근사엔트로피와 상관차원을 이용한 비선형 신호의 분석

A study on the nonlinearity in bio-logical systems using approximate entropy and correlation dimension

이해진*·최원영**·차경준**·박문일***·오재응†

Hae-Jin Lee, Won-Young Choi, Kyung-Joon Cha, Moon-Il Park and Jae-Eung Oh

Key Words : Approximate entropy(근사엔트로피), Correlation dimension(상관차원), Chaotic dynamics, Small-for-gestational age

ABSTRACT

We studied how linear and nonlinear heart rate dynamics differ between normal fetuses and uncomplicated small-for-gestational age (SGA) fetuses, aged 32-40 weeks' gestation. We analyzed each fetal heart rate time series for 20 min and quantified the complexity (nonlinear dynamics) of each fetal heart rate (FHR) time series by approximate entropy (ApEn) and correlation dimension (CD). The linear dynamics were analyzed by canonical correlation analysis (CCA). The ApEn and CD of the uncomplicated SGA fetuses were significantly lower than that of the normal fetuses in all three gestational periods (32-34, 35-37, 38-40 weeks). Canonical correlation ensemble in SGA fetuses is slightly higher than normal ones in all three gestational periods, especially at 35-37 weeks. Irregularity and complexity of the heart rate dynamics of SGA fetuses are lower than that of normal ones. Also, canonical ensemble in SGA fetuses is higher than in normal ones, suggesting that the FHR control system has multiple complex interactions. Along with the clear difference between the two groups' non-linear chaotic dynamics in FHR patterns, we clarified the hidden subtle differences in linearity (e.g. canonical ensemble). The decrease in non-linear dynamics may contribute to the increase in linear dynamics. The present statistical methodology can be readily and routinely utilized in Obstetrics and Gynecologic fields.

1. Introduction

Almost every natural phenomenon, such as pregnancy, has statistical attributes which are not presently characterized. Improved prenatal care is essential in order to maintain a healthy mother and baby which is the primary focus of Obstetrics. Furthermore, approaches such as developing new software by applying new algorithms for collecting new variables or computerized objective assessment of FHR analysis have been reported. It has been shown that there is a poor inter-observer and intra-observer consistency for interpreting the FHR patterns because there is no standardized directive. Computer-assisted analysis of the FHR was introduced about three decades ago, to overcome this reliability problem in FHR interpretation. Since then, various techniques have been used for the automated, objective analysis. Recently, computer-assisted analysis of NSTs and FHR parameters has been developed, and its efficacy in analysis of FHR patterns has been demonstrated.

Approximate entropy (ApEn), a mathematical approach to quantify the complexity of a system, has been introduced in order to analyze FHR tracing, based on a novel systematically biological theory. This theory suggests that healthy dynamic stability arises from the combination of specific feedback mechanisms and spontaneous properties of interconnected networks, and the weak connection between systems or within a system is the mechanism of disease, which is characterized by an increased irregularity of vital sign time series. Chaffin et al. reported that hypoxic fetal sheep study provides basic scientific/bench support for the association of decreased complexity and lowered ApEn with compromised physiology. Correlation dimension has been fruitful in quantifying the periodic and complex dynamics in heart rate variability. In addition, it describes the dimensionality of the underlying process in relation to its geometrical reconstruction in phase space.

Intrauterine growth restriction (IUGR) is related to high perinatal mortality and morbidity rate. Occurrence of fetal distress is known to be high in fetuses with IUGR. They often display abnormal fetal heart beat rate before and/or during delivery.

We have already found that IUGR fetuses show decreased irregularity and dynamics of the fetal heart in ApEn and correlation dimension (CD) based on nonlinearity. However, we have not yet identified the difference of linear characteristics of the fetal heart rate modulating system between small-for-gestational age (SGA) fetuses and normal fetuses using using canonical correlation analysis (CCA) based on linearity.

