Changes in Circadian Rhythm due to Possibly Sympathetic Nerve Disorders in Patients with Preeclampsia as Assessed by Ambulatory Blood Pressure Monitoring

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Abstract

Objectives: Women with hypertensive disorders of pregnancy (HDP), including both preeclampsia (PE) and gestational hypertension (GH), show fluctuations in BP during the day. This study aimed to assess characteristic changes in BP by Ambulatory blood pressure (BP) monitoring (ABPM) in HDP patients in comparison with PE and GH.

Study design: Among the 106 pregnant women who exhibited hypertension by clinic BP (CBP), 24-hour ABPM were performed. ABPM determined HDP in 79 women (PE, n=43) and GH, n=36), and white coat hypertension (WCH) in 27 women.

Main outcome measures: The following aspects were analyzed with the circadian rhythms of BP and pulse: 1) changes in BP at night-time and 2) multiple regression percent rhythm (PR, correction coefficient by Cosinor analysis).

Results: Mean BP by 24-hour ABPM was higher in women with PE and GH compared to those with WCH. In systolic BP (SBP), most women with PE and GH were riser or non-dipper. Half of the women with PE and GH experienced a loss of circadian rhythm of SBP (PR<0.16). In women with circadian rhythm (PR ≥0.16), normal maximal SBP at daytime (acrophase time from 12:00 to 18:00) was observed in only 9 of 43 women with PE and 9 of 36 women with GH. Furthermore, PR of pulse was lower in women with PE, but not in those with GH or WCH.

Conclusions: Our findings suggest that the circadian rhythm of BP in women with PE may be abnormal due to possibly sympathetic nerve disorders.

Keywords: Preeclampsia; White Coat Hypertension; Circadian Rhythm; ABPM

Introduction

Blood pressure (BP) assessments in pregnant women have traditionally relied on measurements taken in the clinical setting (i.e., clinic BP (CBP)). Ambulatory BP monitoring (ABPM) with a reliable and accurate device is a logical alternative and provides the advantage of absolute BP values, as well as allowing for the analysis of circadian rhythm variations of BP in pregnant women [1,2]. ABPM, as well as home BP measurement (HBPM), may replace or augment CBP in the diagnosis of hypertension.

The Best Practice Guide 2015 for Care and Treatment of Hypertension in Pregnancy set forth by the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) states that there are two environments for measuring BP: under medical settings and non-medical settings (e.g., HBPM and ABPM). 24-hour ABPM can be used to diagnose white coat hypertension (WCH) and masked hypertension, as well as assess the efficiency of anti-hypertensive drugs and circadian variations in BP [3].

Moreover, ABPM has been used previously to predict hypertensive disorders of pregnancy (HDP), in particular, PE [4,5]. It can also be used as a strong predictor of adverse outcomes of pregnancy, such as preterm delivery and fetal growth restriction (FGR) [6,7].

Hypertensive disorders of pregnancy (HDP) is defined as BP ≥140/90 mmHg, with or without proteinuria (≥300 mg/24 h), emerging after 20 weeks gestation, but resolving by up to 12 weeks postpartum [8,9]. It is mainly classified as preeclampsia (PE) or gestational hypertension (GH). GH is diagnosed in women who have hypertension without proteinuria, and conversely, PE is diagnosed when hypertension is accompanied by proteinuria. There are well-characterized differences between the pathogenesis and management of the two disorders.

The circadian rhythms of BP and pulse are obtainable by ABPM. BP is typically higher during the daytime and lower at night in response to the internal clock and mental and physical activities. In contrast to BP in the daytime (daytime BP), it is normal to see a drop in BP of more than 10% at night (night-time BP) in normotensive pregnant women. Most women with severe PE have an attenuated decrease in night-time BP (<10%; non-dipper) or exhibit increases in night-time BP (riser) [10,11].

Cosinor analysis allows for the evaluation of BP variability in HDP and is calculated using MESOR (mean or midline estimating statistic of rhythms), average value of the rhythmic function fitted to the data), amplitude (Amp, one half the extent of change explainable by the rhythmic fitted curve), and acrophase time (AT, crest time expressed as a lag from a designated reference) in HDP. Amp and MESOR are reportedly larger in women with PE compared to normotensive

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Pregnant women [4].

Percent of coefficient variability (%CV), which is calculated using the formula standard deviation (SD)/mean x 100, and differences between maximum BP and minimum BP (ABP), are also indicators of BP variability. Some pathological states reportedly exhibit increased %CV and ABP [12].

