the AN24 fetal ECG monitor (Monica Healthcare, Nottingham, UK). The electrophysiological signal contains the maternal ECG (mECG), fetal ECG (fECG) and noise, and is recorded with a sample frequency of 1000 Hz using 5 disposable electrodes placed on the maternal abdomen in a standardized manner [15]. The methodology used for fECG signal extraction and analysis has been described in detail by Pieri et al. [17] Fetal ECG complexes were used to calculate true beat-to-beat (R-R) pulse intervals with an accuracy of approximately 1 ms. Short term variability (in ms) was calculated from the derived FHR according to the analysis described by Dawes et al. [14].

For differentiation between the contributions of the parasympathetic and sympathetic branches, a signal processing technique called phase rectified signal averaging (PRSA) was used. PRSA provides separate characterizations of acceleratory and decelera-torymodulations in heart rate, quantified as average acceleration capacity (AAC) and average deceleration capacity (ADC), respectively. The PRSA methodology for AAC/ADC calculation has been found to be promising in adults 11. The PRSA processing steps for analysis of fetal heart rate have been recently described in detail by Huhn et al. [12].

FHR recordings lasted for approximately 15 h (17:00–08:00 h). For the present study, we selected the time frame between 23:00 and 06:00 h for analysis, since signal loss is known to be lowest during that period [15]. Cases with signal loss exceeding 50% of time were excluded from analysis.

Statistics

SPSS for Windows (version 18.01, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Results were summarized with the use of standard descriptives for parametric or non-parametric tests, as appropriate. For both complicated and uncomplicated pregnancies the mean basal FHR, STV, AAC and ADC values were calculated over the selected time period (23:00-06:00 h). All FHR parameters were normally distributed.

A regression model was estimated using a FHR parameter (basal FHR, STV, AAC, ADC) and gestational age (linear and quadratic functions) to calculate reference percentiles. Neonatal sex was considered a potential confounder. The reference ranges were compared with established normograms for FHR and STV as reported in the literature [18,19]. Mean values of the FHR parameters from recordings of SFD fetuses were plotted against the reference curves. Z-scores were calculated for STV, AAC, and ADC with the mean and standard deviation both adjusted for gestational age.

Results

Baseline characteristics for control and SFD pregnancies are displayed in Table I.The control group had a median gestational age at FHR recording of 34 weeks. All neonates were born after 36 weeks' gestation and had a birth weight >10th percentile for GA according to customized growth charts [16]. Five FHR recordings were excluded from analysis due to poor signal quality.

The SFD fetuses in this study had a median gestational age at participation of 31^{+6} weeks. Five fetuses were excluded because of congenital malformations and/or chromosomal abnormalities

Table I. Baseline characteristics of study participants.

	Controls		SFD	
	Median	Range	Median	Range
GA at participation	34+0	21+0 – 40+1	31+6	27+0 – 36+3
GA at birth	39+2	36+1 – 41+6	35+1	28+4 – 41+0
Birthweight (grams)	3170	2660 – 4650	1720	840 – 3045
BMI (m^2/kg)	24.5	16.9 – 40.4	25,5	18.3 – 38.6

GA = gestational age, BMI = body mass index.

diagnosed at delivery ($n = 2$) or due to high signal loss of FHR data ($n = 3$). The characteristics of the remaining 25 SFD fetuses are displayed in Table II.

Neonatal sex did not contribute significantly to the regression models. Gestational age (either linear or linear and quadratic components) had a significant effect on the FHR parameters. The reference curves of FHR, STV, AAC and ADC are displayed in Figure 1A–1D, respectively, with the coefficients used to construct them in Table III. FHR decreased with advancing gestation (Figure 1A), whereas short term variability increased in early gestation with stable third trimester values (Figure 1B). The FHR reference curve was similar to those presented in a large cross-sectional and smaller longitudinal study, respectively [18,19]. Short term variability in our dataset was higher in early gestation when compared to published normal curves [18,19]. Although gestational age contributed significantly to the models of AAC and ADC, both parameters remained relatively constant during pregnancy (Figure 1C and 1D; Table III).