Therefore, in this study, we categorize pregnant

† 교신저자; 한양대학교 기계공학부
E-mail : jeoh@hanyang.ac.kr
Tel : (02) 2220-0452, Fax : (02) 2299-3153

* 한양대학교 대학원 기계공학과

** 한양대학교 수학과

*** 한양대학교 의과대학 산부인과학교실

women with SGA fetuses as high risk pregnancy group and compare them with normal pregnancy group with ApEn, CCA based on linearity which is clearly a superior method of analysis compared to the conventional univariate methods.

2. Materials and methods

2.1 Data collection and preprocessing

A Corometrics 115 model (USA) was used to develop the HYFM system in 1988. The initial data retrieval methods have remained the same, in order to collect consistent FHR data files. The basic concepts of this program are as follows. FHR data were collected by beat-to-beat, 140 times/min (i.e. 2.3 times/s). Fetal movements were recorded simultaneously. All data were sent to a given unit, and its interval was calculated at an average of 100 ms as previously described by Dawes et al.

All the subjects were in a semirecumbent position for a minimum of 10 min before data collection, all of which occurred from 14-18 h. FHR time series were recorded for more than 40 min using the HYFM system, during which external fetal movements and breathing were included. The recorded data was sampled into a personal computer with a digital serial interface. Whenever missing data was found, it was recorded as zero. When the off-line FHR data of zero (i.e., missing data) or below 60 beats per min (bpm) or above 200 bpm were encountered, they were removed. The corresponding R-R intervals were calculated from the heart rate data. They were 1000 Hz linearly interpolated by their R-R interval to construct a real time series of R-R intervals, and 2 Hz sub-sampled. We extracted a 20-min time series of R-R intervals during which fetal movements actively occurred and analyzed them. We finally analyzed 1,000 points of time-series data extracted from a total of 2,400 data points, because missing data causes troubles to compute ApEn and parameter values of NST data.

2.2 Approximate Entropy

ApEn is a measure of system complexity and irregularity that was first introduced by Pincus, and was first applied to FHRs by Pincus and Viscarello. It is defined as the logarithmic likelihood that the patterns of the data that are close to each other will remain close for the next comparison with a longer pattern. ApEn is computed by ApEn using the following equation:

$$ApEn(m,r,N)=\frac{1}{N-m+1}\sum_{i=1}^{N-m+1}\log_{10}C_i^m(r)-\frac{1}{N-m}\sum_{i=1}^{N-m}\log_{10}C_i^{m+1}(r)$$

Where $C_i^m(r)$, N, r, and m represent the correlation integral, the total number of data points in the R-R interval time series, vector comparison length, and embedding dimension, respectively. In the ApEn calculation, N was fixed at 1,000 points and m at 2. The tolerance r was chosen as 20% of the SD of the R-R intervals and $C_i^m(r)$ was the number of vectors with a maximum distance $\leq r$ to the template vector. The natural logarithm of $C_i^m(r)$ was averaged over 1,000 beats and this process was repeated for m=2. These m and r input parameter values are widely used standard choices, and also were selected on the basis of previous studies indicating good statistical validity for ApEn within these variable ranges. Therefore, we selected the parameters m=2 and r=20% in ApEn computation.

2.3 Correlation dimension

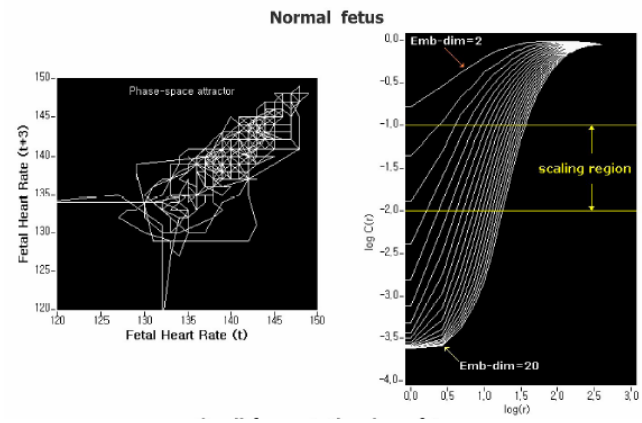
To calculate the correlation dimension we implemented the Grassberger and Procaccia algorithm. Their algorithms utilize the correlation integral $C(r)$ in phase-space:

$$C(r)=\frac{1}{N_{ref}}\sum_{j=1}^{ref}\frac{1}{N-1}\sum_{j<i}^{N}\theta(r-\|z(i)-z(j)\|$$

where z is the strange attractor, ref N_{ref} is the number of reference points and θ is the heavy side function ($\theta(x)=0$ if $x<0$, $\theta(x)=1$ if $x\geq 0$).

