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Complexity analysis of fetal heart rate preceding intrauterine demise

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ABSTRACT

Background: Visual non-stress test interpretation lacks the optimal specificity and observer-agreement of an ideal screening tool for intrauterine fetal demise (IUFD) syndrome prevention. Computational methods based on traditional heart rate variability have also been of limited value. Complexity analysis probes properties of the dynamics of physiologic signals that are otherwise not accessible and, therefore, might be useful in this context.
Objective: To explore the association between fetal heart rate (FHR) complexity analysis and subsequent IUFD. Our specific hypothesis is that the complexity of the fetal heart rate dynamics is lower in the IUFD group compared with controls.
Study design: This case-control study utilized cases of IUFD at a single tertiary-care center among singleton pregnancies with at least 10 min of continuous electronic FHR monitoring on at least 2 weekly occasions in the 3 weeks immediately prior to fetal demise. Controls delivered a live singleton beyond 35 weeks' gestation and were matched to cases by gestational age, testing indication, and maternal age in a 3:1 ratio. FHR data was analyzed using the multiscale entropy (MSE) method to derive their complexity index. In addition, pNN_x, a measure of short-term heart rate variability, which in adults is ascribable primarily to cardiac vagal tone modulation, was also computed.
Results: 211 IUFDs occurred during the 9-year period of review, but only 6 met inclusion criteria. The median gestational age at the time of IUFD was 35.5 weeks. Three controls were matched to each case for a total of 24 subjects, and 87 FHR tracings were included for analysis. The median gestational age at the first fetal heart rate tracing was similar between groups (median [1st–3rd quartiles] weeks: IUFD cases: 34.7 (34.4–36.2); controls: 35.3 (34.4–36.1); $p = .94$). The median complexity of the cases' tracings was significantly less than the controls' (12.44 [8.9–16.77] vs. 17.82 [15.21–22.17]; $p < .0001$). Furthermore, the cases' median complexity decreased as gestation advanced whereas the controls' median complexity increased over time. However, this difference was not statistically significant [−0.83 (−2.03 to 0.47) vs. 0.14 (−1.25 to 0.94); $p = .62$]. The degree of short-term variability of FHR tracings, as measured by the pNN metric, was significantly lower ($p < .005$) for the controls (1.1 [0.8–1.3]) than the IUFD cases (1.3 [1.1–1.6]).
Conclusions: FHR complexity analysis using multiscale entropy analysis may add value to other measures in detecting and monitoring pregnancies at the highest risk for IUFD. The decrease in complexity and short-term variability seen in the IUFD cases may reflect perturbations in neuroautonomic control due to multiple maternal-fetal factors.

Introduction

Identification and timely delivery of the compromised fetus remains a compelling, yet elusive goal of modern obstetrics. Recent data suggest that roughly 3.2 million cases of intrauterine fetal demise (IUFD) occur world-wide each year [1]. Controversy exists whether standard antepartum cardiotocography based on non-stress testing reduces stillbirth rates [2]. This approach is grounded in the understanding that the fetal heart rate (FHR) baseline fluctuations, as well as accelerations and decelerations, arise from the complex interplay of cortical regulatory centers (controlling sleep-wake cycles), the autonomic nervous system (through baroreceptors and chemoreceptors) [3] and multiple other

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physiologic components. At various stages of pregnancy, certain FHR variability profiles have been interpreted as markers of fetal well-being and serve as the basis for contemporary non-stress testing strategies. However, visual interpretation of the cardiotocograph has been reported to lack sufficient specificity and observer-agreement to make it a reliable screening tool in preventing IUFD [4,5]. Efforts at creating computerized systems for cardiotocographic analysis and interpretation have gained little clinical traction. Direct tests such as contraction-stress testing are not feasible or safe for routine antepartum use. These limitations motivate the search for more reliable and reproducible adjuncts to current cardiotocographic analysis. One promising approach expands the analysis of FHR time series by using measures derived from dynamical systems theory, also called nonlinear dynamics or complexity science [6–11].

Quantification of the complexity of various physiological signals is a relatively novel field [12] of research, and only a small number of studies have explored its applicability to various aspects of fetal monitoring [6–11]. Biologic complexity arises from the interaction of myriad physiologic processes and regulatory feedback loops that operate over a wide range of temporal and spatial scales, enabling the organism to adapt to the stresses of everyday life [13–16]. Complexity and variability are two distinct concepts. Complex signals are variable, but not all variable signals are complex [17,18]. For example, uncorrelated random sequences, such as those that would arise from shuffling the words of a text or the sequence of mean heart rate values over the course of a day, are maximally entropic (variable), but not complex. A musical analogy may also help convey the difference between variability and complexity. For example, the noisy output produced by an infant randomly striking keys at a piano is highly unpredictable and variable but it is not complex or musical. In addition, the highly predictable output of robotically executed scales also lacks musical complexity. A captivating piece of music possesses a balance between the predictable and the unexpected that derives from its complex structure.

