Early Human Development 93 (2016) 47–55

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Sex-related differences in the development of fetal heart rate dynamics

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ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form 15 December 2015
Accepted 18 December 2015

Keywords:
Approximate entropy
Computerized fetal monitoring
Correlation dimension
Fetal heart rate
Female
Male
Non-stress test
Vibroacoustic stimulation test
Modified nonlinear reactive criteria

ABSTRACT

Background: Despite previous efforts to explain the general advantages of female fetuses over males regarding health, sex-related differences in the dynamics or complexity of fetal heart rate (FHR) variability and FHR maturation patterns have not yet been identified.
Aim: To make linear and nonlinear comparisons of antepartum FHR indices, dynamics, complexity, and reactivity to the non-stress test (NST) and vibroacoustic-stimulation test (VAST) in male and female fetuses.
Study design: A total of 3835 singleton term deliveries without maternal and fetal complications were divided into female (n = 1849) and male (n = 1986) groups, and subjected to comparison and analyses.
Subjects: Linear FHR indices, approximate entropy (ApEn), sample entropy (SampEn), short-term/long-term exponents (α1/α2), correlation dimension (CD), NST and VAST criteria, and modified nonlinear reactive criteria (MNRC) were used to evaluate outcomes.
Results: ApEn was consistently higher in female fetuses than in male ones. ApEn in female fetuses was maximal at 29–30 gestational weeks, while the increase in ApEn was delayed in male fetuses but more rapid, reaching its peak at 31–32 gestational weeks. In both sexes, CD increased up to term, and α2 rapidly decreased up to 31–32 weeks in an analogous manner. The two sexes differed significantly in response to VAST at <31 gestational weeks and there was a structural difference in reactive patterns under MNRC.
Conclusions: Female fetuses exhibit greater heart rate dynamics in early gestational periods, suggesting that their cardiovascular system matures earlier than that of males. Male fetuses undergo a compensatory period of rapid change to catch up with females at term.

1. Introduction

Females are known to have a general advantage in health over males, such as a longer lifespan. Numerous studies report that such differences derive from multiple biological and environmental factors, all contributing to a lower risk of coronary heart disease [1] and serious arrhythmias [2] in females. Male and female fetuses are known to have biological differences from the point of conception. However, there is still a lack of understanding of the correlation between fetal gender and pregnancy outcomes.

Female fetuses have a higher prenatal survival rate than male fetuses [3], and male gender itself has been designated a risk factor for preterm delivery [4–7], macrosomia [8], gestational diabetes [8], cord complications [8], and emergency cesarean delivery [3,8]. The risk of spontaneous abortion has also been reported to be 30% higher in male fetuses [7]. Furthermore, analysis of the acid–base balance of cord artery blood at term delivery of acidotic infants revealed a higher rate of acidemia (pH < 7.0) in male newborns [3].

Although there are several recent studies that address the sex differences in fetal cardiac function [9] or complex heart rate dynamics in relation to fetal antepartum behaviors [10], the results are within our expectations. Therefore, in this work we investigated, in a large sample, male and female differences in fetal heart rate dynamics and complexity with gestational age, using linear and non-linear indices. We anticipate that our analysis will contribute to a better understanding of sex-related differences in perinatal outcomes.

2. Materials and methods

A total of 3835 subjects, 1849 female and 1986 male, were selected from non-stress test (NST) data from 2003 to 2013, gathered using the computerized system at Hanyang University Hospital. All subjects were singleton pregnancies between 20 and 42 gestational weeks. FHR tracings were recorded for 50 min by NST for the 1st and 2nd 20-min intervals, and VAST for the last 10 min. VAST was performed using a fetal vibroacoustic stimulator (Corometrics model 146, Wallingford, CT, USA; audible sound 20–9000 Hz, vibrations 67–83 Hz, sound level 74 dB at 1 min air) applied to the maternal abdomen above the fetal

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http://dx.doi.org/10.1016/j.earlhumdev.2015.12.005
0378-3782/

head for 1 s [11]. Only one FHR tracing from the 1st NST was used from each mother. All births were normal without any major malformations, chromosomal anomalies, or perinatal complications. A total of 3096 pregnancies were delivered vaginally and 739 through Cesarean section due to breech presentation, placenta previa, fetal distress, or a history of previous Cesarean section.

2.1. Linear fetal heart rate indices

Linear FHR indices and external fetal movements were monitored using an external electric FHR monitor (Corometrics 115 external fetal monitor, Medical Systems, Wallingford, CT, USA) and a computerized cardiotocography analysis system (Hanyang Fetal Monitoring System, HYFM) [12].

Linear FHR indices including baseline FHR (beats per minute, bpm), number of fetal movements (FMs), variability (amplitude and mean minute range, AMP and MMR), number of accelerations (10 bpm–10 s and 15 bpm–15 s, Acc1010 and Acc1515, respectively), and number of decelerations (Dec1515) were analyzed using the 1st 20-min NST [12]. AMP and MMR refer to the average difference between maximum and minimum FHR at each gestational week in beats per minute (bpm) and milliseconds (msec), respectively.