If the imbedding dimension and data point (N) are sufficiently large, the correlation dimension is the slope at the scaling region in $C(r)$.

Figure 1 (left) shows a two dimensional phase-space plot. Figure 1 (right) is $\log_{10}$–$\log_{10}$ plot of the correlation integral $C(r)$ for the embedding dimension m=2, 3, 4,···, 20. The correlation dimension is the slope of the correlation integral curve of m=20 at the scaling region. The scaling region is in the range of $-2<\log_{10}C(r)<-1$.



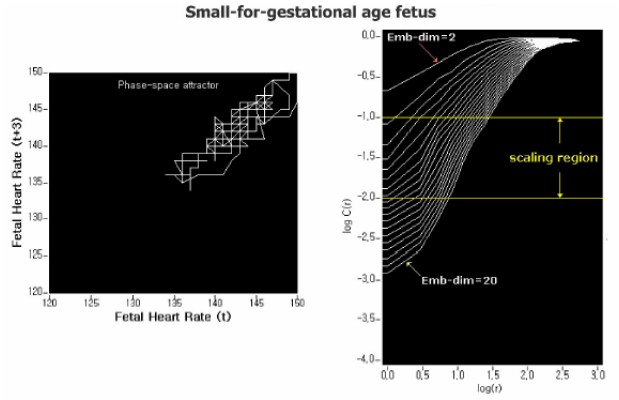


Figure 1 The corresponding reconstructed attractor plots (left) and correlation integral curve (right).

2.4 Canonical correlation analysis

Canonical correlation analysis (CCA) is a way of measuring the linear relationship between two groups and each has multidimensional variables. It finds two bases, one for each variable, that are optimal with respect to correlations and, at the same time, it finds the corresponding correlations. In other words, it finds the two bases in which the correlation matrix between the variables is diagonal and the correlations on the diagonal are maximized. The dimensionality of these new bases is ≤ the smallest dimensionality of the two variables. The canonical correlation coefficients (i.e. canonical ensemble) measure the strength of association between the two sets of variables. The maximization aspect of the technique represents an attempt to concentrate a high-dimensional relationship between two sets of variables into a few pairs of canonical variables. In this study, we considered baseline FHR and variability (amplitude; AMP, mean minute range; MMR) as parameters associated with functional development of the fetus, such as the cardiovascular and nervous system. Amplitude and mean minute range were used as the index of variability. Amplitude was calculated by the difference between maximum and minimum measurements in each minute. The average of the amplitude for the duration of recording (20min) was expressed in bpm. In each minute the computer acquired 16 measurements of fetal pulse intervals: each measurement was the average interval in milliseconds over a period of 3.75s. The difference between the minimum and the maximum of the measurements was calculated as the minute range.

The average of the minute ranges over the duration of recording, i.e., the mean minute range in milliseconds, was calculated as an index of long-term FHR variability. We regarded number of fetal movements (FM), loss of signal (Sloss), and gestational weeks (NST weeks) as indirect parameter of FHR, such as the maternal adaptation to pregnancy. We applied a quantified CCA of the canonical ensemble and linear functional development to these two sets of variables. For CCA, one set consists of NST weeks, FM and Sloss, another set consists of baseline FHR, AMP, and MMR.

3. Results

There were no significant differences in FHR parameters between SGA and normal fetuses (Table 1). However, there were significant differences in ApEn and CD between SGA and normal fetuses in all 3 gestational ranges (32-34, 35-37, 38-40 weeks) (Table 2).

