Cross-correlation of fetal cardiac and somatic activity as an indicator of antenatal neural development

Janet A. DiPietro, PhD,a Rafael A. Irizarry, PhD,b Melissa Hawkins, PhD,a
Kathleen A. Costigan, RN, MPH,c and Eva K. Pressman, MDc
Baltimore, Md

OBJECTIVE: In this study, we wanted to model the emergence of coupling between fetal cardiac and somatic activity in normal and at-risk fetuses.

STUDY DESIGN: One hundred six fetuses of uncomplicated pregnancies were longitudinally monitored at 20, 24, 28, 32, 36, and 38 weeks of gestation by using a fetal actocardiograph and computerized data collection. Twenty-six fetuses of complicated pregnancies were also included. Statistical time series analysis techniques were used to examine the relation between fetal movement and fetal heart rate.

RESULTS: A linear increase was found in the magnitude of the cross-correlation function between fetal movement and fetal heart rate as gestation advanced, with coalescence around a peak lag of 5 seconds by 32 weeks. Fetuses that delivered before term evidenced accelerated fetal movement and fetal heart rate coupling, whereas fetuses affected by deleterious conditions showed a decline in developmental trajectory.

CONCLUSIONS: The cross-correlation between fetal cardiac and somatic activity is an indicator of neuroregulation in human fetuses. (Am J Obstet Gynecol 2001;185:1421-8.)

Key words: Fetal heart rate, fetal movement, neurologic development, preterm birth

The development of the nervous system before birth has been of long-standing interest, but its investigation has been hampered by the inaccessibility of the fetus. Recent renewed interest in neural development during the prenatal period has been generated by models of fetal programming of adult disease,1 partitioning of variance for constitutional attributes into genetic versus that conferred by the prenatal environmental milieu,2 and recognition of the antenatal origins of many functional childhood morbidities like cerebral palsy.3

Recent advances in technology and analysis techniques provide an opportunity to determine whether features of fetal neurobehavior can serve as markers of neural development during pregnancy. Fetal neurobehavioral development during gestation is multifaceted and includes changes in patterns of heart rate, motor activity, and sleep-wake cycles. At the core of these features of development lies the emergence of a temporal association between motor activity and heart rate. As gestation advances, fetal motor activity becomes increasingly associated with transient accelerations of fetal heart rate. Individual variation in the strength of this relationship has been proposed as an indicator of general fetal well-being,4 and its developmental nature has been interpreted as a sign of the developing integration between sympathetic and parasympathetic innervation of the autonomic nervous system.5-8

Most existing investigations of the cardiac-somatic relationship have been limited by several factors, including lack of a longitudinal perspective and reliance on visual inspection of tracings. More important, investigators use different a priori criteria to define how much heart rate must change with movement to be considered evidence of coupling, as well as the window of time around the movement during which a change must occur (eg, requiring an increase in heart rate of 15 bpm for at least 10 seconds within 15 seconds of the onset of a movement). Such definitions can greatly influence results and are based on assumptions regarding the fetal movement-fetal heart rate (FM-FHR) relation, not on existing empirical information regarding the actual nature of this relation. The goal of this study is to determine how FM and FHR change in relation to one another on a continuous, dynamic basis. We rely on a computerized system for collecting FM and FHR data and apply time series analysis, a statistical technique that can explicitly depict

From the Department of Population and Health Sciences,a the Department of Biostatistics,b and the Division of Maternal-Fetal Medicine,c Johns Hopkins University.
Supported by the National Institutes of Health (HD R01 27592) awarded to the first author, and by a Johns Hopkins Faculty Innovation Fund awarded to the second author.
Received for publication January 30, 2001; revised June 20, 2001; accepted July 30, 2001.
Reprint requests: Janet A. DiPietro, PhD, Department of Population and Health Sciences, The Johns Hopkins University, 624 N Broadway, Baltimore, MD 21205. E-mail: jdpriet@jhsph.edu.
Copyright © 2001 by Mosby, Inc.
0002-9378/2001 $3.00 + 0 6/1/119108
the relation between FHR and FM, to examine the development of cardiac-somatic coupling during gestation.

