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Nonlinear analysis of fetal heart rate dynamics in fetuses compromised by asymptomatic partial placental abruption

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ABSTRACT

Introduction: We analyzed fetal heart rate (FHR) parameters, dynamics, and outcomes in pregnancies with asymptomatic partial placental abruption (PPA) compared with those in normal pregnancies.
Methods: We examined nonstress test (NST) data acquired from 2003 to 2012 at our institution. Normal pregnancies (N = 170) and PPA cases (N = 17) were matched for gestational age, fetal sex, and mean FHR. NSTs were performed at 33–42 weeks of gestation. FHR parameters obtained from the NST and perinatal outcomes were analyzed using linear methods. Nonlinear indices, including approximate entropy (ApEn), sample entropy (SampEn), short-term and long-term scaling exponents (α_1 and α_2), and correlation dimension (CD), were used to interpret FHR dynamics and system complexity. The area under a receiver operating characteristic curve (AUC) was used to evaluate the nonlinear indices.
Results: There were no significant differences in general characteristics and FHR parameters between the PPA and control groups. However, gestational age at delivery, birth weight, 5-min Apgar scores, ApEn, SampEn, and CD were significantly lower in the PPA group than in the control group ($P < 0.05$). The long-term scaling exponent (α_2) and crossover index (α_2/α_1) of the PPA fetuses were significantly higher than those of the controls ($P < 0.01$). A multiple regression model showed better performance in predicting PPA (AUC, 0.92; sensitivity 82.35%; specificity, 94.12%).
Discussion: Nonlinear dynamic indices of FHR in asymptomatic PPA were qualitatively different from those in normal pregnancies, whereas the conventional FHR parameters were not significantly different.

1. Introduction

Placental abruption (PA) is defined as the premature separation of a normally implanted placenta before delivery and is a major cause of poor pregnancy outcomes. Premature separation of the placenta causes acute deficiency in the oxygen supply to the fetus. In addition, maternal hemorrhage and uterine hypertonus caused by placental detachment can exacerbate the condition of the fetus [1]. This situation often requires an emergency cesarean section and intensive care of the neonate [2]; however, some cases of suspected PA due to intermittent hemorrhage throughout the pregnancy are not associated with fetal abnormalities at delivery. The lack of detectable abnormalities in the fetal heart rate (FHR) makes both diagnosis and treatment difficult. Such cases are most often attributable to chronic abruption [3] or to asymptomatic partial placental abruption (aPPA).

It is known that a variety of nonreassuring FHR patterns, including recurrent late decelerations, variable decelerations, and bradycardia, occur with PA [1]. However, at present, it is only after delivery that we can make a diagnosis of aPPA. In other words, it is unclear whether FHR patterns differ between aPPA and normal pregnancies and, if so, what effect such differences might have on the nonlinear dynamics of FHR.

We suspected that there would be differences in the nonlinear indices of FHR patterns between cases of aPPA and normal pregnancies. Therefore, the aim of our study was to analyze antenatal FHR patterns and their association with aPPA and pregnancy outcomes using both linear and nonlinear analyses.

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2. Materials and methods

2.1. Subjects and computerized analysis system for FHR monitoring

A Corometrics 115 external fetal monitor (GE Medical, Wallingford, CT, USA) was used to record FHR for approximately 40 min [4]. Corresponding R–R intervals were calculated from the heart rate data. Data were interpolated linearly at 1000 Hz by R–R interval to construct a real-time series and subsampled at 2 Hz. We extracted and analyzed the first 20-min nonstress test (NST) ($20 \times 60 \times 2$ Hz $= 2400$ points) time series of R–R intervals during which fetal movements occurred actively (Fig. 1) [5,6].

We used a computerized cardiotocography analysis system (Hanyang University's dedicated Fetal Monitoring system, HYFM) [4] to analyze the following FHR parameters: baseline FHR (beats per minute, bpm), number of fetal movements, amplitude (in bpm), mean minute range (MMR in milliseconds, ms), and number of accelerations and decelerations (15 bpm–15 s).

aPPA is defined as incomplete separation of a placenta that retains the blood supply required for fetal maintenance. As this condition does not have any specific clinical manifestation and by definition is sonographically undetectable, it can only be verified after delivery. Our group routinely carries out a gross inspection of the placenta after each delivery, and if there is abruption its area based on the total area of the placenta is recorded to the nearest 10%. Seventeen cases of aPPA were chosen for this study, all of which were diagnosed at delivery by gross investigation of the extracted placentas. These women underwent NSTs between January 2003 and December 2012 in the Obstetrics Department of Hanyang University Hospital, Seoul, Korea. Tests were performed between 33 and 42 weeks of gestation and we used data from the last one before delivery for this study. We excluded cases with other obstetrical complications, including preeclampsia, intrauterine growth restriction, chronic hypertensive disease, fetal anomalies, gestational diabetes, or idiopathic fetal tachycardia.

