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Complexity-loss in fetal heart rate dynamics during labor as a potential biomarker of acidemia[☆]

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Abstract

Background—Continuous fetal heart rate (FHR) monitoring remains central to intrapartum care. However, advances in signal analysis are needed to increase its accuracy in diagnosis of fetal hypoxia.

Aims—To determine whether FHR complexity, an index of multiscale variability, is lower among fetuses born with low (< 7.05) versus higher pH values, and whether this measure can potentially be used to help discriminate the two groups.

Study design—Evaluation of a pre-existing database of sequentially acquired intrapartum FHR signals.

Subjects—FHR tracings, obtained from a continuous scalp electrocardiogram during labor, were analyzed using the multiscale entropy (MSE) method in 148 singletons divided in two groups according to umbilical artery pH at birth: 141 fetuses with pH > 7.05 and 7 with pH < 7.05. A complexity index derived from MSE analysis was calculated for each recording.

Results—The complexity of FHR signals for the last two hours before delivery was significantly ($p < 0.004$) higher for non-acidemic than for acidemic fetuses. The difference between the two

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groups remained significant ($p < 0.003$) when FHR data from the last 30min before delivery were excluded.

Conclusion—Complexity of FHR signals, as measured by the MSE method, was significantly lower for acidemic than non-acidemic fetuses. These results are consistent with previous studies showing that decreased nonlinear complexity is a dynamical signature of disrupted physiologic control systems. This analytic approach may have discriminative value in FHR analysis.

Keywords

Cardiotocography; Complexity analysis; Fetal monitoring; Heart rate; Multiscale entropy

1. Introduction

Continuous fetal heart rate (FHR) monitoring remains a key component of intrapartum surveillance. A central aim is identification of fetuses exposed to decreased oxygen supply during labor, thereby prompting early obstetric intervention to avert fetal morbidity or even mortality. Despite its widespread use over many decades, conventional FHR analysis has important limitations. Expert interpretation has poor reproducibility [1–3] and the method has only moderate specificity leading to potentially unnecessary interventions. Furthermore, its use has not been shown to improve important clinical outcomes, including perinatal death and cerebral palsy [4]. From a technical viewpoint, the nonstationarity of the signals (e.g., abrupt changes during uterine contractions) poses major challenges in assessing FHR by eye or by algorithm.

For these reasons, multiple computational methods for FHR analysis have been proposed aimed at providing more reproducible and physiologically relevant evaluations. One historic focus is the measurement of fluctuations around the FHR baseline, a property referred to by obstetricians under the rubric of “variability” [5,6]. In addition to conventional measures of variability, typically based on assessments of the variance or standard deviation, recent FHR studies have also explored techniques related to spectral analysis, entropy measures (primarily single-scale based) and methods for assessing fractal exponents. However, only a limited number of such studies have been performed during labor [7–13]. The need for FHR dynamical markers of acidemia motivates the search for new, physiologically-based approaches.

Toward this goal, we speculated that multiscale entropy-based measures might be particularly attractive since: i) dynamical changes in FHR associated with acidemia may not only evoke changes in the amplitude (variance) of FHR fluctuations, but also in their temporal structure, and ii) FHR changes with acidemia may affect the dynamics over multiple time scales. Therefore, we adopted an approach based on a computational method introduced by our group, termed *multiscale entropy* (MSE) [14,15].

MSE has been widely used in probing a wide range of physiologic systems under the conceptual framework that the complexity of the dynamics of healthy physiologic systems is higher than the complexity of those with advanced aging or pathology [16–20]. As implied

by the name, the MSE method is particularly suitable for the analysis of physiologic variables that exhibit fluctuations over a range of scales of time or space.

