A Consistent Abnormality in the Average Local Smoothness of Fetal Heart Rate in Growth-Restricted Fetuses Affected by Severe Pre-Eclampsia

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An abnormality in cardiovascular regulation during the prenatal period has been suggested to be the pathophysiological link between fetal growth restriction and adult hypertension. The purpose of this study was to determine how consistently abnormal the local smoothness of the very-short-term heart rate is in growth-restricted fetuses associated with severe pre-eclamptic pregnancy. Multifractal Hurst analysis on the structure function of heart rate was performed in control fetuses \( n = 150 \), in fetuses affected by severe pre-eclampsia and not showing growth restriction \( n = 66 \) and in fetuses affected by severe pre-eclampsia and showing growth restriction \( n = 58 \). The very-short-term ( \( \leq 15 \) heart beats) generalized Hurst exponents of the order of - 5 to 5 in three groups were compared. Each exponent quantifies an average local heart rate smoothness at 15-successive-heart rate sites, which were specified by the magnitude of the heart rate variation within the sites determined by and positively correlated with the order of the exponent. This means that the fetal heart rates within the sites of \( q \geq 2 \) have a large fetal heart rate (FHR) variation, and those within the sites of \( q \leq -2 \) have a small FHR variation. In the fetuses affected by severe pre-eclampsia and not showing growth restriction, only values of the exponents of the order \( \geq 2 \) were abnormally lower. In the fetuses affected by severe pre-eclampsia and showing growth restriction, the values of the exponents of all orders were abnormally lower. In conclusion, the local smoothness of heart rate is consistently abnormal regardless of the magnitude of heart rate variation within a very-short-term period in growth-restricted fetuses affected by severe pre-eclampsia. (Hypertens Res 2004; 27: 911–918)

**Key Words:** multifractal analysis, heart rate dynamics, intrauterine growth restriction

**Introduction**

Growth restriction (GR) in fetuses has attracted a great deal of attention in medical fields outside obstetrics, since it has been linked with adult systemic cardiovascular diseases, including hypertension (1, 2). Animal studies have shown that adult hypertension in growth-restricted fetuses is due to cardiovascular dysregulation during the prenatal period (3–6). In order to clarify the fetal origin of adult hypertension in humans, extensive studies on the cardiovascular dysregulation during the prenatal period are needed. Furthermore, since in humans the etiology of the GR is diverse, such investigations should be individualized according to the etio-
Pre-eclampsia was defined as a blood pressure greater than 140/90 mmHg on two or more occasions at least 6 h apart during bed rest induced by pregnancy after the 20th week of gestation with persistent proteinuria, exceeding 300 mg in 24 h or 1+ on a reagent strip. Severe pre-eclampsia was defined as pre-eclampsia with at least one of the following characteristics: blood pressure (≥160/110 mmHg), proteinuria (≥500 mg/24 h or 2+ on a reagent strip, oliguria below 400 ml/24 h, a cerebral or visual disturbance, an epigastric or a right upper quadrant pain, an at least two-fold elevation of the liver enzymes, a platelet count below 100,000/mm³, pulmonary edema, or a fetal GR (24). The inclusion criteria were the absence of any history of cardiovascular disease, renal disease or diabetes mellitus; absence of a history of recreational-drug or cigarette use; a singleton fetus; and absence of evidence of a fetal anomaly or infections. The gestational age was estimated by the date of the last menstrual period and ultrasonography. A fetal GR was defined in cases in which the fetus was below the tenth percentile of the birth weight for gestational age (25). Informed consent was obtained from the pregnant mothers and the study was approved by the Institutional Review Board. The investigation also conformed with the principles outlined in the Declaration of Helsinki.

Data Collection

The data were recorded for more than 40 min with the mothers in a semirecumbent position using a Corometrics 115 external monitor (Corometrics, Minster, USA). The mothers were not in labor and not taking any medication that had any cardiovascular effect during the measurement period. The recorded data (FHR, uterine contraction, and fetal movements) were sampled into a personal computer with a digital serial interface. Whenever missing data were found, they were recorded as being zero. When the off-line FHR data was zero (missing data) or below 60 beats per min (bpm) or above 200 bpm, it was excluded. The 3,000 successive FHR sequences where the fetal movements were included were used (Fig. 1).