Moreover, percent rhythm (PR), which is the square of the correlation coefficient by Cosinor analysis, is typically used to assess circadian rhythm by fitting data. However, PR has not been used to evaluate circadian rhythm in the context of HDP, given its unsuitability for analyzing HDP [4].

Changes in pulse are known to reflect potential dysfunction of the sympathetic system in certain pathological states. Indeed, pulse variation might be observed in women with HDP due to the influence of pathological changes. Furthermore, night-time hypertensive patients have a lower awake heart rate and heart rate variability than night-time normotensive patients [13-15].

For this backdrop, the present study aimed to assess characteristic changes in circadian rhythms of BP and pulse using 24-hour ABPM in pregnant women with PE and GH who were diagnosed with hypertension by CBP.

Methods

In this study, pregnant women who had SBP ≥140 mmHg and/or DBP ≥90 mmHg during pregnancy, as assessed by CBP, underwent 24-hour ABPM at Nagoya City West Medical center between 2014 and 2015 and at Aichi Medical University Hospital between 2015 and 2018. CBP, defined as BP measured in the outpatient clinic, was measured at least twice on two separate occasions after at least five minutes of rest in the sitting position. When all-day ABPM revealed an SBP ≥130 mmHg and/or DBP ≥80 mmHg, patients were classified as having a hypertensive disorder (HDP), whereas patients with both SBP<130 mmHg and DBP<80 mmHg were classified as having WCH [1]. Exclusion criteria were as follows: a history of hypertension (not SBP<130 mmHg and DBP<80 mmHg were classified as having WCH), type 1 diabetes, renal dysfunction, hepatic damage, ischemic heart disease or other cardiac diseases, congestive heart failure (serum creatinine 41.2 mg/dL), arrhythmias, stroke, or other major concomitant non-cardiovascular diseases.

Age, parity, and body mass index (BMI) before pregnancy, gestational weeks of delivery, and infant body weight were evaluated. FGR was diagnosed according to Japanese fetal growth standards [16]. Soluble flm-like growth factor 1 (sFlt-1) in serum was measured as a biomarker of HDP using a sFlt-1 ELISA kit (R & D Systems, Inc, USA).

ABPM

Noninvasive ABPM was performed during pregnancy with an automatic validated system (TM-2430; A & D Co., Ltd., Tokyo). These BP data were synchronized according to the sleep-wake cycle and analyzed [19]. The circadian BP pattern was classified as a riser pattern if the mean night-time BP exceeded the mean daytime BP, and a non-riser pattern if the mean night-time BP was equal to or lower than the mean daytime BP [4,5,11,20]. The non-riser group consisted of both non-dipper (nocturnal BP fall<0% but<10%) and dipper (nocturnal BP fall>10%).

Another circadian BP pattern was assessed by Cosinor analysis. The regression model for a single component can be expressed as Y=M+Amp X Cos (T+ϕ), where M is the MESOR (circadian rhythm-adjusted mean based on parameters of a cosine function fitted to the raw data), Amp is the amplitude (amplitude of a cosine curve best fitted to the biological rhythm data), and ϕ is the acrophase (phase that represents the maximum value of a cosine curve best fitted to the biological rhythm data). Percent of coefficient variability (%CV), an indicator of BP variability, was calculated as standard deviation (SD)/mean x 100. Percent rhythm (PR) was calculated as the square of the multiple correlation coefficients (R2) between the measured value and the cosine curve best fitted to the biological rhythm data.

Patients were divided into two groups, i.e., those with circadian rhythm (PR≥0.16) and those without circadian rhythm (PR<0.16). The patients with circadian rhythm were divided into four categories by acrophase time (AT) as follows: AT0-6 (AT set at 0:00-6:00; reverse type), AT6-12 (AT set at 6:00-12:00), AT12-18 (AT set at 12:00-18:00; normal type), and AT18-24 (AT set at 18:00-24:00). In 36 patients, ABPM was also performed at postpartum three months and results were compared with those obtained during pregnancy.

This study was approved by the Institutional Review Board of Aichi Medical University, and all participants provided informed consent.

Statistical analysis

All statistical analyses were performed with Excel Toukei 2012 (SSRI Co., Ltd., Tokyo, Japan). Data are expressed as mean ± S.D. Unpaired t-test, chi-square test, and one-way analysis of variance were performed for comparisons. The hypothesis was rejected when the probability value was<0.05.

