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Orthostatic Stress Response During the Menstrual Cycle Is Unaltered in Formerly Preeclamptic Women With Low Plasma Volume

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Plasma volume (PV) varies with the menstrual cycle not only in healthy parous controls (CON) but also in formerly preeclamptic women with a subnormal PV (LPV). It is unknown whether formerly preeclamptic women with LPV are more susceptible to orthostatic stress than healthy controls. In this study, the authors compared autonomic responses to acute (standing from supine position) and gradual (menstrual cycle) orthostatic stress between LPV and CON. In 11 LPV (PV ≤49 mL/kg lean body mass) and 7 CON, beat-to-beat blood pressure (BP) and heart rate (HR) were measured in supine position and after an orthostatic stress test, during the follicular phase (FP) and luteal phase (LP) of the menstrual cycle. Spectral analysis (fast Fourier transform) was performed on beat-to-beat signals to quantify the magnitude of the spontaneous BP and pulse interval (PI) fluctuations. The absolute powers within the low-frequency (0.04-0.15 Hz) and high-frequency (0.15-0.4 Hz) ranges of BP and PI were used as estimates for sympathetic and parasympathetic activity, respectively. Baroreflex sensitivity was calculated as the transfer function gain from low-frequency systolic BP to PI. Differences between groups, menstrual phase, and response to standing were compared by analysis of variance. Basal BP was comparable in both study groups. However, basal PI and spontaneous baroreflex sensitivity were lower in LPV than in CON. The autonomic responses to acute and gradual orthostatic stress were similar in the 2 groups, irrespective of the phase of the menstrual cycle. The cardiovascular response to acute and gradual orthostatic stress in both FP and LP is comparable in LPV and CON.

Key words: Plasma volume, autonomic function, baroreflex, preeclampsia, spectral analysis.

Hormonal changes with the menstrual cycle are accompanied by fluctuations in the autonomic and circulatory functions. Likewise, the circulatory function in the luteal phase (LP) undergoes slight changes relative to the follicular phase (FP) in response to the mild systemic vasorelaxation that is prevalent in the LP.[1,2] These changes include activation of the renin-angiotensin-aldosterone system, resulting in a mild rise in both plasma volume (PV) and muscle sympathetic nerve activity.[3] This cyclic vasorelaxation occurs not only in parous women with a normal PV but also in formerly preeclamptic women with a subnormal PV.[4] A subnormal PV interferes with the ability to increase venous return, in response to higher demands for cardiac output.[5,6] This mechanism is compensated for by a rise in sympathetic tone. The observation that formerly preeclamptic women with a subnormal PV have a 3-fold higher chance to develop recurrent disease in their next pregnancy as compared to their counterparts with a normal PV supports this concept.[7]

The ability to cope with the orthostatic challenges of daily life is expected to require adequate venous capacitance.[8] As a large proportion of formerly preeclamptic women display a subnormal PV along with lower venous capacitance,[4,6] their ability to cope with the relatively modest

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challenges of orthostasis is also expected to be reduced. This study aims to test the hypothesis that formerly preeclamptic women with a subnormal PV and healthy parous controls elicit different autonomic responses to acute (rapid standing from supine position) and gradual (menstrual cycle) orthostatic stress. To test this hypothesis, we determined in 11 formerly preeclamptic women the autonomic response to acute and chronic orthostatic stress in both FP and LP of the menstrual cycle and compared the results with those obtained in 7 healthy parous controls.

METHODS

Patient Inclusion

Eleven normotensive formerly preeclamptic women with subnormal PV (LPV) and 7 healthy parous controls participated in this study. All women had self-reported regular menstrual cycles (28 ± 2 days). We planned the data acquisition 6 to 12 months postpartum in the FP (day 5 ± 2) and the LP (day 21 ± 2) of the menstrual cycle and, if applicable, after discontinuation of breastfeeding. These time points were proven appropriate for the study of the effects of hormonal changes on cardiovascular function in the menstrual cycle.[1,9] Participants were instructed to discontinue the use of oral contraception at least 2 months prior to data acquisition. Formerly preeclamptic women were recruited from our outpatient clinic at the 6-week postpartum checkup. All these women had a history of early-onset (<34 weeks amenorrhea) preeclampsia.[10] Because of a higher likelihood of having a reduced ability to cope with orthostatic challenges,[5,6] we invited all women with a PV <49 mL/kg lean body mass^{-1} to participate in the study. All women who gave informed consent were enrolled. Healthy parous controls were selected from volunteers responding to an advertisement in a local newspaper.

Participants were also instructed to discontinue the use of any vitamin supplements or any other medication at least 2 weeks prior to measurements to avoid potential confounding effects of over-the-counter substances. After an overnight fast, we measured hemodynamic and autonomic functions. All subjects were Caucasian and gave written informed consent. Recruitment was preceded by approval of the study protocol by the hospital's medical-ethical board.

Experimental Procedure

Measurement of central hemodynamic function. The experiment started at 9:00 AM. Participants were instructed to refrain from drinking caffeine- or alcohol-containing beverages and from smoking and eating for at least 10 hours prior to each measurement. We carefully explained the study protocol to the participants, with special emphasis on factors that could influence measurements (eg, smoking, eating, full bladder, etc). All participants took part in a pretrial measurement to familiarize them with the study protocol. The protocol was as follows: participants were positioned in semirecumbence with left-lateral tilt (further referred to as supine position). Arterial blood pressure (BP) and heart rate (HR) were recorded intermittently using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, Fla).