Patients and methods

One hundred six women with uncomplicated pregnancies, and their normally developing fetuses, were monitored at successive gestational ages of 20, 24, 28, 32, 36, and 38 weeks by using a fetal actocardiograph (MT320, Toitu Corp, Tokyo, Japan). Eligibility was restricted to nonsmoking women aged at least 20 years, with singleton pregnancies, of which dating was validated by early first trimester pregnancy testing, examination, or ultrasonography. As a group, the patients tended to be well educated (mean maternal education = 16.6 years), employed (96%), and married (92%). Half of the fetuses (51%) were male. All were born with a normal birth weight and without significant neonatal conditions. This research was approved by the governing institutional review board, and informed consent was obtained from all participants after they were given a thorough explanation of the project.

Twenty-six additional participants met eligibility criteria at the onset of the study, but either complications developed during their pregnancy or they gave birth to offspring with previously undetected conditions of fetal origin. There were no statistically significant sociodemographic differences between the complicated and uncomplicated groups. The complications represented were as follows:

1. Preterm (<37 weeks of gestation) delivery (14)
2. Arrested preterm labor without preterm birth (5)
3. Intrauterine growth retardation (4)
4. Other fetal conditions (3)

The fetal monitor (MT320, Toitu Corp) used in this study simultaneously records FM and FHR through the use of a single wide array transabdominal Doppler transducer and processes this signal through a series of filtering techniques. The actograph detects fetal movements by preserving the remaining signal after bandpassing frequency components of the Doppler signal that are associated with FHR and maternal somatic activity. Reliability studies that compare actograph-based versus ultrasonound-visualized fetal movements have found the performance of this monitor to be highly accurate in detecting both fetal motor activity and quiescence.9-11 Fetal data were visualized using a single wide array transabdominal Doppler transducer and processes this signal through a series of filtering techniques. The actograph detects fetal movements by preserving the remaining signal after bandpassing frequency components of the Doppler signal that are associated with FHR and maternal somatic activity. Reliability studies that compare actograph-based versus ultrasonound-visualized fetal movements have found the performance of this monitor to be highly accurate in detecting both fetal motor activity and quiescence.9-11 Fetal data were sampled at 1000 Hz by using an internal analog-to-digital board and concurrently digitized-via-streaming software. Subsequent processing of fetal data, including application of algorithms to interpolate segments with artifact, was accomplished by using software developed through our laboratory (GESTATE: James Long Company, Caroga Lake, NY). Fig 1 presents sample-time synchronized output of digitized FM and FHR data. Fifty minutes of data were collected for each patient at each gestational age. The data were reduced by resampling at 1 Hz, producing time series measurements \((X_1, Y_1), (X_2, Y_2), ..., (X_T, Y_T)\) of FM and FHR, respectively, where \(T\) is the total number of measurements. In this case, because there were 50 minutes of data sampled each second, \(T = 3000\). The FM and FHR measurements, seen in Fig 1, can be considered outcomes of a 2-component stationary time series. A standard way to measure the association between 2 components in a time series is through the cross-correlation function,12 which is obtained by computing the correlation coefficient between FM and FHR at various lags. The mathematical details for this procedure are included in the appendix. This time series analysis yields 2 descriptive values. The first is the lag, in seconds, at which the strongest association occurs, as measured by the cross-correlation function. The second is the magnitude or strength of this association.

The plots in Fig 2 show averaged sample cross-correlation functions collapsed across all subjects for each gestational age. SD for each are shown as dotted lines. Two features of this series of plots are particularly salient. First, the magnitude of the maximum sample cross-correlation increases linearly from a value of .12 at 20 weeks of gestation to .25 at 38 weeks. The stabilization at .24 by 36 weeks of gestation corresponds to the standard definition of term birth 1 week later, with little evidence of additional development once this gestational age is attained. Note that the cross-correlation between FM and FHR of .25 at term is a lower value than the associations reported by others,13-17 although the increase over gestation is the same. This is because the manner in which the relation was assessed in the current study is not predicated on large movements as in earlier studies. The magnitude of the cross-correlations we observed over gestation corresponds to 6% to 9% of shared variance between FM and FHR when measured on a second-by-second basis. Whereas the overall strength of this association may be relatively low, it represents the average over a 50-minute period that includes times of quiescence and both weak and strong movements.