In the context of fetal and adult heart rate regulation, the complexity of the fluctuations in the cardiac interbeat interval time series is postulated to reflect the integrative capability of the autonomic nervous and other interacting control systems to respond to transient stressors and to adapt to the demands of an ever-changing environment. The complete breakdown of these regulatory mechanisms in adults leads either to uncorrelated random signals (e.g., atrial fibrillation) or to patterns that are highly regular (e.g., sinusoidal oscillations with central apnea syndromes or very flat heart rate dynamics, both seen in chronic heart failure). These two classes of outputs, one random and the other highly regular, both have low complexity in comparison with signals derived from healthy systems [17,18].

To our knowledge, the MSE method has previously been applied only to FHR analysis of antepartum signals. For example, Ferrario et al. [19,20] reported significantly decreased FHR complexity in fetuses with intrauterine growth retardation. The inter-related aims of the present study were to: 1) test the hypothesis that FHR complexity during labor is lower in fetuses born with severe acidemia compared with non-acidemic fetuses; 2) investigate whether any decrease in complexity could be solely attributed to changes in the dynamics that occur in the last 30 min of labor; and 3) assess whether this measure could help discriminate the two populations.

2. Materials and methods

2.1. Database

We utilized an existing database of continuous FHR signals acquired at a tertiary care university hospital, as described in detail in [21]. Ethics committee approval for the study had been obtained, and written informed consent for enrollment was provided by all subjects.

Consecutive cases were enrolled if they fulfilled the following inclusion criteria: singleton pregnancy, more than 36 completed gestational weeks, fetus in the cephalic presentation, absence of known fetal malformations, active phase of labor, and a generally accepted indication for internal FHR monitoring (poor signal quality, heavy meconium staining, high-risk pregnancy). All patients underwent continuous internal FHR monitoring with an electrocardiographic (ECG) scalp electrode, using a STAN 21 or STAN 31 monitor (Neoventa Medical, Mölnbdal, Sweden). Enrolled patients were subsequently excluded if one of the following situations occurred: FHR tracing lasting less than 60 min, signal loss in the last hour exceeding 15%, complications with the potential to influence fetal oxygenation between tracing end and delivery (such as difficult vaginal or abdominal fetal extractions, cord prolapse, maternal hypotension, or shoulder dystocia), anesthetic complications taking place at the time of surgery, or inadequate umbilical cord blood samples. For practical reasons related to the time needed for application of a ventouse or for the preparation of a cesarean section, patients in which the interval between tracing-end and vaginal delivery exceeded five minutes or until cesarean birth exceeded 20 min were also excluded. In all cases the umbilical cord was doubly clamped immediately after birth, and blood was

aspirated from both artery and vein into previously heparinized syringes. After vestigial air was expelled, blood gas analysis was carried out within 30 min after birth. Patients were excluded from the analysis if paired samples were not obtained, pH values between the two samples differed by more than 0.03 units, or PaCO₂ values between the two samples differed by more than 7.5 mm Hg.

A total of 148 (141 non-acidemic, 7 academic) FHR tracings were obtained from an equal number of singleton pregnancies, with signals sampled at 4 Hz. The academic group included 4 females and 3 males; the non-academic group included 71 females and 70 males. The median, 25th – 75th percentile values of newborn birth-weights were 3.16, 2.88 – 3.26 kg for the academic group and 3.21, 2.98 – 3.49 kg, for the non-academic group.

2.2. Data analysis

As noted, our analyses were motivated by the goal of testing both whether there was an overall reduction in the FHR complexity of fetuses born with acidemia vs. those without acidemia and whether such a reduction could be detectable more than 30 min before delivery. Accordingly, the complexity of the FHR time series was assessed over two different epochs: analysis #1– from delivery up to a maximum of 2 h prepartum; analysis #2 – from 30 min up to a maximum of 2 h prepartum.

