Time-frequency analysis of fetal heartbeat fluctuation using wavelet transform

YOSHITAKA KIMURA, KUNIHIRO OKAMURA, TAKANORI WATANABE, NOBUO YAEGASHI, SHIGEKI UEHARA, AND AKIRA YAJIMA
Department of Obstetrics and Gynecology, Tohoku University School of Medicine, 1–1 Seiryomachi, Aobaku, Sendai 980-8574, Japan

Kimura, Yoshitaka, Kunihiro Okamura, Takanori Watanabe, Nobuo Yaegashi, Shigeki Uehara, and Akira Yajima. Time-frequency analysis of fetal heartbeat fluctuation using wavelet transform. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1993–H1999, 1998.—We examined whether the nonlinear control mechanism of the fetal autonomic nervous system would change in various fetal states. Eight thousand or more fetal heartbeats were detected from normal, hypoxemic, and acidemic fetuses. Fetal heart Doppler-signal intervals were determined in a high-precision autocorrelation method, and a time series of fetal heart rate fluctuation was obtained. The distribution of the amplitude of temporal fluctuation in the low-frequency component of fetal heart rate frequency was studied using a method of time-frequency analysis called wavelet transform. Spline 4 was used as the mother wavelet function. A gamma distribution was observed from 17 wk of gestation onward. The value of the parameter \( \nu \) of this gamma distribution was \( \sim 1.6 \) and remained constant regardless of the gestational age or the time of day. The value of \( \nu \) decreased significantly to 0.77 when the fetus developed acidemia and was 1.51 in hypoxemia and 1.54 in a normal condition. This study elucidates a nonlinear structure of the time series of heart rate fluctuation of the gamma distribution in the human fetus. This technique may provide a new quantitative index of fetal monitoring to diagnose fetal acidemia.

gamma distribution; fetal monitoring; fetal acidosis

Ever since Akselrod et al. (1) performed frequency analysis on the fluctuation of electrocardiogram (ECG) R-R intervals in dogs using fast-Fourier transform (FFT) and pointed out the relation between the activities of the autonomic nervous system and the low-frequency (LF) and high-frequency (HF) peaks of the frequency domains, frequency analysis of heart rate fluctuation has been performed widely (6). In the fetal field as well, studies of heart rate fluctuation based on frequency analysis have been carried out, and applications to fetal distress have been attempted (7, 8, 10, 11). However, its effectiveness has not been recognized because the fetal heartbeat may behave in a nonlinear manner (2). Fetal heart rate fluctuations do not show a long-term stationarity in the resting or the active state; they show stationarity only for a short period. In our study, stationarity was not observed for \( > 300 \) beats (2–3 min). Therefore, FFT is not suitable because various fetal states would then be included. Through these studies, the possible temporal fluctuation of LF and HF peaks gradually came to be pointed out, and their changes followed a transition from one status to another, e.g., rest, movement, etc. Their changes during sleep or their relation to the circadian rhythm began to be studied. How are the LF and HF peaks, and thus the LF and HF components including them, controlled? The first report on this issue was made by Ivanov et al. (9) in their thesis published in 1996. They used a method of time-frequency analysis called a wavelet transform on ECG R-R fluctuation in adults to study the structure of temporal fluctuation of the HF component. According to their report, all the amplitude distributions of the temporal fluctuation of the HF component in normal cases are almost perfectly identical to one another and present a gamma distribution regardless of the case. They also state that the structure of distribution during sleep fluctuates in cases of sleep apnea and that a gamma distribution is also presented in the other frequency domains. Their results suggest that, for healthy individuals, there may be a common structure in heartbeat control during nighttime hours as well as during daytime hours. In the present study, we paid attention to the LF component of the fetal heart rate frequency. We studied its temporal fluctuation using wavelet transform and statistical distribution structure analysis of the amplitude to examine whether the structure of a temporal fluctuation similar to that in adults could be observed in fetuses and to determine when the particular distribution structure would be observed and when it would collapse from the fetal period onward. We also examined whether the study of such fluctuation would be helpful in clinical diagnosis of fetal hypoxemia or acidemia, since any current diagnostic methods including fetal heart rate monitoring are not reliable enough in clinical settings.