The development of the more defined peaks in subsequent plots is a result of the second feature, the consolidation of peak lag times. The peak lag, the time lapse at which there is maximal association between FM and FHR, appears to stabilize at a lag of 5 seconds beginning at 32 weeks of gestation and is maintained through term. A lag close to 5 seconds is evidenced at 24 and 28 weeks of gestation (6 seconds), but before this, there is evidence of only a diffuse relationship, which suggests that the maximum rate of development for this function occurs between weeks 20 and 28 of gestation.

The histograms presented in Fig 3 provide further information on the development of the peak cross-correlation. The range of individual peak lag times at 20 weeks of gestation is highly dispersed but progressively coalesces around 5 seconds as gestation advances. We suspect that
this reflects variability in maturation rates among individual fetuses, and that at 20 weeks of gestation, individuals who do not cluster around the mean have not yet developed substantive neural integration between FM and FHR. The robust nature of the emergent relation between FM and FHR at lag 5 seconds suggests that this value best characterizes the coupling between FM and FHR in normally developing fetuses; hence, we define the magnitude of the correlation at a lag of 5 seconds as $\hat{\rho}(5)$, our indicator of neural integration in the fetus.

Longitudinal recordings for the subset of 26 participants that had pregnancy complications were available until the time of delivery and analyzed by using the same time series techniques. Inspection of the lagged relations (not shown) reveal curves consistent with those presented in Fig 2 for the first group, with peak lags at 5 seconds after 28 weeks of gestation for the group with fetal conditions, and from 4 to 5 seconds for the preterm group. Fig 4 presents average values of the sample cross-correlation function evaluated at lag 5 ($\hat{\rho}(5)$), stratified into 3 groups: uncomplicated, preterm birth/preterm labor, and fetal conditions (including intrauterine growth retardation). The preterm group includes cases of preterm delivery and preterm labor. Because treatment with tocolytic agents for preterm contractions can have independent effects on the fetus, data collection did not proceed for women in this category once the condition was detected, thus reducing the sample size at subsequent times. Of the participants who delivered prematurely, one delivered at 35 weeks of gestation, all others at 36 weeks. As is typical, approximately one third of preterm births were associated with spontaneous premature rupture of membranes and one third with spontaneous labor, and one third were delivered as a result of maternal/fetal conditions (ie, oligohydramnios, gestational hypertension, and preeclampsia). During preliminary analyses, no detectable differences in cross-correlation

![Figure 1](image-url). Thirty-minute sample of digitized movement and fetal heart rate data from a fetus aged 32 weeks. The top plot provides fetal movement data in arbitrary units of 0 to 100, representing calibrated voltage outputs of the Doppler-based actograph. The second plot shows fetal heart rate. The slow change in baseline over time was present for most recordings. To consider these measurements as outcomes of a stationary time series, the slow trend was removed using a local regression. The estimated smooth trend is represented with a dotted line. The last plot shows only the positive part of the detrended fetal heart rate, because we are interested in the acceleration in heart rate associated with fetal movements. This relationship becomes evident when the first (fetal movement) and last (fetal heart rate) plots are compared.
Fig 2. Sample cross-correlation functions of fetal movement and fetal heart rate averaged across all patients from 20 weeks of gestation through term. Values at lags -50 seconds through +50 seconds are included. *Dotted lines* represent SD.
Fig 3. Histogram of individual peak lags at each gestational age. For each visit of every patient, the lag at which the maximum of the sample cross-correlation function occurred was computed. For each lag, the height of the histogram bar represents the percentage of patients who had that peak lag.
functions were observed between the spontaneous and delivered preterm groups, so they were combined. Patients in the fetal condition group include 4 with intrauterine growth retardation (determined by a birth weight of <10th percentile for gestational age as well as clinical ascertainment), and the following: intrauterine death at 31 weeks (1), Down syndrome (1), and diaphragmatic hernia (1; 20-week data only). The infants with intrauterine growth retardation were delivered at term; accompanying antepartum factors included fetal distress, oligohydramnios, and gestational hypertension.

With the consideration of the developmental trajectory of the first group of patients as the standard, the preterm group demonstrates accelerated development beginning at 28 weeks of gestation, whereas the affected group begins to fall off the expected course of development. If regression lines are fit to the values observed in each group, with the use of either ordinary least squares or generalized estimating equations, the slope estimates are statistically significant as are the differences between the estimated slopes for each group.