Furthermore, we configured our analyses to accommodate the variable length of the recordings. The median, 25th – 75th percentile values of tracing duration (unit hour) were: 2.43, 1.68 – 4.13 for the academic group and 2.80, 1.75 – 4.43 for the non-academic group. The minimum record duration in the academic group was 90 min; four out of the seven recordings lasted more than two hours. In the non-academic group, the minimum record duration was one hour; 68% (96 of 141) of the recordings lasted more than 2 h and 83.7% (118 of 141) more than 90 min.

In analysis #1, we included all 148 subjects, using the last 2 h of data before delivery from recordings lasting ≥ 2 h and the entire length of data available for recordings lasting < 2 h. For analysis #2, we excluded recordings lasting < 90 min (23 non-academic, 0 academic) and analyzed the full length of the remaining datasets.

2.3. Multiscale entropy (MSE) method: algorithm and specific implementation for FHR signals

As noted, the MSE method was used to measure FHR complexity. The method, previously described in detail [14,15], comprises three steps: 1) construction of a set of derived time series, each of which represents the system's dynamics on a different time scale, through a procedure known as a “coarse-graining.” The coarse-grained time series for scale n is obtained by dividing the original time series into non-overlapping segments of n data points and then calculating the average value of the data points in each of these segments. 2) Quantification of the degree of irregularity of each of these coarse-grained time series using the sample entropy (SampEn) metric. SampEn is a conditional probability measure quantifying the likelihood that if a vector of m consecutive data points ($x_i, x_{i+1}, \dots, x_{i+m-1}$) and a template of the same length ($x_j, x_{j+1}, \dots, x_{j+m-1}$) match within a tolerance

r (i.e., the absolute difference between their components is less than r), then they will still match when their length increases from m to $m + 1$ data points. 3) Calculation of the complexity index (unitless) obtained by summing the SampEn values over a pre-defined range of time scales [22,23].

The calculation of SampEn requires the definition of two parameters m and r ; here we used $m = 2$ and $r = 15\%$ of the time series' standard deviation, which are the most commonly employed values reported in the literature for the analysis of heart rate time series. The sequence of entropy values for a given range of scales is called the MSE curve. In this study, we analyzed scales one through eight.

The interpretation of the MSE results, as well as of those derived from traditional time and frequency (i.e., spectral) domain analyses, can be misleading if the original signals are highly non-stationary, as typically occurs with the FHR during labor due to frequent decelerations and accelerations caused by uterine contractions. To help overcome this major signal analysis challenge posed by FHR non-stationarities, we developed a “parsing” algorithm designed to filter out periods of marked decelerations and accelerations. This algorithm is described in detail in the Appendix. The complexity analysis could then be performed on the relatively stationary FHR segments between these decelerative and accelerative periods.

Finally, in addition to the MSE measures, the mean and standard deviations of the data segments were computed.

2.4. Statistical analyses

Two-tailed Wilcoxon rank sum tests were used to compare the difference in the values of analyzed variables (complexity index and standard deviation) between academic and non-academic fetuses. Results are reported as median values with 25th and 75th percentile cut-offs, unless otherwise indicated. Analyses were performed with a 5% level of significance. The area under the receiver operating characteristic (ROC) curve (c-statistic) was computed as a measure of the ability to discriminate between academic and non-academic fetuses. SAS statistical software (version 9.3 for Windows, SAS Institute, Cary, NC) was used for all analyses.

3. Results

Mean FHR values (beats/min) were higher for the academic (152.6, 129.3 – 159.4) vs. non-academic (142.4, 133.8 – 152.1) groups. However, this difference was not statistically significant ($p = 0.4$).

The results of the MSE analysis (#1) for the FHR time series up to two hours before delivery are presented in Fig. 1. The complexity index was significantly lower ($p < 0.004$) for academic (10.16, 9.64 – 10.98) than non-academic fetuses (12.46, 11.25 – 13.34).