Complex signals, such as those generated by self-regulatory (homeostatic) physiologic systems, present spatial and/or temporal structures over a wide range of scales. Typically, these signals are nonlinear and non-stationary. Consequently, conventional signal analysis techniques, such as mean, standard deviation and higher order moments fail to fully characterize and quantify their properties [15].

Complexity analysis was first applied to adult heart rate time series from healthy subjects of different ages and patients with a wide variety of conditions including heart failure, stroke, trauma and sepsis [19–24]. Observations in these groups support the conceptual framework of complexity loss in aging and pathologic states [14]. Subsequent applications of complexity analysis to FHR signals have shown promise in identifying intrauterine growth restriction and fetal acidemia in labor [3,7].

This pilot study focused on heart rate dynamics obtained from cardiotocographic recordings during non-stress tests in fetuses with subsequent intrauterine demise as compared to matched high-risk controls. Our specific hypothesis was that heart rate dynamics in the former group would have decreased complexity compared to those in the latter group.

Methods

Subjects

This retrospective case-control study was performed at the Beth Israel Deaconess Medical Center from June, 2011 through June, 2013. Cases of IUFD were identified by review of the birth log of all deliveries occurring beyond 24 weeks of gestation at our center from January 2002 through January 2011. Only cases of IUFD among singleton pregnancies with at least 10 min of continuous electronic FHR monitoring on at least two occasions in the three weeks immediately prior to the date of the fetal demise were deemed eligible. Exclusion criteria included major fetal malformations, multiple gestation, intrapartum death, and gestational age (GA) less than 28 weeks at the time of antenatal testing. Controls were matched for GA (within 2 weeks), antenatal testing indication, and maternal age (within 5 years) to cases in a 3:1 ratio. Controls were identified by review of the antenatal testing unit schedule. Patients who underwent non-stress testing within 3 days of the cases and matched the above inclusions were selected. An additional criterion for the control group was delivery of a live born singleton at 36 weeks' gestation or greater. Subjects were assigned a unique study identification number, all personal health information was password protected, and informed consent was waived. We received approval for this study from the Institutional Review Board of the Beth Israel Deaconess Medical Center.

Fetal heart rate recordings

All electronic FHR monitoring was performed for the purpose of antenatal non-stress testing on the Philips OB TraceVue® hardware and software platform (Philips Healthcare, Andover, MA). The raw FHR signals, sampled at 4 Hz, were exported using a program provided by Philips Healthcare. The data were then analyzed using open-source software available at www.physionet.org [25].

Fetal heart rate analysis

For each heart rate time series, the following measures were calculated: (i) mean; (ii) standard deviation (SD); (iii) pNN_{1-20}; and (iv) degree of complexity. PNN_x, the percentage of differences between adjacent NN intervals that are greater than x ms, is a measure of short-term heart rate variability that, in adults, is ascribable primarily to cardiac vagal tone modulation [26]. To avoid selecting an arbitrary threshold, here we used pNN_{1-20}, the sum of pNN_x values for x ranging from 1 to 20 ms with increments of 1 ms. While SD quantifies the overall amount of variability, pNN_{1-20} is a measure of local (beat-to-beat) variability, less affected by the presence of trends and prolonged accelerations/decelerations.

To probe the multiscale dynamical properties of FHR time series we used the multiscale entropy (MSE) algorithm [17,18], which quantifies the degree of complexity of a signal. MSE comprises three steps: (1) construction of a set of coarse-grained time series, each of which represents the system's dynamics on a different time scale. The coarse-grained time series for scale s is obtained using a non-overlapping moving window of length s. (2) Quantification of the degree of irregularity of each of the coarse-grained time series using the sample entropy (SampEn) algorithm. SampEn is a conditional probability measure quantifying the likelihood that sequences of m consecutive data points $(x_i, x_{i+1}, \ldots, x_{i+m-1})$ and $(x_j, x_{j+1}, \ldots, x_{j+m-1})$ matching each other within a tolerance r, will still match when their length increases from m to $m+1$ data points. (3) Calculation of the complexity index (unitless) by summing the SampEn values over a pre-defined range of time scales [7]. The calculation of SampEn requires the definition of two parameters m and r; here we used $m = 2$ and $r = 1.2$ bpm. In this study, we analyzed time scales ranging from 1 to 5 s.

Statistical analysis

Changes in complexity with GA were assessed by linear regression (slope of best-fit line of complexity versus GA). Group