Results

This study retrospectively enrolled a total of 106 pregnant women who showed hypertension by CBP during pregnancy. Mean all-day ABPM determined HDP in 79 women and WCH in 27 women. In HDP, 43 women were classified as PE and 36 as GH according to HDP criteria by JSSHP [3,8].

The number of women who delivered at gestational week ≥34 was smaller for women with PE than for women with GH. FGR was more prevalent among women with PE than those with GH. Serum sFlt-1 concentrations were higher in women with PE and GH compared to those with WCH.

Hypertension, as assessed by CBP at three months postpartum, was less prevalent in women with PE than in those with GH (PE, 5/43; GH, 7/36) (Table 1).

Circadian rhythm of BP

SBP riser were observed in 21 and 15 women with PE and GH, respectively, while DBP riser were observed in 11 and 5 women with PE and GH, respectively (Table 2). With regard to mild hypertension, as assessed by CBP, SBP between 140-159 mmHg and/or DBP between
<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>GH</th>
<th>WCH‡‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>43</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td><strong>Age</strong> year</td>
<td>33 ± 5††</td>
<td>37 ± 5**</td>
<td>33 ± 5</td>
</tr>
<tr>
<td><strong>Parous</strong> PP/MP</td>
<td>37/6</td>
<td>37 ± 5**</td>
<td>17/10</td>
</tr>
<tr>
<td><strong>BMI kg/m²</strong></td>
<td>25 ± 6</td>
<td>26 ± 6</td>
<td>27 ± 7</td>
</tr>
<tr>
<td><strong>CBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic mmHg</td>
<td>158 ± 15**</td>
<td>153 ± 16**</td>
<td>142 ± 12</td>
</tr>
<tr>
<td>Diastolic mmHg</td>
<td>92 ± 16**</td>
<td>95 ± 14**</td>
<td>81 ± 10</td>
</tr>
<tr>
<td><strong>Severe hypertension by CBP¶</strong> (%)</td>
<td>20§ (47%)</td>
<td>10 (28%)</td>
<td></td>
</tr>
<tr>
<td><strong>Time of ABPM</strong> gestational weeks</td>
<td>34 ± 3</td>
<td>34 ± 5</td>
<td>22 ± 9</td>
</tr>
<tr>
<td><strong>SFlt-1 in serum pg/mL</strong></td>
<td>3215 ± 65** (n=37)</td>
<td>3190 ± 185* (n=26)</td>
<td>3054 ± 385 (n=25)</td>
</tr>
<tr>
<td>Administration of drugs at ABPM (%)</td>
<td>10 (24%)</td>
<td>9 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>All day BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic mmHg</td>
<td>150 ± 14**</td>
<td>146 ± 17**</td>
<td>118 ± 6</td>
</tr>
<tr>
<td>Diastolic mmHg</td>
<td>93 ± 8**</td>
<td>92 ± 8**</td>
<td>73 ± 7</td>
</tr>
<tr>
<td><strong>Daytime BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic mmHg</td>
<td>151 ± 14**</td>
<td>148 ± 16**</td>
<td>122 ± 7</td>
</tr>
<tr>
<td>Diastolic mmHg</td>
<td>94 ± 9**</td>
<td>92 ± 8*</td>
<td>76 ± 8</td>
</tr>
<tr>
<td><strong>Nighttime BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic mmHg</td>
<td>149 ± 17**</td>
<td>145 ± 21**</td>
<td>109 ± 7</td>
</tr>
<tr>
<td>Diastolic mmHg</td>
<td>91 ± 9**</td>
<td>88 ± 10**</td>
<td>67 ± 7</td>
</tr>
<tr>
<td><strong>Delivery at ≥34 gestational weeks (%)</strong></td>
<td>35*†† (81%)</td>
<td>34* (94%)</td>
<td>27 (100%)</td>
</tr>
<tr>
<td><strong>Cesarean section (%)</strong></td>
<td>39**††† (91%)</td>
<td>17** (47%)</td>
<td>9 (33%)</td>
</tr>
<tr>
<td><strong>Fetal growth restriction (%)</strong></td>
<td>25***††† (58%)</td>
<td>7 (13%)</td>
<td>1 (4)%</td>
</tr>
<tr>
<td><strong>Postpartum hypertension by CBP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All mmHg</td>
<td>5† (12%)</td>
<td>10 (19%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Severe hypertension§ mmHg</td>
<td>4/20‡ (20%)</td>
<td>5/10‡† (50%)</td>
<td></td>
</tr>
<tr>
<td>Mild hypertension§§ mmHg</td>
<td>1/23 (3%)</td>
<td>5/26 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PE: Preeclampsia; GH: Gestational Hypertension; WCH: White coat hypertension; BMI: Body Mass Index; CBP: Clinic Blood Pressure; PP: Primiparous; MP: Multiparous. Data were expressed as mean ± s.d.