In all but two of the SFD fetuses, FHR was within the boundaries of the reference curve (Figure 1A). Short term variability was abnormal (i.e. below the 2.5th percentile) in 4/25 (16%) SFD fetuses (Figure 1B). Abnormal AAC and ADC values occurred in 9 (36%) and 10 (40%) of these, respectively, and comprised the four fetuses with abnormal STV values (Figure 1C and 1D); the differences in number compared with the latter were not statistically significant (Fisher exact test; $p = 0.196$ and $p = 0.113$, respectively).

Compared with control group values (mean of z-scores, 0; SD, 1), the mean z-scores for STV, AAC, and ADC in SFD fetuses were lower by 1.0 SD, 1.5 SD, and 1.7 SD, respectively ($p < 0.0001$ for all comparisons; Figure 2). In the SFD group, the AAC and ADC z-scores did not differ statistically ($p = 0.084$), but both were lower than the STV z-scores ($p < 0.02$ and $p < 0.002$, respectively; Figure 2). Z-scores for STV and AAC were highly correlated, both in the control group ($R = 0.486$; $p < 0.0001$) and the SFD group ($R = 0.787$; $p < 0.0001$), with a steeper slope of regression in the latter ($\beta = 0.459$ vs. $\beta = 1.157$, $p < 0.0001$; Figure 3). Similar observations were made for the relationships between STV and ADC z-scores in the control and SFD fetuses ($\beta = 0.483$ vs. $\beta = 1.365$, $p < 0.0001$). This indicates that fetuses with a low STV z-score (<−1 SD) become more accentuated if their AAC z-score (Figure 3) or ADC z-score (data not shown) is considered. However, we found no specific characteristic of the fetuses with abnormal FHR parameters relative to the classification based on PI measurements (Figure 1A–1D), hypertensive disorder, and the use of antihypertensive drugs or corticosteroids.

Discussion

This study has provided reference values of a potential new FHR parameter for assessment of the fetal condition in pregnancies complicated by fetal growth restriction. Furthermore, our preliminary data showed that in small-for dates fetuses both the acceleration capacity and deceleration capacity reveal more prominent differences from the normograms than short term variability of FHR.

Recently, the advanced technique of phase rectified signal analysis (PRSA) has gained interest in fetal medicine [12,13]. PRSA

Table II. Characteristics of pregnancies complicated by fetal growth restriction.

No.	GA at recording (wks)	Hypertensive disorder	Nr. days antenatal steroids	PI UA before	PI UA after	PI UA category	GA at delivery (wks)	BW at delivery	BW percentile
1	27+0	–	35	normal	>2SD	2	35.1	1635	<p5
2	27+1	PE	8	normal	>3SD	2	29.9	840	<p10
3	27+5	–	2	normal	normal	1	34.0	1405	<p5
4	27+5	–	20	>2SD	–	3	33.2	1370	<p10
5	28+1	PE	1	normal	–	1	30.7	1000	<p10
6	29+0	–	1	normal	normal	1	34.8	1890	<p10
7	30+0	–	4	normal	>2SD	2	37.2	2075	<p5
8	30+2	PE	4	>3SD	>3SD	3	30.7	856	<p10
9	30+6	–	6	>3SD	>3SD	3	32.6	1075	<p5
10	31+0	PIH	22	normal	normal	1	34.0	1400	<p5
11	31+1	PE	4	>3SD	>3SD	3	31.4	1120	<p5
12	31+1	PIH	30	normal	normal	1	34.0	1405	<p5
13	31+5	–	–	normal	normal	1	40.1	2800	<p5
14	32+2	PE	2	normal	>2SD	2	33.3	1510	<p10
15	32+4	–	7	>2SD	>2SD	3	34.9	1505	<p5
16	32+6	PE+	–	normal	>2SD	2	35.9	2130	<p10
17	33+3	–	–	normal	–	1	33.4	1330	<p5
18	34+0	–	–	normal	>2SD	2	38.2	2430	<p10
19	34+2	–	–	normal	>2SD	2	38.6	2300	<p5
20	35+0	–	–	normal	normal	1	41.0	3045	<p10
21	35+0	PIH	21	>2SD	>2SD	3	35.4	1590	<p5
22	35+1	PE	–	normal	normal	1	37.0	2090	<p5
23	36+0	PE+	–	normal	normal	1	37.1	1995	<p5
24	36+2	–	–	normal	normal	1	40.0	2240	<p5
25	36+3	–	–	normal	normal	1	36.7	1985	<p10

