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COMMENTARY

New Mathematical Thinking About Fetal Heart Rate Characteristics

Commentary on the article by Yum and Kim on page 915

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While fetal heart rate monitoring is time-honored and widely practiced, its intuitively apparent benefits have not been realized in clinical trials (1–3). One possible explanation is the qualitative and categorical nature of its interpretation, with the characteristic abnormalities of reduced variability and transient decelerations being identified by eye. It remains a completely reasonable hypothesis that an improved and quantitative analysis of fetal heart rate patterns might lead to improved outcome.

Quantitative analysis of heart rate variability in adults is a well-advanced science. The abnormality of interest, though, is fundamentally different. Adults with many kinds of illness have reduced heart rate variability, but do not have transient decelerations. As a result, the workhorse analytical measures used in the study of adults do not discriminate normal fetal heart rate records from abnormal. Hence there is ripe opportunity for newer approaches to mathematical analysis, especially those from the exciting field of nonlinear dynamical analysis, or chaos theory.

A mathematician sees the transient decelerations (or accelerations) as *cusps* on a wave and calls them *singularities*. The shape of the cusp – called the degree or sharpness of the singularity – can be measured by the *Holder exponent*. This measure is extrapolated from calculations performed on pairs of data points with varying time lags in-between them, and characterizes the limiting behavior of adjacent heartbeats. The Holder exponent is related to the important concept of fractal dimension that is central to chaos theory.

Traditionally, mathematical models of heart rate dynamics have a Holder exponent that remains the same, and the models are thus called *monofractal* (4). Recently, analysis of heart rate records has produced the surprising result that the Holder exponent changes with time. As a result, heart rate control has been described as a *multifractal* process, and the range of Holder exponents found in such a record is called the *singularity spectrum*. Notably, heart rate dynamics for healthy adults are multifractal – with a broad singularity spectrum – while in congestive heart failure the process is monofractal (5). This finding presents new challenges and opportunities for developing novel heart rate variability measures for identifying illness and for understanding the physiology of heart rate dynamics (6). Tutorials, software, and test data for multifractal analysis and other heart rate analysis methods from the field of nonlinear dynamics are available at the National Center Of Research Resources PhysioNet web site (www.physionet.org).

In this issue, Yum and Kim apply to fetal heart rate data some of the same multifractal analytical techniques that have been successfully used in studies of adults (7). In particular, a measure derived from the singularity spectrum, called the *very short-term intermittency*, is used as a heart rate index to measure the severity of transient decelerations. The very important new finding is that this new measure is highly correlated with the gestational age of the fetus. Moreover, the correlation is significantly higher than that obtained with traditional measures, such as mean, SD, low frequency power, and high frequency power of the heart rate data. The very short-term intermittency is also shown to have a higher correlation than measures of monofractal processes. In addition to pointing to a multifractal nature of fetal heart rate dynamics, this promising result suggests that these kinds of novel mathematical approaches can be successfully used to assess fetal health and development.

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Potential for conflict of interest: Medical Decision Networks of Charlottesville, VA, which supplied partial funding for this study has a license to market technology related to heart rate characteristics (HRC) monitoring of newborn infants. As of the submission date of the final version of the article, none of the authors had received consultants fees or owned equity in Medical Decision Networks or related companies. However, Drs. Griffin and Moorman have been offered an equity share of a new company, Medical Predictive Science Corporation that owns the HRC technology license.

Work remains on possible refinements to the method. First, the method used to calculate the measure, sometimes called the structure function approach, is cumbersome and somewhat subjective. It might be profitably replaced by a more recent approach using wavelet analysis (8, 9). Second, the measure is calculated separately for time increments of 4 to 16 heart beats (very short term) *versus* 32 to 128 beats (short term) and does not capture information directly from adjacent beat correlations. Finally, and most importantly, the mathematical mechanistic link between the proposed measure and the severity of transient decelerations remains to be established formally. None of these areas for further research, however, precludes investigating the use of this new heart rate index as an aid for fetal health care.

What is the physiologic mechanism of the reduced variability and transient decelerations in distressed fetuses? This crucial question remains almost entirely open. In the final analysis, the timing of threshold depolarizations of sinus node cells is determined by ion channel activity, a process highly regulated by intracellular signal transduction processes. It is tantalizing to speculate that circulating peptide regulator factors called *cytokines*, which are known both to increase early in the course of sepsis and to alter signal transduction processes, are causally involved. Cytokines have been implicated in fetal distress resulting in perinatal asphyxia with hypoxic-ischemic encephalopathy (10–16) and in neonatal sepsis (17). Interestingly, premature newborn infants have the same abnormal heart rate characteristics of reduced variability and transient decelerations early in the course of sepsis and sepsis-like illness (18). This clinical syndrome, which has been called the systemic inflammatory response syndrome, or SIRS, has been clearly linked to cytokines in a variety of illnesses (19, 20).

It will be exciting to see how the new sciences of nonlinear dynamics/chaos theory and cellular signaling can join forces to elucidate basic mechanisms of disease and to produce new and useful clinical tools.

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