**Comment**

The association between FM and FHR has been most often attributed to centrally mediated coactivation of cardiac and somatomotor processes. In animal preparations, stimulation of single central loci can rapidly increase both heart rate and blood flow to muscles, and muscle paralysis does not eliminate cardiovascular responses to direct afferent stimulation. Cardiac-somatic coupling is predominantly considered a function of parasympathetic control that becomes the increasingly prominent influence as gestation advances. Changes in autonomic control of the heart from the medulla oblongata to higher cortical processes between 27 and 30 weeks of gestation have been inferred from a study of fetuses with progressive levels of neural tube defects. Our demonstration of the close temporal synchrony between FM and FHR, the orderly pattern in emergence of FM-FHR sample cross-correlation functions during the latter half of pregnancy, and the consolidation in peak lag times that occurs between 20 and 32 weeks provide convergent support of this measure as reflective of the development of the fetal nervous system.

The etiologies of both preterm birth and growth retardation are multifaceted and not isomorphic, although conditions affecting uteroplacental sufficiency and fetal well being, including infection, uteroplacental dysfunc-

1. In the current study, we did not find evidence of accelerated neural development in growth-retarded fetuses, but in preterm infants. Two recent lines of research provide information that may be applicable to our findings. First, experimental manipulation of preterm contractions in sheep through pulsatile oxytocin
administration has been associated with acceleration of cardiovascular measures and electroencephalogram patterns, which suggests functional effects on both autonomic and central maturation. Second, elevations in corticotropin-releasing hormone have been observed as early as 18 to 20 weeks of gestation in pregnancies that terminate in preterm delivery. Thus, episodic mild early as 18 to 20 weeks of gestation in pregnancies that complicated and at-risk pregnancies.

In summary, data generated by this investigation provide a clear illustration of the development of cardiac and somatomotor coupling in the fetus. The time series method allowed empirical analysis of this relation without requiring a priori constraints on the size of heart rate or movement excursions to be evaluated. Findings are consistent with central and autonomic neuroregulation of these systems before birth and are among the first documentation of accelerated maturation in preterm fetuses. Further investigative pursuit of these findings may ultimately yield clinical applications in evaluation of uncomplicated and at-risk pregnancies.

We are grateful for the insight into these processes provided by Timothy R. B. Johnson.

REFERENCES

Appendix
Under the assumption that the measurements are the outcome of a stationary stochastic process, we define the cross-correlation function with

\[ \rho(h) = \frac{\sum_{t=0}^{N-1} X_t Y_{t+h} - \bar{X} \bar{Y}}{\sum_{t=0}^{N-1} (X_t - \bar{X})(Y_t - \bar{Y})}, \quad h = 0, \pm 1, \pm 2, \pm K \]  

with \( \bar{X} = \frac{1}{N} \sum_{t=0}^{N-1} X_t \) and \( \bar{Y} = \frac{1}{N} \sum_{t=0}^{N-1} Y_t \), the expected value of \( X_t \) and \( Y_t \), respectively, and \( \sigma_X^2 \) and \( \sigma_Y^2 \) the variance of \( X_t \) and \( Y_t \), respectively. With the assumption of stationarity, none of these quantities depend on time \( t \). If fetal heart rate tends to increase
whenever there is fetal motor activity we expect $\rho(0)$ (the common definition of correlation between $X_I$, $K$, $X_T$ and $Y_I$, $K$, $Y_T$ is the cross-correlation at lag 0) to be relatively high. However, if fetal heart rate tends to increase some time ($h$) after fetal movement occurs, then it is $\rho(h)$ that we expect to be high. Notice that $\rho(h)$ has an intuitive definition as the correlation between $X_I$, $K$, $X_{T-h}$ and $Y_{h+1}$, $K$, $Y_T$. The sample cross-correlation function is:

$$
\hat{\rho}(h) = \frac{\sum_{t=1}^{T-h} (X_t - \bar{X})(Y_{t+h} - \bar{Y})}{\hat{\sigma}_X \hat{\sigma}_Y}
$$

with $\bar{X}$ and $\bar{Y}$ the sample averages of $X_I$, $K$, $X_T$ and $Y_I$, $K$, $Y_T$, respectively, and $\hat{\sigma}^2_X$ and $\hat{\sigma}^2_Y$ the sample variances of $X_I$, $K$, $X_T$ and $Y_I$, $K$, $Y_T$, respectively. The sample auto-correlation is the standard estimate of the cross-correlation function.