§, Severe hypertension is SBP ≥ 160mmHg and/or DBP ≥ 110mmHg by CBP during pregnancy or postpartum. §§mild hypertension is SBP at 140 to 159 mmHg and/or DBP at 90 to 109 mmHg by CBP during pregnancy or postpartum. ¶ Ten of WCH anvanced and one advanced PE.

Table 1: BP and clinical data in hypertension disorders in pregnancy patients.

90-109 mmHg was observed more frequently among women with PE compared to those with GH (PE, 11/23; GH, 4/26).

MESOR, amplitude and %CV in SBP, DBP and pulse was not different between women with PE and with GH (Table 3).

Mean PR of BP was similar across subjects (0.19±0.18 mmHg in women with PE vs. 0.16±0.14 mmHg in women with GH for SBP, and 0.14±0.15 mmHg in women with PE vs. 0.14±0.12 mmHg in women with GH for DBP).

In women who had circadian rhythm (PR ≥0.16), normal maximal SBP at daytime (AT12-18) was detected only in 9/43 women with PE and 9/36 women with GH. In women with HDP with PR ≥0.16, AT showed maximal SBP at night-time from 00:00 to 06:00 only in 6/21 women with PE and 2/13 women with GH, while it showed maximal DBP at night-time in 4/18 women with PE and 1/5 women with GH. Mean PR of pulse was smaller in women with PE than in women with

<table>
<thead>
<tr>
<th>Severe/mild hypertension by CBP</th>
<th>Number</th>
<th>Dipper</th>
<th>Non-dipper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>43</td>
<td>20/23</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>36</td>
<td>10/26</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>White coat hypertension</td>
<td>27</td>
<td>12/27</td>
<td>15 (56%)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>43</td>
<td>20/23</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>36</td>
<td>10/26</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>White coat hypertension</td>
<td>27</td>
<td>12/27</td>
<td>15 (56%)</td>
</tr>
</tbody>
</table>

Table 2: Classification of dipper, non-dipper and riser in HDP patients.

| GH and WCH (PE, 0.27±0.7; GH, 0.32±0.19; WCH, 0.37±0.18). PR ≥0.16 of pulse was also smaller in women with PE (28/45, 62%) than in women with GH (27/31, 84%). In women with HDP with PR ≥0.16, the acrophase of pulse was at 12:00 to 18:00 for 27/30 women with PE and... |
Discussion

ABPM has been reported to be effective for excluding a diagnosis of WCH [3]. In the present study, all-day BP, as assessed by 24 h-ABPM, was able to diagnose HDP as well as WCH. CBP, as well as all-day BP as assessed by ABPM, were similar in women with PE and GH, although the outcome of pregnancy was more severe in women with PE due to the higher rate of early delivery, cesarean section, and FGR. Furthermore, concentrations of sFlt-1 did not differ between women with PE and GH, although concentrations were higher in both groups of women compared to women with WCH.

WCH has been reported to be a high risk factor for HDP, including PE [10]. In the present study, nearly 40% of women with WCH developed HDP, in particular, GH. Interestingly, the frequency of persistent hypertension after delivery (postpartum hypertension) was higher in women with GH than in those with PE, although the outcome of pregnancy was worse in women with PE than in those with GH; half of the women with GH who had severe hypertension remained hypertensive postpartum. Recent studies have reported differences in the pathophysiology of PE and GH [3,9]. ABPM could make the differences between these women clearer, not only in terms of clinical manifestations, but also in recovery processes.

Circadian rhythm in women with HDP

ABPM allows for the assessment of patterns in diurnal BP changes; i.e., it can be used to differentiate between non-dipper, riser, and dipper. The decrease of BP at night-time (sleeping) is reduced in non-dipper, and disappears among riser with HDP. The dipper pattern was not observed in 80% of HDP cases in this study. However, in over 40% of HDP cases, SBP was strongly elevated during night-time and exhibited a riser pattern. In mild hypertension cases, this effect was larger in women with PE than in those with GH. Among women with PE, the rate of riser was similar regardless of the severity of hypertension, while among women with GH, the rate was higher in women with mild hypertension.