Multifractal Hurst Analysis

t-th FHR was denoted as \( y(t) \), and the non-overlapping fluctuations of the difference in the structure function of FHR, \( \Delta y(t) = y(t + \tau) - y(t) \) for different time increments \( \tau \), is the number of successive heartbeats, was calculated (14, 18, 19). The \( \Delta y(t) \) is the magnitude of the local FHR variation across the \( \tau \)-heartbeats long region in the FHR. In order to perform a multifractal analysis, this study estimated the statistical moments of these local variations, which depended on the time increment in a scaling way as follows:

\[
\langle |\Delta y(t)|^\alpha \rangle \sim \tau^{\mu(q)\alpha},
\]

In order to quantify the scaling behavior of the \( \langle |\Delta y(t)|^\alpha \rangle \).
it was plotted for log₂ (τ) = 1, ..., 10 and q = -5, -4, -3, -2, -1, 1, 2, 3, 4, 5. The scaling region was then obtained and the slopes of the \( <\Delta y(t)> \) were calculated against τ at the scaling region, which yielded a \( q^*H(q) \). The \( H(q) \) (q ⊆ 0) is the generalized Hurst exponent. The \( H(1) \) is the parameter characterizing the average smoothness or the temporal correlation in a time series.

As previously demonstrated, when the values of log₂(<\Δy(t)> vs. log₂τ (Fig. 2) were plotted, two distinct linear scaling relations could be observed at 4 ≤ τ ≤ 80 heartbeats, and the separations of the linear scaling behavior happened at approximately τ < 16 heartbeats. Therefore, very-short-term and short-term generalized Hurst exponents \( H_α(q), \) τ ≤ 15 heartbeats, and \( H_β(q), \) 16 heartbeats ≤ τ ≤ 80 heartbeats, respectively) could be obtained from Eq. (1). This study considered only the very short-term generalized Hurst exponent \( H_α(q) \), which is denoted as \( H_α \) for convenience.

**Statistical Method**

A Kruskal-Wallis test was performed to compare the differences in each very-short-term generalized Hurst exponent as well as other heart rate indices among the control, sPE, and sPEGR groups, with a Mann-Whitney rank-sum test being used to assess any significant differences identified. A Fish-
er’s exact test was used to examine significant statistical differences in the incidence of urine protein ≥2 between the two groups. All statistical analyses used SAS (version 8.01; SAS Institute, Cary, USA) and all data were presented as the median (interquartile range).

**Results**

It was determined that the structure function $\Delta y(t)$ is the magnitude of the FHR variation across the number of successive heartbeats $\tau$. It was also found that when $q≥2$, the $\Delta y(t)^q$ in Eq. (1) markedly amplifies the large $\Delta y(t)$ values, which are values of the large magnitude of the FHR variation, and less markedly amplifies the small $\Delta y(t)$ values, which are values of small magnitude of FHR variation. Consequently, the very-short-term generalized Hurst exponents whose order $q≥2$ ($H_{2a}$, $H_{3a}$, $H_{4a}$, and $H_{5a}$) captures the average local smoothness at 15-successive-FHR sites within which there is a large FHR variation. Moreover, as the positive order, $q$, increases, the exponent of the order captures the average local smoothness at the 15-successive-FHR sites where there is a larger FHR variation within the sites (for example, $H_{2a}$ captures the average local smoothness at the 15-successive-FHR sites distinctly where there is a FHR variation of ≥20 bpm as shown in Fig. 2). The mathematical method used to determine the exact magnitude of the FHR variation for each exponent of a positive order was beyond the scope of this paper and is not presented in this report. When $q≤ -2$, the $\Delta y(t)^q$ values in Eq. (1) markedly reduce the small $\Delta y(t)$ values and less markedly reduce the low $\Delta y(t)$ values. Consequently, the exponents whose order is $H_{-2a}$, $H_{-3a}$, $H_{-4a}$, and $H_{-5a}$) measure the average local smoothness at the 15-successive-FHR sites with a small FHR variation within the sites. Moreover, as the negative order, $q$, becomes increasingly negative, the exponent of the order captures the average local smoothness at the 15-successive-FHR sites with smaller FHR variation (for example, $H_{-2a}$). The sPEGR group showed a significant decrease in all the exponents compared to the control group and the sPE group.

