Preeclamptic pregnancy is associated with increased sympathetic and decreased parasympathetic control of heart rate

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Yang, Cheryl C. H., Te-Chang Chao, Terry B. J. Kuo, Chang-Sheng Yin, and Hsing I. Chen. Preeclamptic pregnancy is associated with increased sympathetic and decreased parasympathetic control of heart rate. Am J Physiol Heart Circ Physiol 278: H1269–H1273, 2000.—Previous work from our laboratory using heart rate variability (HRV) has demonstrated that women before menopause have a more dominant parasympathetic and less effective sympathetic regulations of heart rate compared with men. Because it is still not clear whether normal or preeclamptic pregnancy coincides with alternations in the autonomic functions, we evaluated the changes of HRV in 17 nonpregnant, 17 normotensive pregnant, and 11 preeclamptic women who were clinically diagnosed without history of diabetic neuropathy, cardiac arrhythmia, and other cardiovascular diseases. Frequency-domain analysis of short-term, stationary R-R intervals was performed to evaluate the total variance, low-frequency power (LF; 0.04–0.15 Hz), high-frequency power (HF; 0.15–0.40 Hz), ratio of LF to HF (LF/HF), and LF in normalized units (LF%). Natural logarithm transformation was applied to variance, LF, HF, and LF/HF for the adjustment of the skewness of distribution. We found that the normal pregnant group had a lower R-R value and HF but had a higher LF/HF and LF% compared with the nonpregnant group. The preeclamptic group had lower HF but higher LF/HF compared with either the normal pregnant or nonpregnant group. Our results suggest that normal pregnancy is associated with a facilitation of sympathetic regulation and an attenuation of parasympathetic influence of heart rate, and such alterations are enhanced in preeclamptic pregnancy.

heart rate variability; power spectral analysis; parasympathetic activity; sympathovagal balance

A LEADING CAUSE OF MATERNAL and neonatal death worldwide, preeclampsia is a syndrome that arises in pregnancy and is diagnosed by increased arterial pressure and proteinuria. A lot of tests have been recommended to predict or identify the woman at risk for future production of preeclamptic pregnancy. The pathophysiological mechanisms underlying this disorder are not completely understood. Airaksinen et al. (1) suggest that impairment of the autonomic nervous system (ANS) functions may be the cause of preeclampsia. For this variable, however, women with preeclampsia have been reported to have higher (7, 21), lower (28), or similar (23) concentrations of plasma catecholamines compared with those levels in normal pregnancy. Other ANS tests have also revealed contradictory conclusions for preeclampsia (1, 8). It is still a debate whether preeclampsia pregnancy is associated with disturbance in the sympathetic and/or parasympathetic functions.

Frequency-domain analysis of heart rate variabilities (HRV) is a sophisticated, albeit noninvasive, tool for the detection of ANS regulation of the heart. It has been well established that HRV can be categorized into high-frequency (HF, 0.15–0.40 Hz) and low-frequency (LF, 0.04–0.15 Hz) components according to its oscillating frequency and developing mechanism (27). The HF component is equivalent to the well-known respiratory sinus arrhythmia (RSA) and is considered to represent parasympathetic control of heart rate (11). The LF component is jointly contributed to by both sympathetic and parasympathetic nerves (3). The ratio LF/HF is considered by some investigators to mirror sympathovagal balance (2, 20) or to reflect the sympathetic modulations (19, 20, 22, 27). Because it is accessible, frequency-domain analysis of HRV has gained its popularity with broad application as a functional indicator of the ANS. Previous work from our laboratory has demonstrated that such a technique has the sensitivity to detect the effects of gender, aging, and even critical illness on changes in ANS activities (16, 32). In particular, we have noted that women before menopause have more dominant parasympathetic and less effective sympathetic regulations of heart rate compared with men (16). In the field of gynecology, HRV is especially suitable for pregnant women because it is virtually noninvasive and produces the least stress on mother and infant. Because it is still not clear whether normal or preeclamptic pregnancy coincides with alterations in the autonomic functions, we applied the standard method of short-term HRV analysis defined recently (16, 27) to evaluate the ANS functions in preeclamptic, normotensive pregnant, and nonpregnant women. This study tests the hypothesis that HRV analysis is capable of detecting the changes in sympathetic and parasympathetic controls of heart rate in normal and preeclamptic pregnancies.