GA: gestational age, PE: Preeclampsia, PE': preeclampsia with Labetalol treatment from 17 and 21 weeks pregnancy onwards, respectively, PIH: pregnancy induced hypertension, Nr.days between antenatal steroid administration and fECG recording. PI UA: pulsatility index of the umbilical artery. PI UA before and after fECG recording. PI UA categories: 1 = normal PI UA before and after FHR recording, 2 = normal PI UA before, abnormal PI UA after recording, 3 = Abnormal PI UA before and after recording, BW: birth weight.

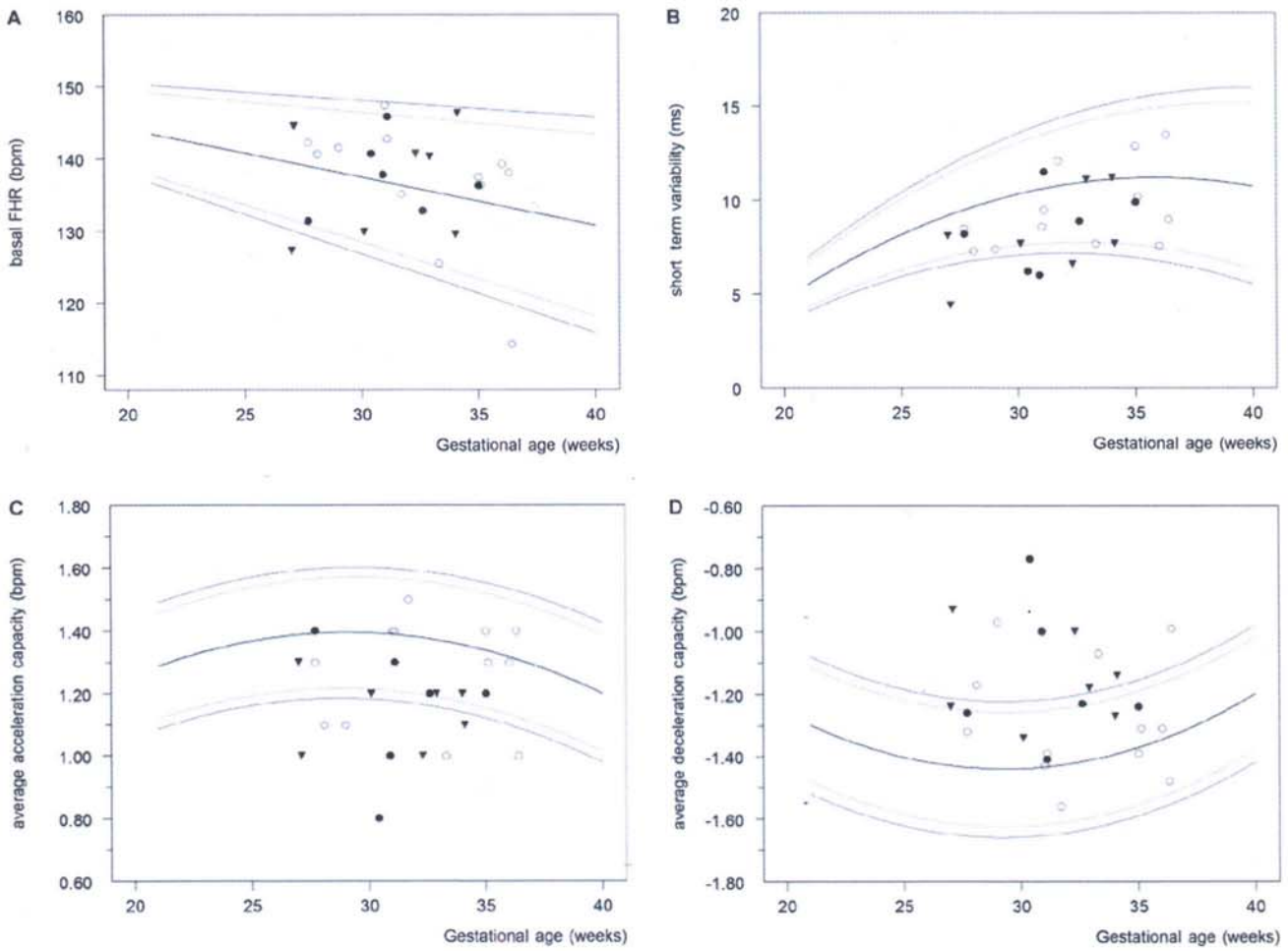

Figure 1. Reference curves for fetal heart rate (A), short term variability (B), average acceleration capacity (C), and average deceleration capacity (D). Presented are the median and 90th and 95th confidence intervals for the control group, together with heart rate parameters of individual small-for dates (SFD) fetuses according to pulsatility index of the umbilical artery (PI UA); o = normal PI UA before and after FHR recording, ▼ = normal PI UA before, abnormal PI UA after recording, ● = Abnormal PI UA before and after recording.

Table III. Model coefficients for basal fetal heart rate (FHR), short term variability (STV), average acceleration capacity (AAC), and average deceleration capacity (ADC) with gestational age in weeks (WGA).

y	b	a1	a2
FHR (bpm)	157.5	−0.667	–
STV (ms)	−22.2	1.867	−0.0261
AAC (bpm)	0.0085	0.095	−0.0016
ADC (bpm)	0.3560	−0.1229	0.0021

The equations must be read as $y = b + a1(WGA) + a2(WG)^2$.
All estimates contributed significantly to a specified model ($0.01 < p < 0.001$).

enables differentiation of the FHR components of the parasympathetic and sympathetic nervous system. Since chronic oxygen and nutrient deprivation are suggested to lead to delayed maturation of the sympathetic nervous system [5,8], separate analysis of the sympathetic (or cardio-acceleratory) and parasympathetic (or cardio-inhibitory) nervous system might offer a better recognition of compromise in small-for dates fetuses.