Sleep or nocturnal hypertension is a common finding in HDP, particularly among women with PE (PE, 79%; GH, 45%) when sleep hypertension is defined as BP>117/68 mmHg at 26-30 weeks or 123/72 mmHg after 30 weeks of gestation [21]. Our results are consistent with this finding. Blunting of the nocturnal drop in BP and the reverse pattern of circadian rhythm of BP both have important clinical implications. Several possibilities have been proposed to explain these phenomena, including:

1) Disturbance in hypothalamic pituitary adrenal periodicity,
2) Disorders of the sympathetic nervous system, and
3) A compensatory mechanism to maintain organ blood flow during sleep in response to ischemia.

Several humoral agents are known to control circulation and BP, such as the renin-angiotensin aldosterone system, free epinephrine, and free norepinephrine. The latter two agents show a temporal sequence of circadian rhythmicity in non-pregnant and normotensive pregnant women, while in women with PE, the circadian rhythmicity of these agents might be blunted.

BP variability, including %CV and ΔBP, can be used to evaluate outcomes of acute ischemic stroke [12]. MESOR, AT, and %CV may be useful for evaluating circadian rhythm changes in HDP. According to one report, PB variation, MESOR, and AT increased in women with PE [11], while %CV has not been assessed, to our knowledge, in women with PE. In the present study, MESOR of BP was higher and MESOR of pulse was lower in both women with PE and GH compared to women with WCH. However, neither amplitude nor %CV differed significantly across groups.

For BP, the cosine curve represented the best fitted model, and the least squares fit of a cosine curve is frequently used for rhythm detection. PR is the square of the multiple correlation coefficients between the measured value and the cosine curve best fitted to biological rhythm data. In the present study, there were no differences in the PR of BP among the three groups of women (i.e., PE, GH, and WCH). However, this may have been due to the fact that circadian rhythm using the cosine curve might not be as powerful as the simultaneous fit of all statistically significant components [4].

Patients were also divided into two groups by PR (i.e., PR<0.16 and PR≥0.16). According to this analysis, more than 50% of women with HDP were found to lack circadian rhythm. Our findings are consistent with previous reports that BP variation may be reduced among women with PE [4]. In the group with PR>0.16, patients were further classified into four subgroups by acrophase time (AT). Among these groups, normal AT12-18 was observed less frequently in women with PE and GH compared to those with WCH, and AT shifted to the night-time despite the circadian rhythm. In this respect, our results are consistent with a study reporting that AT shifted to the night from the evening [22]. Circadian rhythm of BP disappeared in about 60% of patients with HDP, and only 20% of patients with HDP showed normal AT with circadian rhythm.

The circadian rhythm of pulse was abnormal more frequently in women with PE compared to those with GH. This suggests that sympathetic nerve disorders may cause characteristic changes in the circadian rhythm of BP, given that the circadian rhythms of both BP and pulse are abnormal in women with PE.

Baroreflex reportedly is reduced in women with PE [13,14]. Indeed, the sympathetic system is abnormal under some pathological conditions. Circadian rhythm is regulated by a circadian rhythm gene, and in the context of PE, this gene may function abnormally in some ways [22].

VEGF reportedly is involved in the adjustment of circadian rhythm. In the present study, sFlt-1 concentrations increased, and this in turn has anti-VEGF receptor effects [23]. In addition to this, PE may also influence circadian rhythm. Another relevant factor is NO. According to a previous report, abnormal NO activity can lead to abnormalities in circadian rhythm [24]. We previously reported the reduced activity of NO-GMP in the context of vascular function in women with PE [25,26]. Thus, PE may impact circadian rhythm not only by affecting BP, but the sympathetic nerve system as well. This underscores the difference between PE and GH in modulating circadian rhythm.

Conclusion

In conclusion, most women with PE and GH showed changes in the circadian rhythm of BP such as decreases in PR or shifts in peak time, while only women with PE showed changes in pulse. Our findings suggest that the circadian rhythm of BP in women with PE could potentially be disrupted due to sympathetic nerve disorders.

Acknowledgments

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Conflict of Interest

None.

References