MATERIALS AND METHODS

Study sample and experimental setup. A total of 45 young women were enrolled in this study: 11 women with preeamp-
sia; 17 normotensive pregnant women matched with the preeclampsia group for age, week of gestation, and body weight; and 17 normotensive nonpregnant women of similar age (Table 1). Preeclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy (6). These criteria include no history of hypertension, cardiovascular, or renal diseases before pregnancy and arterial pressure values $140/90$ mmHg after the 20th wk of gestation, confirmed by two consecutive readings at least 6 h apart, with arterial pressure reverting to normal within 2 mo after delivery. Arterial pressure was measured by sphygmomanometry. All women with preeclampsia had proteinuria of $300$ mg/24 h or $1$ g/l in a random urine sample. We excluded subjects with diabetic neuropathy, cardiac arrhythmia, or other cardiovascular diseases that affect HRV (19). Drugs that have been reported to affect cardiovascular fluctuations, such as hypnotics or autonomic blockers, were not used. An informed consent was obtained from each participant.

Processing of electrocardiogram signals. The detailed procedures for HRV analysis have been reported previously (16). In brief, precordial electrocardiogram (ECG) was taken for 5 min in the daytime, while each subject lay quietly and breathed normally. The raw ECG signals were recorded using an 8-bit analog-to-digital converter with a sampling rate of 256 Hz. The digitized ECG signals were analyzed on-line and were simultaneously stored on a hard disk for off-line verification. The signal acquisition, storage, and processing were performed on a IBM portable PC compatible computer. Our computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template. The stationary R-R values were resampled and interpolated at the rate of 7.11 Hz to accomplish the continuity in time domain.

Frequency-domain analysis of HRV. Frequency-domain analysis was performed using a nonparametric method of fast Fourier transform (FFT). The DC component was deleted, and a Hamming window was used to attenuate the leakage effect (15). For each time segment (288 s, 2048 data points), our algorithm estimated the power spectral density based on FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window (26). The power spectrum was subsequently quantified into standard frequency-domain measurements as defined previously (27), including total variance, LF (0.04–0.15 Hz), HF (0.15–0.40 Hz), LF/HF, and LF%. Variance, LF, HF, and LF/HF are logarithmically transformed to correct the skewness of distribution (16).

Statistical methods. Values are expressed as means ± SE. Data between groups were compared by ANOVA followed by Duncan’s multiple-range tests for a posteriori comparison of individual means. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The systolic and diastolic blood pressures were significantly higher in women with preeclampsia compared with normal pregnant and nonpregnant women (Table 1). Time-domain analysis of successive R-R values from a nonpregnant woman revealed a prominent RSA fluctuating around a mean R-R value of 800 ms in a 5-min time window (Fig. 1A). Frequency-domain analysis of the R-R series provided a more detailed observation of HRV. The woman with

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age, yr</th>
<th>Body Height, cm</th>
<th>Body Weight, kg</th>
<th>Gestational Age, wk</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17</td>
<td>29 ± 1</td>
<td>160 ± 1</td>
<td>55 ± 1</td>
<td>108 ± 3</td>
<td>68 ± 2</td>
<td></td>
</tr>
<tr>
<td>Normal pregnancy</td>
<td>17</td>
<td>28 ± 1</td>
<td>160 ± 1</td>
<td>69 ± 3*</td>
<td>34 ± 1</td>
<td>69 ± 2</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>11</td>
<td>30 ± 1</td>
<td>158 ± 1</td>
<td>75 ± 5*</td>
<td>35 ± 1</td>
<td>97 ± 2‡</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as means ± SE; n is no. of subjects/group. SBP, systolic blood pressure; DBP, diastolic blood pressure. *$P < 0.05$ vs. control group, †$P < 0.05$ vs. normal pregnancy group in Duncan test.