We randomly selected 10 control subjects who were matched by fetal sex, gestational age, and mean FHR per nPPA case. For the aPPA group (n = 17) versus matched control group (n = 170), the data, expressed as number (%) or median (range), were as follows: female fetus, 9 (52.94%) versus 90 (52.94%); gestational age, 38 weeks (33–42) for both groups; and mean FHR 142 bpm (135–150) for both groups. In all cases, we used ultrasonographic data for the fetus, placenta, and amniotic fluid that had been recorded a month before delivery.

2.2. Nonlinear dynamic indices

2.2.1. Approximate entropy and sample entropy

Approximate entropy (ApEn) or sample entropy (SampEn) is a nonlinear analysis tool that quantifies the unpredictability of fluctuations in a time series and has been shown to be useful in FHR analysis [7]. The calculation of ApEn and SampEn requires three parameters, N, m, and r, which represent the total number of data points, the embedding dimension, and the vector comparison length, respectively. In this study, N was fixed at 2400 points, m at 2, and r at 20% of the standard deviation of the R–R intervals [8,9].

2.2.2. Detrended fluctuation analysis

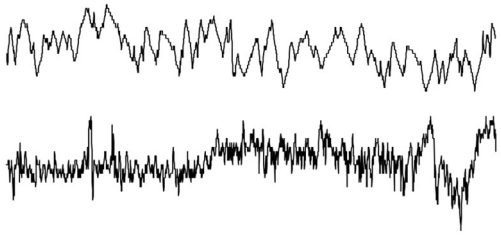
Detrended fluctuation analysis (DFA) is a method for analyzing the autocorrelation properties of a signal and has proven useful for the analysis of heart rate variability (HRV), allowing differentiation of healthy subjects from patients with cardiac nervous system dysfunction [10–14]. DFA estimates the scaling exponent α, the value of which signifies the characteristics of the signal noise and indicates the temporal correlation [12,13]. The exponent α is the slope of a line fitted in a plot of log $F(n)$ versus log n, where $F(n)$ is the root mean square of the integrated and detrended R–R interval time series. Furthermore, depending on circumstances, some curves in the log–log plot are better explained by two fitted lines having different slopes α_1 and α_2, which represent the short-term and long-term correlations, respectively. To characterize the difference in short-term and long-term correlations, the crossover index is defined as α_2/α_1 [10]. In this study, the total beat length (N) was 2400 and the box size (n) was 480 (Fig. 2, *left*).

2.2.3. Correlation dimension (CD)

The CD approximates the number of variables involved in the regulation of HRV and the degree of nonlinear coupling between these variables [5]. To illustrate the characteristics of a HRV time series, the phase space was plotted (Fig. 2, *middle*) where the x coordinate represents the fetal heart rate (FHR [n]) and the y coordinate represents the heart rate after a delay (FHR [$n + delay$]). In the phase space plot the respective periodicity and complexity can be assessed by observing whether the trajectory is a closed loop or diffuse over the phase space. Furthermore, the calculation of CD gives information about whether the HRV is deterministically chaotic or random [15]. The CD value can be obtained directly from a plot of the natural logarithm of the correlation integral $C(r)$ to that of r (Fig. 2, *right*), for the embedding dimension $m = 2, 3, \ldots, 20$) [16]. The CD value is equal to the slope of the curve (of $m = 20$) at the scaling region. The scaling region is in the range of $-2 < \log C(r) < -1$ as reported [5,6,10].

2.3. Statistical analysis

SAS software (version 9.3; SAS Inc., Cary, NC, USA) was used for the statistical analysis. Baseline characteristics of women with aPPA and those with normal pregnancies were compared using the



A. asymptomatic Partial Placental Abruption (%)=40;
GA (weeks)=37, FHR (bpm)=142, Amplitude (bpm)=20,
ApEn=0.68, α_2=1.09, CD=2.78,
Baby weight (kg)=2.70, Apgar score 5 min.=7.

B. Normal fetus;
GA (weeks)=37, FHR (bpm)=142, Amplitude (bpm)=19,
ApEn=1.24, α_2=0.73, CD=4.15,
Baby weight (kg)=3.40, Apgar score 5 min.=9.

Fig. 1. Examples of heart rate time series (20 min), linear parameters, nonlinear indices, and neonatal outcomes for cases of asymptomatic partial placental abruption (aPPA) **(A)** and a normal fetus **(B)** at 37 weeks of gestation. Key: GA, gestational age; FHR, fetal heart rate; bpm, beats per minute; ApEn, approximate entropy; α_2, long-term scaling exponent; CD, correlation dimension. Note that despite apparent superficial similarities in FHR parameters between the two groups, the beat-to-beat heart rate dynamics showed significant differences between aPPA cases and normal pregnancies with regard to irregularity, roughness, and complexity (aPPA versus normal fetus): ApEn = 0.68 versus 1.24; $\alpha_2 = 1.09$ versus 0.73; and CD = 2.78 versus 4.15.