MATERIALS AND METHODS

Forty normal pregnant women who came to the Department of Obstetrics and Gynecology of Tohoku University Hospital for clinical checkup at 17 to 40 wk of gestation were included in the study, with consent, to investigate the changes with the advance of gestational age. Another series of studies was designed to investigate the change by fetal state. In 17 cases in which the umbilical blood \( P_O_2 \) level was found to be \(< 20 \) mmHg, 10 cases with \( pH \sim 7.2 \) were grouped together as a hypoxemia group, and the remaining 7 cases with \( pH < 7.2 \) were grouped as an acidemia group. The umbilical blood \( P_O_2 \) was determined in blood prenatally collected by fundipuncture under ultrasonic guide through the maternal abdominal wall (fetal blood sampling) in 14 cases with written informed consent or in the umbilical blood obtained in an elective cesarean section in 3 cases. No significant difference was observed in the mean gestational age of the fetus between the hypoxemia and the acidemia groups (Table 1). The normal control group for matched gestational age included elective
cesarean section cases under various indications for which umbilical cord blood gas values turned out normal.

Data collection. Data were collected between 9:00 AM and 3:00 PM in the normal group. In three cases in the normal group, data were collected on a 24-h basis. In the hypoxemia and acidemia groups, data were collected at times as close to blood collection times as possible.

A 1.15-MHz ultrasonic transducer (Ultrasonic Transducer 5700, Corometrics) was attached to the maternal abdominal wall with the mother in a semisupine position at rest. Eight thousand (\( \times 8000 \)) or more fetal heartbeats were detected with uterine activity being monitored with a tocotransducer. Fetal heart Doppler-signal intervals were determined by high-precision autocorrelation based on the method by Divon et al. (5), and a time series of fetal heart rate fluctuation was obtained. This time series was input to a microcomputer (PC-9801 NS/A, NEC) either directly or off-line.

Method of analysis. The flow chart of the analysis is shown in Fig. 1. A time series of 8,000 or more heartbeats was included in the study.

Preprocessing for noise exclusion. The mean value of the immediately preceding 10 data points (\( \times 10 \)) was computed and was called the expected mean (\( M \)). We defined an interbeat interval larger than 1.5\( M \) as a “hole” and an interval shorter than 0.5\( M \) as a “short interbeat interval.” Subsequent processing was continued when overall noise was confirmed to be \( \leq 5\% \). Any hole was interpolated by the integer-multiplied M value(s). Short interbeat intervals were simply removed. All the other noise components were rejected. Resampling of the interpolated signal time series was performed every 0.3 s in a Berger method.

Wavelet transform. Wavelet transform is generally defined, as in the following equation, as the inner product of the input signal \( s(t) \) and the wavelet function group \( g_{ab}(t) \) obtained by dilating and shifting the function \( g(t) \) (the mother wavelet function), locally present in the temporal region and the

Table 1. Gestation age of the fetuses and blood gas findings in the hypoxemia and acidemia groups

<table>
<thead>
<tr>
<th></th>
<th>Hypoxemia Group</th>
<th>Acidemia Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>31.5 ± 3.6</td>
<td>31.0 ± 4.6</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 ± 0.02</td>
<td>7.08 ± 0.04</td>
</tr>
<tr>
<td>Po2, mmHg</td>
<td>11.4 ± 4.7</td>
<td>12.5 ± 4.5</td>
</tr>
<tr>
<td>PCO2, mmHg</td>
<td>56.7 ± 7.7</td>
<td>58.8 ± 18.9</td>
</tr>
</tbody>
</table>

Values for gestational age and blood gas findings are means ± SD; \( n = no. \) of fetuses. No significant difference was observed in mean gestational age of fetuses, which was 31 wk of gestation in both groups. pH and Po2 levels are within defined limits. Although PCO2 tended to increase in the acidemia group, no significant difference was observed.

Fig. 1. Flow chart of analysis by wavelet transform in low-frequency (LF) domain. A: ultrasound Doppler signals reflected from moving fetal heart valves. B: time series of beat-to-beat intervals resampled 0.3 s from original beat-to-beat intervals (\( T_1, T_2, T_3, \ldots, T_n \)) obtained by a high-precision autocorrelation method from A. C: spline 4 wavelet used in this study. D: variation of class 32 (C32), corresponding to LF domain at \( -0.1 \) Hz, is extracted by spline 4 wavelet. Using this process, we obtain the time series of variation of the LF domain, which is presumptively displayed in E. P, power; \( t \), time.
frequency domain, by the scaling parameter $a$ and the shift parameter $b$

$$S(a, b) = (g_{a,b}(t) \cdot s(t))$$

where

$$g_{a,b}(t) = g\left(\frac{t}{a} - b\right)/\sqrt{a}$$

Spline 4 was used as the mother wavelet function (3). Spline 4 is a family of well-localized and smooth functions, such as a localized sine wave. This wavelet function has one of the best possible simultaneous concentration properties in both the time domain and the frequency domain (13).