Figure 1a, b, and c shows three FHR time series obtained at 38 weeks of gestation from a sample fetus from the normal control group (a), a sample fetus of the sPE group (b), and a sample fetus of the sPEGR group (c). Each solid arrow indicates a representative local 15-successive-FHR site with a large magnitude variation of approximately 20 bpm within the site. Each dotted arrow indicates a local 15-successive-FHR site within which there is a small FHR variation of 4 bpm. Figure 1d, e, and f shows the enlarged versions of the three representative local 15-successive-FHR sites indicated by the solid arrows in Fig. 1a, b, and c, respectively. The local FHR smoothness values at the three sites differ from each other, although the magnitude of the local FHR variation is large (approximately 20 bpm). The local smoothness in the

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**Fig. 2.** a, b, c: Multifractal Hurst analyses of the structure function, $<\Delta y(t)^q>^{H_q}$ of the FHR time series shown in Fig. 1a, b, and c, respectively. Figure 1a shows the analysis for normal fetuses, Fig. 1b that in fetuses affected by severe pre-eclampsia and not showing growth restriction (GR), and Fig. 1c that in fetuses affected by severe pre-eclampsia and showing GR. Two linear scaling regions, the very-short-term range (4 ≤ $\tau$ ≤ 15 heartbeats) and the short-term range (16 ≤ $\tau$ ≤ 80 heartbeats) are indicated. Note that, in the fetus affected by severe pre-eclampsia and showing GR (c), there is a consistent decrease in the steepness of the linear slope for any $q$ at the very-short-term range compared to the normal fetus (a).
Table 1. Clinical Profile of Each Group

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 150)</th>
<th>sPE (n = 66)</th>
<th>sPEGR (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28 (27–30)</td>
<td>29 (27–32)</td>
<td>29 (27–36)</td>
</tr>
<tr>
<td>Nullipara (%)</td>
<td>53.4</td>
<td>57.9</td>
<td>69.6*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120 (110–125)</td>
<td>160 (160–165)***</td>
<td>170 (160–175)<em><strong>.</strong></em></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 (70–85)</td>
<td>110 (110–110)***</td>
<td>115 (110–125)<em><strong>.</strong></em></td>
</tr>
<tr>
<td>Urine protein≥2 + (%)</td>
<td>0</td>
<td>68.2***</td>
<td>81.3***</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth</td>
<td>38.5 (35–39)</td>
<td>36.5 (35–39)</td>
<td>37.0 (34.0–38.0)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,230 (3,030–3,490)</td>
<td>2,755 (2,180–3,210)***</td>
<td>2,020 (1,675–2,395)<em><strong>.</strong></em></td>
</tr>
</tbody>
</table>

Values are medians (interquartile ranges). sPE, fetuses affected by severe pre-eclampsia and not showing growth restriction (GR); sPEGR, fetuses affected by severe pre-eclampsia and showing GR; BP, blood pressure. * p<0.01, *** p<0.0001 compared with control group. □□□ p<0.0001 compared with sPE group.

Table 2. Statistics of the Very-Short-Term (≤15 Heartbeats) Generalized Hurst Exponents (H_q)

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 150)</th>
<th>sPE group (n = 66)</th>
<th>sPEGR group (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (bpm)</td>
<td>144 (138–148)</td>
<td>142 (135–148)</td>
<td>143 (138–146)</td>
</tr>
<tr>
<td>SD (bpm)</td>
<td>6.0 (4.7–7.6)</td>
<td>6.7 (5.5–7.8)</td>
<td>6.0 (4.3–7.0)</td>
</tr>
<tr>
<td>H_{-5α}</td>
<td>0.068 (0.055–0.081)</td>
<td>0.067 (0.055–0.084)</td>
<td>0.053 (0.041–0.072)***.□□</td>
</tr>
<tr>
<td>H_{-4α}</td>
<td>0.083 (0.066–0.098)</td>
<td>0.082 (0.067–0.103)</td>
<td>0.064 (0.049–0.087)***.□□</td>
</tr>
<tr>
<td>H_{-3α}</td>
<td>0.104 (0.082–0.124)</td>
<td>0.104 (0.085–0.130)</td>
<td>0.0794 (0.058–0.110)***.□□</td>
</tr>
<tr>
<td>H_{+2α}</td>
<td>0.132 (0.100–0.161)</td>
<td>0.133 (0.106–0.169)</td>
<td>0.097 (0.060–0.138)***.□□</td>
</tr>
<tr>
<td>H_{+1α}</td>
<td>0.146 (0.105–0.190)</td>
<td>0.141 (0.109–0.204)</td>
<td>0.096 (0.058–0.158)***.□□</td>
</tr>
<tr>
<td>H_{1α}</td>
<td>0.515 (0.473–0.557)</td>
<td>0.505 (0.451–0.547)</td>
<td>0.462 (0.405–0.518)***.□□</td>
</tr>
<tr>
<td>H_{2α}</td>
<td>0.481 (0.431–0.521)</td>
<td>0.456 (0.394–0.501) *</td>
<td>0.396 (0.346–0.461)***.□□</td>
</tr>
<tr>
<td>H_{3α}</td>
<td>0.435 (0.385–0.489)</td>
<td>0.392 (0.332–0.476) *</td>
<td>0.323 (0.264–0.408)***.□□</td>
</tr>
<tr>
<td>H_{4α}</td>
<td>0.386 (0.326–0.454)</td>
<td>0.332 (0.282–0.421) *</td>
<td>0.272 (0.200–0.365)***.□□</td>
</tr>
<tr>
<td>H_{5α}</td>
<td>0.350 (0.279–0.430)</td>
<td>0.293 (0.252–0.384) *</td>
<td>0.236 (0.161–0.313)***.□□</td>
</tr>
</tbody>
</table>