Fig. 1. Condensed tracing of 5-min R-R intervals and corresponding power spectral density (PSD) in frequency domain from a control nonpregnant woman (A), a normal pregnant woman (B), and a preeclamptic pregnant woman (C).
a normotensive pregnancy had a similar pattern of R-R values in time domain with a lower mean and smaller amplitude of RSA (Fig. 1B). Although LF and HF of the normal pregnant woman could be clearly identified by frequency-domain analysis, their powers were smaller compared with the nonpregnant woman. A more dramatic change of HRV was observed in the case of preeclampsia (Fig. 1C). The R-R intervals were generally small without overt RSA in the time domain. Frequency-domain analysis showed that both LF and HF were significantly suppressed. It was also noted that the LF became the dominant component over the whole spectrum. Figure 2 provides the quantitative analysis of the standard frequency-domain parameters of HRV, including LF, HF, LF/HF, and LF% from the three groups of this study. We found that the preeclamptic group had significantly lower variance and HF, but higher LF/HF compared with either normal pregnant or nonpregnant group. In addition, the normal pregnant group had significantly lower R-R and HF and higher LF/HF and LF% compared with the nonpregnant group.

DISCUSSION

Although frequency-domain analysis of HRV has been applied for more than 20 years (13), a standard procedure and interpretation have not been well defined until 3 years ago (27). In that extensive report, both absolute and relative measurements of HRV were considered as functional indicators of ANS control of heart rate. The absolute measurements are largely influenced by vagal function, the relative measurements are effected through sympathetic activity. Our previous study further demonstrated that despite having a likely normal distribution in some relative measurements (e.g., LF%) all absolute measurements of HRV had a distribution skewed severely to the right. The skewness could be corrected by a logarithm transform (16). Such idea was first applied in the present study to detect the change of ANS functions in normal and preeclamptic pregnancies. We analyzed the neural regulation of heart rate by the standard methodology of frequency-domain HRV analysis. Our results suggest that normal pregnancy is associated with a facilitation of sympathetic regulation and an attenuation of parasympathetic influence of heart rate, and such alterations are enhanced in preeclamptic pregnancy. This study provides a more detailed description of the changes in the ANS functions during physiological and pathological states of pregnancy using a noninvasive method of HRV analysis.

It has been reported that HRV at supine rest in a quiet and relaxing atmosphere can be used as assessment of vagal control of heart rate (11). More recently, transfer function analysis has shown that vagal control of heart rate can extend to both HF and LF. The sympathetic control, however, is limited to the LF component because of its frequency response (3). Therefore, the absolute value of the HF component in this study is considered to represent vagal control of heart rate, and LF jointly contributed by sympathetic and parasympathetic nerves. Relative measurements (LF/HF and LF%) appear to provide quantitative evaluations of graded changes in the state of sympathovagal balance (2, 20). LF% and LF/HF have also been considered by previous investigators to reflect sympathetic and parasympathetic function (2, 20, 22, 27).

It is interesting to note that preeclamptic pregnancy is associated with higher sympathetic but lower parasympathetic control of heart rate. For the peripheral vascular resistance, patients with preeclampsia have been shown to have a higher excitability of sympathetic function (5, 24). With the technique of muscle sympathetic nerves recording, Schobel et al. (25) suggested that preeclampsia is a state of sympathetic overactivity, which reverts to normal after delivery. Øian et al.
(21) reported that in the preeclamptic group, arterial epinephrine was significantly increased, which was correlated with mean arterial pressure and heart rate. For the vagal system, the finding of higher heart rate (18) and diminished heart rate fluctuation by a deep breathing test has suggested an impairment of vagal reflex in preeclampsia (1). This is later supported by the frequency-domain analysis (10). Although individual change in sympathetic and parasympathetic systems has been reported, few have been documented for the coexistence of the changes in the two systems in preeclampsia. This study first demonstrated that the facilitation of sympathetic function and the attenuation of vagal function could be simultaneously detected by proper analysis of HRV, i.e., frequency-domain analysis coupled with logarithmic transformation. Thus HRV analysis may be an effective technology to detect the distortion in ANS functions during preeclampsia.