Here, the scaling parameter $a$ provides a frequency band to be extracted. The larger the scaling parameter $a$, the higher the frequency it represents. In the discrete wavelet transform $a = 2^{-n}$, we assumed $a$ to be $1/32$. Consequently, the extracted frequency band centers around $1/(32 \times 0.3) = 0.104$ Hz, corresponding to a low-frequency domain in which $0.3$ s was the resampling interval. The shift parameter $b$, which signifies the passage of time, is a nonnegative integral value.

A time series expressed as $S(a, b)$, where $b = 0, 1, 2, 3, 4, ...$, is called a class $1/a$ of $s(t)$. Thus what we determined was class $32$.

Multiple resolution analysis was used, and a decomposition sequence was approximated with a tap number of 41 (3).
Class 32 was then determined by down sampling one by one alternately. Thus the abscissas represented a time base divided into 0.3 × 32 = 9.6-s intervals.

The tertiary moving average of the absolute value of $S(1/32, b_i)$ was defined as

$$\sum_{i=1}^{3} |S(1/32, b_i)|/3$$

and used as a time series representing the amplitude of this class (Fig. 2A).

Plotting amplitude distribution graphs. The whole range from zero to the maximum value of the time series of the amplitude of class 32 derived above was equally divided into 100 segments, and the frequency distribution of the points in each segments was determined. The maximum value was taken within the time frame of observation. Thus the ordinate of the distribution in Fig. 2B represents the percent ampli-
tude with the maximum value in the time series corresponding to 100%. The distribution thus obtained was smoothed using a low-pass filter with a band edge of 0.1 $\mu$N. $N\%$ was defined as the percent value at the maximum peak of the frequency distribution (Fig. 2B). The standardized mode of amplitude (or simply “mode” hereinafter) was defined as a concrete value $X_0$ that corresponded to $N\%$ in the frequency distribution. The mode was also expressed as the product of the maximum value in the time series of amplitude and the most frequent percent value ($N\%$, Fig. 2A).

The frequency distribution was normalized to a unit area. This is a probability distribution (Fig. 3A). When the ordinate was rescaled by $1/P_{\text{max}}$ and the distributions were normalized to a unit area, the fitness of the data to the gamma distribution was examined (Fig. 3C).

Surrogate data set for analysis. To test the nonlinearity of the variation of the low-frequency domain in fetal heartbeat variation, we performed parallel analysis on surrogate data obtained by Fourier transforming the original time series of fetal heartbeat variation, preserving the amplitude of the Fourier transform but randomizing the phase, and performing an inverse Fourier transform. The wavelet transform was performed on the surrogate time-series data obtained by the inverse Fourier transform, and the distribution of class 32 was examined as in the original fetal heartbeat time series and compared with the distribution from the original time series.

Statistical processing. Pearson's test was used to test goodness of fit of the distribution function. The Kruskal-Wallis test was used to test the significance of the difference among the parameters obtained, and the $t$-test was used for the other statistics.

RESULTS

The mode increased with the gestational age of the fetus. In the gestational age ranging from 26 to 34 wk, the mode in normal cases was $0.365 \pm 0.04$. In the hypoxemia cases it reduced to $0.268 \pm 0.027$, and in the acidemia cases it further reduced to $0.110 \pm 0.028$.

When the abscissa was rescaled by $1/P_{\text{max}}$ and the distributions were normalized to a unit area, the fitness of the data to the gamma distribution was examined (Fig. 3C).

Table 2. Changes in $\nu$ with the advance of gestational age

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>$n$</th>
<th>$\nu$</th>
</tr>
</thead>
<tbody>
<tr>
<td>17–20</td>
<td>10</td>
<td>$1.61 \pm 0.05$</td>
</tr>
<tr>
<td>21–25</td>
<td>17</td>
<td>$1.67 \pm 0.08$</td>
</tr>
<tr>
<td>26–40</td>
<td>13</td>
<td>$1.54 \pm 0.06$</td>
</tr>
</tbody>
</table>

Values for $\nu$ are means ± SE; $n =$ no. of fetuses. No significant difference was observed among gestational age groups.
These differences were significant with a significance level of 0.05 (Fig. 4).