Values are medians (interquartile ranges). sPE, fetuses affected by severe pre-eclampsia and not showing growth restriction (GR); sPEGR, fetuses affected by severe pre-eclampsia and showing GR. Mean: mean heart rate; SD: SD of heart rate. * p<0.01, *** p<0.0001, compared with control group. □ p<0.01, □□ p<0.001, □□□ p<0.0001 compared with sPE group.

sample fetus of the sPEGR group (Fig. 1f) appears to be lower than that of the sample fetus from the control group (Fig. 1d). This is because the FHR of the former fetus increases discontinuously and abruptly compared to the FHR of the latter fetus, which increases continuously and gradually. The local smoothness of the sample fetus from the sPE group (Fig. 1e) also appears to be lower than that of the sample fetus from the control group, although the decrease is not as apparent as that of the sample fetus from the sPEGR group.

Figure 1g, h, and i shows enlarged images of the three local 15-successive-FHR sites indicated by the dotted arrows in Fig. 1a, b, and c, respectively. Each site contains a small FHR variation of 4 bpm. In the sample fetus from the sPEGR group (Fig. 1i), the local smoothness appears abnormally lower compared to that of the sample fetus from the control group (Fig. 1g). This is because the FHR of the former fetus oscillates rapidly in a saw-tooth manner, while the FHR of the latter fetus changes gradually. However, the local smoothness of the sample fetus from the sPE group (Fig. 1h) appears to be similar to that in the sample fetus from the control group (Fig. 1g).

Accordingly, on a visual inspection, in the sample fetus of the sPEGR group, the local smoothness decreases abnormally not only at the site with a large FHR variation but also at the site with a small FHR variation. The consistent abnormal decrease is corroborated by the reduced steepness of the slope of $\log_{2} \langle \Delta y(t) \rangle$ against $\log_{2} \tau$ at the very-short-term range not only for $q \geq 2$ but also for $q \leq -2$ (Fig. 2c) compared to those of the sample fetus from the control group (Fig. 2a). As previously shown, $q \geq 2$ and $q \leq -2$ correspond to the sites with a large FHR variation and the sites with a small FHR...
variation, respectively. The consistent decrease is quantitatively confirmed by both the lower $H_{sa}$ value and the lower $H_{-2a}$ value (0.189 and 0.123, respectively) compared to those (0.401 and 0.231, respectively) of the sample fetus from the control group.

In contrast, in the sample fetus of the sPE group, the steepness of the slopes of $log_{10} <\Delta y(t)\rangle$ against $log_{10}\tau$ in the very-short-term range is abnormally lower only for $q \geq 2$. This also corroborates the visual inspection, which showed that an abnormal decrease in local smoothness is inconsistent since it does not occur at the sites with a small FHR variation but occurs only at the sites with a large FHR variation. The inconsistent decrease is quantitatively confirmed by the lower $H_{sa}$ value (0.239 vs. 0.401) and similar $H_{-2a}$ value (0.239 vs. 0.231) compared to those of the sample fetus from the control group.

**Discussion**

The very-short-term generalized Hurst exponents allowed the average local smoothness of the FHR to be measured at distinct 15-successive-FHR sites with the magnitude of the FHR variation specified by the order of the exponent. When the average local smoothness of FHR is measured at the exclusive sites with a large FHR variation, only values of the exponents of a positive order $\geq 2$ should be considered. In contrast, when the average local smoothness of FHR is measured exclusively at the sites with a small FHR variation, only values of the exponent of order $\leq 2$ should be considered.

A main finding in this study was that in fetuses affected by severe pre-eclampsia and not showing GR, only the values of the exponents of order $\geq 2$ ($H_{2a}$, $H_{1a}$, $H_{sa}$, and $H_{ao}$) decreased abnormally. The second and more important main finding was that in fetuses affected by severe pre-eclampsia and showing GR, the values of all the exponents regardless of the order ($H_{-2a}$, ..., $H_{ao}$) decreased abnormally.