2.2. Nonlinear indices

Approximate entropy (ApEn) [13,14] and *sample entropy* (SampEn) [15] are nonlinear measures obtained by direct signal estimation and capable of robustly quantifying signal complexity (or irregularity) over short segments [16]. SampEn is computed in a similar manner to ApEn but differs in that it does not count self-matches, allowing less bias than ApEn. Both indices represent the complexity of the heart regulation system, with lower values corresponding to less irregularity, and vice versa.

In calculating ApEn and SampEn, we used a total number of 2400 data points ($N = 2400$ beats, corresponding to the 1st 20 min of NST in our HYFM system) and values of $m = 2$ and $r = 0.10$ sd (standard deviation of the signal segment) [14–17]. These values were calculated based on theoretical analysis, and led to reasonable statistical validity for ApEn and SampEn.

Correlation dimension (CD), a type of chaos index, determines the number of functional components involved in regulating the heart rate variability and the degree of nonlinear coupling. We implemented the Grassberger and Procaccia algorithm [18] to calculate CD.

Within each embedding dimension we calculated the distance (r) from each point to another. Plotting the logarithm of the correlation integral and of the distance resulted in a sigmoid curve, and we calculated the slope of its linear region. This process was carried out in successively higher embedding dimensions ($m = 2$ to 20). In calculating CD, we used a total number of 2400 data points ($N = 2400$ beats), where CD represents the slope of the linear segment of $m = 20$ at the scaling region. The scaling region, as previously reported [17,19], is in the range of $-2 < \log C(r) < -1$.

Detrended fluctuation analysis (DFA) is regarded as a robust method to quantify the scale-invariant (fractal) correlation property of a time series, especially when the signal class cannot be precisely determined [20]. Previous studies have used this method to identify subtle alterations of heart rhythm, and thus to evaluate the fractal dynamics of heart rate in various diseases [21–23].

The heart rate time series (length $N = 2400$ beats) was first integrated, $y(k)$, and divided into boxes of equal length, n. A least squares line, indicated as $y_n(k)$, was fitted in each box. The root-mean-square fluctuation of this detrended time series is calculated from the formula: $F(n) = \sqrt{(1/N)\sum_{k=1}^{N}[y(k) - y_n(k)]^2}$. This computation was repeated over all time scales (box sizes, $n = 480$) to identify the relationship between $F(n)$ and n. On a double-log graph, a linear relationship indicates the presence of scaling. The fractal scaling exponent is determined by the slope of the line, which relates log $F(n)$ to log n. However, in most of the heart rate time series we found that the log-log plot was not strictly linear but rather consisted of two distinct linear regions of different slope separated by a break point near 35 beats (i.e., the crossover point) [21]. Therefore, the fractal correlation of heart rate was defined separately for short-term (≤ 35 beats, *short-term fractal scaling exponent*, α_1) and long-term (> 35 beats, *long-term fractal scaling exponent*, α_2) fluctuations of heart rate.

2.3. Fetal reactivity

Fetal reactivity was monitored using a standard NST (defined by Acc1010 2 durations within a 20-min period for gestational age < 32, Acc1515 2 durations within a 20-min period for gestational age 32), VAST criteria (duration within a 10-min period), and the modified nonlinear reactive criteria (MNRC) which we used in our previous studies regarding reactivity [24]. We compared our MNRC data with previously established cutpoints (Acc1010 ≥ 2 or SampEn >0.92 for <32 and Acc1515 ≥ 2 or SampEn >0.92 for ≥32 gestational weeks within a 20-min period). The rate of reactive tests of linear (i.e., 1st, 2nd NST and 3rd VAST) and nonlinear (MNRC) criteria were calculated and compared.

2.4. Statistical analyses

Statistical analyses were performed using SAS, version 9.3 (SAS, Inc., Cary, North Carolina, USA) software. Baseline characteristics of the study population are shown as means and standard deviations (means ± sds) or frequencies (percents), which were then compared using Student t-test or Fisher's exact test.

Regression analysis was used to determine the relationship between gestational age and linear/nonlinear FHR indices, while

Table 1
General characteristics and perinatal outcomes in female and male cases.

Variables	Total N = 3835	Female N = 1849	Male N = 1986	p-value
Maternal age (year)	29.53 ± 3.96	29.63 ± 4.04	29.43 ± 3.88	0.1271
BMI (kg/m^2)	24.89 ± 2.62	24.91 ± 2.60	24.87 ± 2.64	0.6092
Nulliparity	2685 (70.01)	1276 (69.01)	1409 (70.95)	0.1922
Previous C-section	676 (17.63)	337 (18.23)	339 (17.07)	0.3512
GA (weeks)	35.70 ± 3.96	35.76 ± 3.91	35.63 ± 3.99	0.3249
Delivery weeks (weeks)	40.22 ± 1.98	40.18 ± 2.07	40.26 ± 1.90	0.2575
Birth weight (g)	3272 ± 504	3226 ± 501	3316 ± 504	<0.0001
Birth height (cm)	48.90 ± 3.46	48.66 ± 3.52	49.12 ± 3.40	<0.0001
Apgar 1 min.	6.72 ± 0.98	6.70 ± 1.00	6.73 ± 0.97	0.2833
Apgar 5 min.	8.71 ± 0.80	8.70 ± 0.82	8.73 ± 0.78	0.2459

Values are means ± SD or frequencies (percent).
BMI = body mass index, GA = gestational age.
P-values were calculated by Student t-test or Fisher's exact test.