The standard deviation values calculated for the same time series were slightly lower for the academic group (1.72, 1.71 – 1.96) compared with the non-academic group (2.01, 1.74 – 2.15) but the differences did not reach statistical significance ($p = 0.2$). The area under the

ROC curve (AUC) was 0.83 (95% CI: 0.75 – 0.88) for the complexity index and 0.64 (95% CI: 0.56 – 0.72) for the standard deviation. The *p* values for testing the null hypotheses that the AUCs were actually equal to 0.50, were <0.0001 for the complexity index and 0.27 for the standard deviation. However, the difference between the ROC curves for the complexity index and standard deviation did not reach statistical significance (*p* = 0.21).

The MSE analysis (#2) of FHR time series up to two hours before delivery, excluding the last 30min, yielded complexity indexes that were also significantly (*p* < 0.003) lower for the acidemic (10.04, 9.78–11.22) than the non-acidemic (12.28, 11.22 – 13.28) group.

The standard deviation values calculated for the same time series were slightly lower for the acidemic group (1.70, 1.67 – 2.00) compared with the non-acidemic group (2.04, 1.78 – 2.17), but the difference was not statistically significant (*p* = 0.21). The area under the ROC curve was 0.84 (95% CI: 0.76 – 0.90) for the complexity index and 0.64 (95% CI: 0.55 – 0.73) for the standard deviation. The significance levels (compared to AUC = 0.5) were *p* < 0.0001 and *p* = 0.32 for the complexity index and the standard deviation, respectively. However, the difference between the two ROC curves did not reach statistical significance (*p* = 0.18).

4. Discussion

The major physiologic findings of this study were that: 1) the complexity of FHR baseline time series for the last 2 h of labor was significantly lower for the acidemic than the non-acidemic fetuses; 2) complexity remained significantly lower for the acidemic group when the last 30 min were excluded from the analysis; and 3) the standard deviation values, the basis of contemporary clinical FHR variability analyses, did not differentiate the two groups, with or without the inclusion of the last 30 min of labor.

These findings suggest that acidemia at birth may not only reflect acute, but also sub-acute perturbations of neuroautonomic control. In addition, they also support the hypothesis that an altered (less complex) temporal structure of FHR baseline fluctuations detectable on multiple time scales may be a dynamical marker of acidemia. Furthermore, such alterations in complexity do not necessarily need to be accompanied by changes in the magnitude (e.g., standard deviation) of the baseline fluctuations.

Although the area under the ROC curve indicates that the complexity index is a potentially highly discriminative measure of FHR acidemia, the difference between the ROC curves for the complexity index and the standard deviation was not statistically different by a two-tailed test. A likely reason is the low number of acidemic cases.

This study is also notable for the introduction of an automated method, termed the “parsing” algorithm, for isolating relatively stationary segments from transient marked changes in baseline values (accelerative/decelerative episodes). This pre-processing procedure is of crucial importance because entropy-based methods, such as MSE, can yield misleading results when applied to non-stationary signals. From a technical point of view, this algorithm may also be of interest to investigators outside the field of FHR monitoring and analysis who analyze highly non-stationary signals.

4.1. Limitations

The major limitation of this study is the relatively small number of academic cases. This limitation is inherent in the re-analysis of a well-characterized, previously published database [21]. However, despite this limitation, the statistical differences observed between the academic and non-academic groups are compelling and warrant validation in future studies. We also note that this study was not intended to compare complexity analysis with the long inventory of other FHR methods, including spectral (Fourier) analysis [8,12,13,24,25]. No consensus exists on how to pre-process data for such analyses and the nonstationarity of the data will confound spectral measures performed on the original signals. Future studies are also needed to help resolve these issues.

One clinical factor that could not be fully controlled in this cohort was the possibility of drug administration affecting FHR variability. In one non-academic case displaying very low-complexity, retrospective analysis showed that systemic anticholinergic agents had been administered to the mother, which could explain the false positive finding. For the remaining non-academic cases with relatively low FHR complexity, no drug administration was registered, but it is still possible that some of this information could be missing from the case notes.