Although statistically insignificant, ApEn and CD of the normal fetuses were higher at 32-34 weeks than other 2 gestational ranges. In the SGA fetuses, the ApEn was highest at 38-40 weeks, and CD at 35-37 weeks (Table 2).

The canonical ensemble according to the three gestational ranges was shown in Figure 3. In the two groups according to gestational ranges no significant changes were found during these pregnancy periods. However, there was a slightly significant difference in 35-37 weeks between the normal and the SGA fetuses (0.489 vs. 0.692 respectively, $p<0.1$).

Table 1 Comparisons of mean for SGA fetus and normal fetus.

	Normal (N=135)	SGA (N=65)	p-value
GA (weeks)	36.10 ± 0.22	36.43 ± 0.32	NS
Sloss (%)	2.30 ± 0.25	3.42 ± 0.53	NS
Mean FHR (bpm)	144.10 ± 0.68	143.02 ± 1.07	NS
FM (No.)	3.17 ± 0.27	2.69 ± 0.35	NS
AMP (bpm)	17.08 ± 0.50	17.39 ± 0.77	NS
MMR (msec)	51.44 ± 1.47	53.53 ± 2.34	NS

Table 2 Approximate entropy and correlation dimension according to gestational period in normal fetuses and SGA fetuses.

		Normal (N=135)		SGA (N=65)		p-value
		N	value	N	value	
32-34 wks	ApEn	41	0.93 ± 0.02	19	0.65 ± 0.04	<0.0001
	CD		3.97 ± 0.02		3.38 ± 0.11	<0.0001
35-37 wks	ApEn	45	0.89 ± 0.02	18	0.59 ± 0.04	<0.0001
	CD		3.88 ± 0.03		3.66 ± 0.05	0.0003
38-40 wks	ApEn	49	0.83 ± 0.03	28	0.71 ± 0.03	0.0024
	CD		3.80 ± 0.04		3.50 ± 0.06	<0.0001

4. Discussion

In the SGA fetuses, the two dimensional phase-space easily reveals some geometric structure (Figure 2-left, bottom). In contrast, the normal fetuses usually do not show any dynamic structure in the two dimensional phase-space (Figure 2-left, top). This suggests that the status of heart rate dynamics in SGA fetuses is less complex than in normal ones. The correlation dimension

quantifies the nonlinearity. In contrast to the correlation dimension of 4.103 in normal fetus, the lower dimension of 2.037 in an SGA fetus quantitatively confirms this decreased complexity (Figure 2-right). To analyze the linear characteristics of the system, we used the canonical ensemble measuring the correlation coefficient simultaneously its system. Canonical ensemble in SGA fetuses is higher than normal ones, indicating that the FHR control system has simple multiple complex interactions. However, since the value did not change significantly according to gestational age, the degree of canonical ensemble does not seem to be age-dependent during these pregnancy periods.

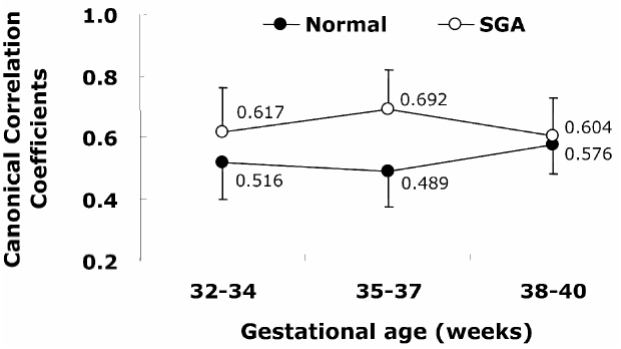


Figure 2 Comparisons of canonical correlation coefficients(canonical ensemble) according to gestational period in normal fetuses and SGA fetuses.