The distribution of class 32 in all the normal cases significantly fit a gamma distribution for which \( \nu = (\ln N) - 1 \) and \( b = \nu/N \), with a significance level of 0.05.

The mean \( \nu \) values among 17 and 20, 21 and 25, and 26 and 40 wk of gestation were 1.61, 1.51, and 0.77, respectively, and no significant difference was observed among these groups (Table 2). The distribution of class 32 in all cases of the hypoxemia group fit the above gamma distribution with a significance level of 0.05. The mean \( \nu \) value was 1.51, which was not significantly different from that in the normal group at 26 wk of gestation. Five cases in the acidemia group fit this gamma distribution significantly, whereas the other two did not. The mean \( \nu \) calculated from the above equation was 0.766, which was significantly different from that of the normal group and the hypoxemia group (Table 3).

Figure 5 shows the distribution plots obtained approximately every 6 h in the morning, in the daytime, toward the evening, and at night in one fetus. As shown in Fig. 5, the \( \nu \) values were all similar. These distribution plots were so indistinguishable from one another statistically that they could be regarded as identical. The same was true of the other two cases.

Both the original and surrogate signals have identical power spectra. The distribution of class 32 on the surrogate signals resulted in a Rayleigh distribution, whereas that on the original time series fits a stable gamma distribution (Fig. 6).

**DISCUSSION**

Data were based on fetal heart Doppler signal intervals. The Doppler signal intervals were determined in a high-precision autocorrelation method with a time constant of 1.0–1.5 by sampling raw signals at 1,000 Hz and producing an envelope at 14 Hz. This corresponds to the application of a low-pass filter to the time series with a cutoff frequency of ~0.6 Hz. The precision at 0.1 Hz and its vicinity examined in the present study is thus ensured. In fact, the fetal ECG R-R intervals determined in an autoregression method correlate well with the integral value of this region (\( r = 0.994 \)). This supports the validity of the precision of the present study (12).

The structure of the gamma distribution was found to exist from 17 wk of gestation onward. Its parameter \( \nu \) remained constant regardless of individual, observation time period, or gestational age of the fetus.

With the application of the spline 4 wavelet to the surrogate signals, the distribution of class 32 in these signals, corresponding to the frequency domain of 0.1 Hz, did not show a gamma distribution but did show a Rayleigh distribution. Our surrogate data clearly indicated that there is a phase correlation in the fetal heartbeat time series. The presence of these correlations is related to the nonlinear underlying dynamics in the fetus.

The fact that the gamma distribution was observed not only in adults but also in the fetuses in the early gestation stage indicates that this is a very fundamental characteristic of the circulation control mechanism of a living body. Because the gamma distribution can be derived only from a nonlinear relation, the nonlinear structure of the circulation control mechanism is considered to play an essential role in a living body. The gamma distribution satisfies the generalized homogeneous functional equation \( P(\lambda^a x, \lambda^b) = \lambda P(x, b) \), where

<table>
<thead>
<tr>
<th>State of Fetus</th>
<th>( n )</th>
<th>( \nu )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13</td>
<td>1.54 ± 0.06†</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>10</td>
<td>1.51 ± 0.05*</td>
</tr>
<tr>
<td>Acidemia</td>
<td>7</td>
<td>0.77 ± 0.24*†</td>
</tr>
</tbody>
</table>

Values for \( \nu \) are means ± SE; \( n = \) no. of fetuses. Normal group consists of those cases found normal in period from 26 to 40 wk of gestation. Mean gestational age in normal group was 31 wk. Parameter \( \nu \) was not different between the normal and hypoxemia groups, but it decreased significantly in the acidemia group.
$\alpha = -1$, $\beta = 1$, and $\lambda$ is a scale factor. The fact that the parameter $\nu$ remains constant at $-1.6$, independent of the number of weeks of gestation, indicates that the most frequent percent value $N$ is $-14\%$. This relation, in which the maximum spatial amplitude determines the temporal mode, seems to provide a principle that ensures the temporal universality of this parameter.