In addition to the alterations of ANS function in preeclampsia, our data also revealed significant differences in ANS functions between normal pregnant and nonpregnant states. It is interesting to note that the normal pregnant women exhibited a lower parasympathetic but higher sympathetic indexes compared with the nonpregnant women. The changes in ANS function during normal pregnancy have been noted in an animal study (4). Kanayama et al. (12) report that a cold-induced stress may evoke the sympathetic activity while producing symptoms of preeclampsia in the pregnant rat. They pointed out that chronic stimulation of the sympathetic system may be the possible cause of preeclampsia. Whether the pathological change in ANS function in preeclampsia is the result of an excessive progression of the normal physiological response during pregnancy warrants further exploration.

The catecholamine concentration has been widely applied as an indicator for sympathetic function. Although arterial epinephrine was shown to increase in preeclampsia (21), several reports revealed a very controversial result in venous catecholamine concentration in patients with preeclampsia (7, 23, 28). It should be noted that the increased arterial plasma catecholamines have been considered as the most reliable biochemical parameter for the increased sympathetic tone in essential hypertension (14). In terms of functional analysis, it is also controversial for the ANS responses during preeclampsia (1, 8). Because traditional tests need to elicit ANS responses through change of arterial pressure by a baroreflex loop, the dysfunction of baroreflex in women with preeclampsia may contribute to the discrepancy of result (31). The pioneer work by Eneroth and Storck (9) and Eneroth-Grimfors et al. (10), using frequency-domain analysis of HRV revealed no significant change in LF from which they interpreted an unchanged sympathovagal balance in preeclampsia. However, evidence has shown that vagal activity is in fact the major contributor of the absolute value of LF with some contribution from the sympathetic activity (3). Thus the standard procedure suggests that LF should be normalized by HF (LF/HF) or total power (LF%) to represent sympathetic activity (19, 20, 22, 27).

Our data reveal that heart rate is higher in the preeclamptic women compared with the normal pregnant women. Because any change in sympathetic or parasympathetic activity may alter heart rate, we cannot determine individual sympathetic or parasympathetic activity from static heart rate value. Thus it is important that frequency-domain analysis may provide additional information of ANS function from HRV. Previous study has revealed that an increase of heart rate due to cholinergic blockade coincides with a decrease of HF without significantly affecting LF/HF (17). On the other hand, LF/HF and LF% are highly correlated with sympathetic discharge (22). The change of ANS function in preeclampsia may result from direct injury to nerve fibers or may be associated with hypertension or latent central nervous system involvement (29, 30).

The progress of medical research is usually accompanied by the development of new technology. For the ANS, various techniques and maneuvers have been developed to detect the function or integrity of sympathetic and parasympathetic systems. At the present time, however, most techniques focus on the evoked response of ANS such as the cold pressor test, Valsalva maneuver, and the tilting table test, etc. These maneuvers induce significant changes in arterial pressure, sympathetic or parasympathetic activity. These tests may be risky for a normal pregnant woman, not to mention for a woman with preeclampsia. Furthermore, the evoked activities may not reflect the spontaneous or tonic state of the body. An important advantage of frequency-domain analysis of HRV is that it utilizes spontaneous fluctuations in heart rate to estimate the tonic ANS functions. Our data demonstrate that the preeclampsia-related changes in ANS control of heart rate, including both sympathetic and parasympathetic divisions, can be detected by a proper analysis of HRV. This is particularly important because the HRV can be measured by a virtually noninvasive procedure, which is a major consideration for the application in pregnant or even preeclamptic women. We suggest that HRV analysis may be a proper tool to detect the physiological or pathological changes of ANS functions during pregnancy.

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