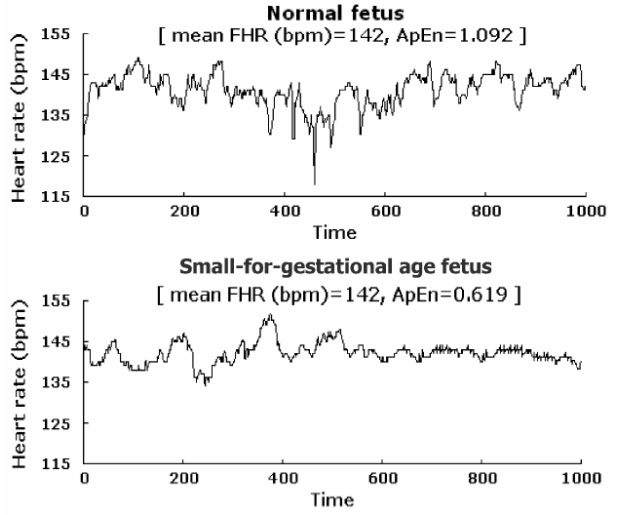


Figure 3 Plots of heart rate time series of the normal (top) and SGA(bottom) fetus aged 37 weeks of gestation.

The present study succeeded in showing that the nonlinearity and linearity heart rate patterns of the SGA fetus are significantly different from that of normal fetuses simultaneously. This result means that the canonical ensemble and chaotic indexes appear to be sensitive statistically in detecting subtle and possibly important changes in FHR signal from SGA fetuses.

Along with the clear difference between the two groups' nonlinear chaotic dynamics in FHR patterns, we discovered the hidden subtle differences in linearity (i.e. canonical ensemble). The decrease in non-linear dynamics may contribute to the increase in linear dynamics.

In conclusion, by demonstrating decreased approximate entropy and correlation dimension and increased canonical ensemble in SGA fetuses, we found that SGA was associated with abnormal heart behavior showing lower nonlinearity and increased linearity in FHR patterns.

Acknowledgements

This work was supported by the Korea Science and Engineering Foundation(KOSEF) grant funded by the Korea government(MOST) (No. R01-2005-000-10866-0)

References

(1) Ayres-de-Campos D., Bernardes J. and Costa-Santos C., 2005, "Prediction of neonatal state by computer analysis of fetal heart rate tracings: the antepartum arm of the SisPorto multicentre validation study", Eur J Obstet Gynecol Reprod Biol, 118(1), pp. 52-60.

(2) Brenner W. E., Edelman D. A. and Hendricks C. H., 1976, "A standard of fetal growth for the United Sates of America", Am J Obstet Gynecol, 126, pp. 555-564.

(3) Buchman T. G., 2002, "The community of the self", Nature, Nov14, 420, pp. 246-251.

(4) Chaffin D. G. Jr, Barnard J. M., Phernetton T. and Reed K. L., 1998, "Decreased approximate entropy of heart rate variability in the hypoxic ovine fetus", J Mater Fetal Investig, 8, pp. 23-26.

(5) Chung I. S., Cha K. J., Kim G. S., Kim Y. C., Lee S. C. and Lim Y. J., 2001, "Nurses' assessment of postoperative pain: can it be an alternative to patients' self-reports?", J Korean Med Sci, 16, pp. 784-788.

(6) Dalton K. J., Dawes G. S. and Patrick J. E., 1983, "The autonomic nervous system and fetal heart rate variability", Am J Obstet Gynecol, 146, pp. 456-462.

(7) Denton T. A., Diamond G. A., Helfant R. H., Karaguezian H. and Khan S., 1990, "Fascinating rhythm: a primer on chaos theory and its application to cardiology", Am Heart J, 120, pp. 1419-1440.

(8) di Renzo G. C., Branconi F., Clerici G., Fioriti V., Montani M., Pardini A., et al., 1996, "Fractal analysis: a new method for evaluating fetal heart rate variability", J Perinat Med 24, pp. 261-269.

(9) Dawes G. S., Moulden M. and Redman C. W., 1990, "Criteria for the design of fetal heart rate analysis system", Int J Biomed Comput, 25, pp. 287–294.

(10) Dawes G. S., Moulden M. and Redman C. W., 1991, "System 8000: computerized antenatal FHR analysis", J Perinat Med, pp. 47-51.