These findings indicate that, in fetuses affected by severe pre-eclampsia and not showing GR, the average local smoothness is inconsistently and abnormally low only at 15-successive-FHR sites with a large FHR variation. In contrast, in fetuses affected by severe pre-eclampsia and showing GR, the average local smoothness of FHR at 15-successive-FHR sites with any magnitude of FHR variation is consistently and abnormally low.

The 15-successive-FHR sites correspond to a very-short-term period with a duration of approximately 6.29 s, since $15 \uplus 60/143 \approx 6.29$, where 143 is the average FHR (Table 2). The local smoothness at the 15-successive-FHR sites is determined by the very-short-term regulation of the FHR smoothness. An abnormal average local smoothness at the 15-successive-FHR sites with a certain magnitude of an FHR variation indicates an abnormality in the very-short-term regulation of the FHR smoothness at the very-short-term periods with the magnitude of FHR variation. Accordingly, the above-described major findings suggest that in fetuses affected by severe pre-eclampsia and not showing GR, the very-short-term regulation of the FHR smoothness can be inconsistently abnormal only during the very-short-term periods with a large FHR variation. In contrast, in fetuses affected by severe pre-eclampsia and showing GR, the very-short-term regulation of the FHR smoothness can be consistently abnormal during the very-short-term periods with any magnitude of FHR variation.

During the fetal life, the magnitude of the FHR variation at the 15-successive-sites or during the very-short-term periods reflects the fetal activity: A large magnitude of the FHR variation occurs only during the gross fetal movement. A small magnitude of the FHR variation, such as the magnitude of a baseline FHR variability, occurs only during fetal sleep or rest. Accordingly, in fetuses affected by severe pre-eclampsia and not showing GR, the very-short-term regulation of the FHR smoothness can be abnormal only during gross fetal movement. In contrast, in the fetuses affected by severe pre-eclampsia and showing GR, the very-short-term regulation of FHR smoothness can be consistently abnormal during any type of fetal activities.

The very-short-term regulating mechanism that determines the local smoothness at the 15-successive-FHR sites must be the autonomic nervous control—specifically, the parasympathetic nervous control. This is because the local smoothness is determined by the fast oscillations of the FHR, which occur within 15-successive-FHR and whose frequency is larger than 0.158 Hz ($>1/6.29 = 0.158$ Hz). Such a very fast oscillation can be modulated only by the parasympathetic nervous system. Accordingly, the consistent abnormality in the average local smoothness seen in the fetuses affected by severe pre-eclampsia and showing GR suggests a consistent abnormality in the autonomic nervous control of FHR.

This study demonstrated that, in the prenatal life of fetuses affected by severe pre-eclampsia and showing GR, there is a consistent abnormality in the average local smoothness of the heart rates and the very-short-term regulation of the heart rate smoothness. The consistent abnormality indicates that during prenatal life, the very-short-term heart rate-regulating mechanisms may be abnormally set to operate in a range of abnormally lower local smoothness values. The abnormal setting during the sensitive period of the ontogeny of the heart rate-regulating network might prevent the normal, healthy ontogeny. The injured prenatal network develops into postnatal life with an instability to easily operate in the abnormal range even in later life. It is not clear whether the consistent abnormality during the prenatal life is a prequel to adult hypertension. If the fetuses with the consistent abnormality are associated with the clustering of multiple risk factors of hypertension in their postnatal life, the risk of development of adult hypertension may be further increased (26). Many studies on adult hypertensive patients show an abnormality in the regulation of the very-short-term heart-rate be-
behavior, such as the baroreflex control or the parasympathetic nervous control (27–30). This study suggests that this abnormality may be programmed early in utero if the patients are fetuses affected by severe pre-eclampsia and showing GR.

In conclusion, the very-short-term generalized Hurst exponent quantifies the average local smoothness at the 15-successive-FHR sites with the specified magnitude of the FHR variation, which was determined by and positively correlated with the order of the exponent. In the fetuses affected by severe pre-eclampsia and not showing GR, only the values of the exponents of order ≥ 2 were abnormally lower. In fetuses affected by severe pre-eclampsia and showing GR, the values of the exponents of all orders were consistently and abnormally lower. Unlike in the fetuses affected by severe pre-eclampsia and not showing GR, the average local smoothness at 15-successive-FHR sites with any magnitude of FHR variation in the fetuses affected by severe pre-eclampsia and showing GR was consistently abnormal. This suggests that during prenatal life, the very-short-term regulation of the heart rate smoothness can be consistently abnormal regardless of the magnitude of the heart rate variation within the very-short-term periods in the growth-restricted fetuses affected by severe pre-eclampsia.

References