4.2. Summary and conclusions

Our finding of a decrease in MSE values of academic fetuses is consistent with the general hypothesis that fetal acidemia is associated with disruption of neuroautonomic control over multiple time scales. Future studies will help determine whether integration of complexity measures with other FHR parameters, including indices related to accelerations and decelerations, can enhance the prepartum discrimination between these groups.

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Appendix

The parsing algorithm comprises the following steps:

1. Decomposing the original FHR signals into their intrinsic mode functions (IMFs), using the *empirical mode decomposition* method developed for the analysis of nonstationary, nonlinear signals [26]. Each IMF is an oscillatory function with a characteristic frequency. The number of IMFs depends on the length of the original signal. For the signals analyzed here, there were typically 10 IMFs. By construction, the high frequency structures of a signal are projected onto the lowest order IMFs (e.g., IMF-1 and IMF-2) and the low frequency structures onto the highest order ones (e.g., IMF-9 and IMF-10). Temporal structures of intermediate frequencies are captured by the intermediate IMFs.

2. Calculating the trend line, $a(t_i) = \sum_{i=5}^{n_{\max}} IMF_i$ (where $n_{\max}$ is the total number of IMFs) that captures the changes in mean FHR caused by decelerations or accelerations (Fig. 2, top plot).
3. Subtracting the trend, $a(t_i)$ (Fig. 2, top plot, red line) from the original data, $x(t_i)$, (Fig. 2, top plot, black line) to calculate the detrended time series $x_d(t_i)$ (Fig. 2, plot (b)).
4. Deriving the time series of the local standard deviation values, $sd(t_i)$ (Fig. 2, plot (c)) for the detrended time series, using a moving window with 40 data points (10 s) sequentially shifted one point at a time.
5. Calculating the trend line, $b(t_i) = \sum_{i=6}^{n_{\max}} IMF_i$, (Fig. 1, plot (c), red line) for the local standard deviation values of the detrended time series.
6. Deriving the binary time series, $c(t_i)$, as $c(t_i)=1$ if $b(t_i)<2.5\text{bpm}$ and $c(t_i) = 0$ otherwise (Fig. 1, plot (c) green line).
7. Using the binary time series to filter the detrended time series by multiplying $c(t_i)$ by the $x_d(t_i)$.

Of note, the concatenation of the relatively stationary periods obtained with the parsing method does not bias the calculation of the entropy values. For example, consider the time series, $\{x_1, x_2, \dots, x_{100}\}$, from which the sequence of values x_{50} to x_{60} was deleted due to a deceleration. The resulting time series is: $\{x_1, x_2, \dots, x_{49}, x_{61}, \dots, x_{100}\}$. In our calculations of the SampEn values, the sequence $\{x_{49}, x_{61}\}$ is never considered, either as a template or a vector. Only consecutive data points were used for the calculations.

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Fig. 1. Multiscale entropy (MSE) analysis of the FHR tracings (beginning a maximum 2 h before birth). For all time scales (see text), the SampEn values were higher for non-acidemic than for acidemic fetuses. The values of the parameters for the calculation of the sample entropy were: $m=2$, $r=15\%$ (see text). Circles and bars represent group median and standard deviation values, respectively.

Fig. 2.

Steps comprising the *parsing algorithm* used to identify and exclude marked FHR accelerations and decelerations. Panel (a): original FHR time series in beats per minute (bpm) (black) and trend (red), calculated using the empirical mode decomposition method. Panel (b): detrended FHR time series (black) obtained by subtracting the trend displayed in panel (a) from the original time series; quantification of FHR complexity was performed on the sequence of relatively stationary segments (blue). Panel (c): local standard deviation (SD) values (black) of the detrended time series; low frequency component of the SD time series (red) and binary signal (green) used to filter the detrended and the original time series. Panel (d): original FHR time series (black) and sequence of segments that were used for analysis (blue).