Class 32 corresponds to the frequency domain of 0.1 Hz. It is known that in fetal heart rate fluctuation, as well as in adult heart rate fluctuation, the LF component can be defined as a frequency domain centering around the peak near 0.1 Hz and is thought to be controlled by the autonomic nervous system, mainly by the sympathetic nervous system (10). Therefore, the fluctuation in class 32 is thought to represent the fluctuation of the fetal autonomic nervous system, in which the sympathetic nervous system plays a main part. On the other hand, the gamma distribution has a distribution structure comprising logarithmic sums of irregular processes. This seems to be related to the fact that a stimulus and a sensation are logarithmically related to each other. In other words, this is probably because $\nu$ stimuli from the center accumulate in an effector and then appear as class 32 fluctuation. The temporal universality of this parameter will be attributable to the fact that the amount of maximum excitation achievable at a time and the amount of accumulation of stimuli to which an effector is responsive in a steady state are fixed as thresholds of the effector in the control mechanism of a living body. The above relation is found to have changed in the acidemia group, probably because the relation between the stimuli from the center and the circulation control mechanism has undergone a change in serious fetal distress. Two possible causes of this are 1) the circulation control mechanism attempts to cope with the worst situation by lowering the thresholds to the stimuli from the center compromised in fetal distress, compared with those in a steady state, or 2) simply organic changes, that is, whereas small fluctuations that are the manifestation of the uncontrolled effector itself ordinarily appear as the mode, large maximum amplitude values sometimes appear via another control mechanism that copes with an emergency. The significance of $\nu$ not being an integer is unknown. However, this is presumably because the
stimuli from the center and the circulation control mechanism are nonstationary in nature.

The mode in class 32 increased noticeably with the gestational age of the fetus concerned in the normal group; it decreased significantly with the seriousness of distress in the fetal distress group ranging from 26 to 34 wk of gestation. Currently available fetal distress monitors are limited in application during these early weeks of gestation. Because fetal distress at these early weeks of gestation has come to be associated with neonatal brain dysfunction, the mode is expected to play an important part clinically as well.

The analysis of heart rate fluctuation using wavelet transform is thought to be useful in chaos analysis, fractal structure analysis, and other nonlinear characteristic analyses of a time series (4). Other means of time-frequency analysis include short-time Fourier transform (STFT) and Wigner distribution. In comparison, wavelet transform excels in time resolution and fractal structure analysis. It is inferior to STFT in frequency resolution, which shows, however, that it is superior in time resolution. Because of the relativity of the frequency window and the time-base window, the product of these two measures is constant. In addition, wavelet transform assumes the enlargement and/or reduction of the mother wavelet function. As such, it is more suited for the analysis of a nonstationary structure than the Wigner distribution, which assumes double autocorrelation, or STFT, which requires multiplication by a certain window. In the thesis mentioned earlier, Ivanov et al. (9) studied class 8 in light of temporal changes of respiratory fluctuation (HF) for its amplitude distribution. They used a Gaussian function as a mother wavelet and Hilbert transform to determine the amplitude of the class. Although the precision of transform is greatly influenced by the appropriateness of a mother wavelet function to the object to be analyzed, no general algorithm is available to determine which mother wavelet function is the most appropriate to a particular time series. The complex modulated Gaussian function is often used in analyzing wavelet transform, and spline 4 is often used in discrete wavelet transform, as in the present study, because they have a relatively short operation sequence, resembling a localized trigonometric function in form, and they have a smaller analysis window for temporal frequency. Hilbert transform was not used to determine the amplitude in the present study. In the data sampling from the fetus suffering from asphyxia, Hilbert transform was unsuitable when a long sampling time was not allowed. It was mostly limited to a time shorter than 1 h. Determining the tertiary moving average of the absolute value, as in the present study, corresponds to determining the effective value of an alternating current in the theory of alternating current circuitry.

Compared with the method of Ivanov et al. (9), in which the maximum value of the distribution was used for standardization, our expression is fundamentally based on the representation by the percent amplitude with respect to the maximum amplitude of the class. This representation provides an easier means of understanding in a physiological sense and facilitates determination of the distribution parameter. Therefore, the equation used to determine ε from the most frequent percent value N was obtained quite simply from an equation expressing the value of the apex in the gamma distribution.

In the present study, we succeeded in elucidating in detail the nonstationary structure of the time series of heart rate fluctuation of the gamma distribution. Thus there is now a possibility that a nonlinear structure between the stimuli from the nervous center and the circulation control mechanism will be elucidated in detail. Because it is suggested that this structure will change if a human fetus should develop acidemia, clinical application of these findings and further elucidation of the nonstationary structure of fetal heart rate fluctuation are expected in the future.

This work was partly supported by a research grant from the Ministry of Education of Japan.

Address for reprint requests: K. Okamura, Dept. of Obstetrics and Gynecology, Tohoku Univ. School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.

Received 24 November 1997; accepted in final form 17 August 1998.

REFERENCES