Although FHR recordings as acquired with Doppler CTG are not ideal for PRSA analysis, previous research using this technique has similarly found significant differences between normal and SFD fetuses, with the AAC showing a better differentiation between normal control fetuses than STV [12,13]. In these studies, the average acceleration capacity (AAC), representing part of the sympathetic nervous system, showed better differentiation between normal and SFD fetuses than the ADC, indicating that the role of the parasympathetic (or cardio-inhibitory) nervous system might not be affected to the same extent as the sympathetic tone.

However, we could not confirm superiority of AAC over ADC. In the present study, the ten SFD fetuses with abnormal ADC values almost invariably had also abnormal AAC values. This suggests simultaneously diminished activities of both branches of the autonomic nervous system possibly due to a suppressive effect on the heart of SFD fetuses by higher (cortical) brain areas. The AAC and ADC parameters of the PRSA method have as yet not been compared with measures of heart rate variability in the frequency domain [21]. Therefore, it remains obscure whether and to what extent abnormal AAC-ADC parameters found in SFD fetuses relate to low-frequency (LF; "sympathetic activity") and high-frequency (HF; "parasympathetic activity") bands, respectively, or to alterations in the LF-HF ratio, and thus to sympathico-vagal (dis) balance.

The reference values as calculated from our control group in the present study are comparable to those found in literature for FHR, but not for STV [18,19]. The latter is most likely due to diurnal differences in FHR variation, with highest