Measurement of plasma volume. PV was measured using the iodine^{125}-albumin (^{125}I-HSA) indicator dilution method and expressed in milliliters per kilogram of lean body mass (LBM).[2] Data for normal values were derived from PV measurements in healthy parous controls as specified in a previous report.[11] In short, we defined the cutoff level for normal PV as the mean PV in the control group minus 2 standard deviations, a level that corresponded with 49 mL/kg LBM^{-1}.

Sympathetic activity and baroreflex sensitivity. Spontaneous fluctuations in systolic BP (SBP) and HR were recorded on a beat-to-beat basis using a continuous finger arterial pressure–monitoring device (Portapres; TNO-BMI, Amsterdam, the Netherlands). Participants were placed in a supine position in a quiet, dimmed room with an average temperature set at 23°C to optimize finger blood flow (prevention of cold fingers). We adopted a 15-minute acclimatization time to reach steady state before initiating the recording of a period of at least 5 minutes. Then we instructed the participants to stand up rapidly (3 seconds). When BP and HR values had returned to a new steady state, we recorded a second period as described above. Beat-to-beat signals of SBP (in millimeters of mercury) and pulse interval (PI; in milliseconds), which is the reciprocal of HR and is derived from the pulsating BP signal, were stored on a personal computer for offline analysis. All traces were individually screened and inspected for irregularities. The recording was discarded if more than 5% of the data showed artifacts or missing values. Each valid recording was then processed using computerized algorithms (fast Fourier transform; FFT) that extract indices of sympathovagal balance and baroreflex sensitivity (BRS) from these spontaneous variations in SBP and PI. Details about these procedures have been reported previously.[12] In

short, each recording was subdivided into multiple data segments of 100 seconds, overlapping 50%. Because the FFT procedure is based on regularly (in time) sampled 2^n data points, these beat-to-beat segments of 100 seconds were resampled at 5.12 Hz, resulting in 512-second-long equidistantly spaced data segments. The FFT procedure searches for regular variations in each data segment and quantifies the contribution of each fluctuation (being a sinus in the spectrum between 0 and 2.56 Hz) to the total variation in the signal. The amplitude (or power) of the fluctuations in SBP and PI is given in $mmHg^2$ and ms^2, respectively. In humans, signals of SBP and PI display regular fluctuations that are usually found around 0.1 Hz and 0.25 Hz. These are known as low-frequency (LF) and high-frequency (HF) fluctuations. Their origin is mainly due to fluctuations in autonomic nervous function. LF oscillations in SBP and PI are predominantly determined by fluctuations in sympathetic nervous activity.[13] HF fluctuations in PI are coherent with the sinus respiratory frequency and are mainly mediated by oscillations in parasympathetic (mainly vagal) activity.[14] Hence, by calculating the ratio between LF and HF power of PI, the influence of both sympathetic and parasympathetic nerves on the heart is appreciated and often used as an index of cardiac autonomic control. As the spectral composition of BP and PI varies over time as well as between subjects, frequency ranges have been defined for LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz) fluctuations. Therefore, spectral powers represent the cumulative power within the indicated frequency range. Cardiac autonomic balance was calculated by the ratio between LF and HF powers of PI.

The FFT method also enabled calculation of transfer functions between SBP (regarded as the input signal) and PI (regarded as the output signal). The gain of transfer function is an estimate for the magnitude of PI fluctuations induced by SBP fluctuation. The transfer gain between PI and SBP is expressed in ms/mmHg and is a measure for the BRS. Low BRS is characterized by a small variation in PI with relatively enhanced SBP fluctuations. A high BRS usually displays significant PI fluctuations with a very stable BP.[13] The phase of the transfer function provides information on the time lag (in seconds) between the PI and SBP variations, whereas the coherence indicates the strength of the correlation between PI and SBP. A coherence of 1 indicates full linear dependence of PI on SBP at that given frequency, whereas a value of 0 indicates that the SBP and PI signals are not correlated at the given frequency. Generally, coherence values greater than 0.4 to 0.5 are considered physiologically relevant. Very-low-frequency components (<0.04 Hz) were not evaluated here because of the relatively short recording period and thus absence of spectral resolution in this frequency band.

Statistical Analysis

Differences between steady-state values of BP and HR as well as their spectral density measures (LF and HF powers of BP and PI and BRS) were compared by a 3-way analysis of variance (ANOVA) with the following interrelations: (1) LPV versus controls, (2) FP versus LP, and (3) supine versus standing position. In addition, we determined the absolute and relative changes by subtracting values obtained during the standing position from those recorded during the preceding supine position. Furthermore, we compared the observed change (between standing and supine condition) between the LPV and controls in both the FP and LP using a 2-way ANOVA. We applied the Bonferroni post hoc *t* test to identify post hoc differences. We considered P values <.05 as being statistically significant.

RESULTS

Demographic characteristics and baseline hemodynamic data are listed in Table 1. Obviously, in conjunction with our patient selection procedure (see the "Methods" section), both gestational age at birth and mean birth weight were lower in LPV than in controls.

Figure 1 depicts absolute changes in SBP, diastolic BP (DBP), and HR as they occurred after standing (steady-state averages). In supine position, SBP and DBP were comparable in both study groups, both in FP and in LP. Standing induced inconsistent changes in SBP. On the other hand, a consistent 7 to 10 mm Hg rise in DBP (3-way ANOVA, $P < .001$) was found in both study groups, with this effect being slightly but consistently larger ($P < .05$) in the LP.

In all conditions, the steady-state HR was slightly higher in LPV than in controls, a difference that was consistent (3-way ANOVA, $P = .01$). In neither group did we find a difference in basal HR between FP and LP. However, as expected, standing induced a consistent, comparable rise in HR in both study groups, both in FP and in LP (3-way ANOVA, $P < .001$).

Although the LF power of SBP (mean ± SD) measured in the supine position in FP and LP seemed lower in controls (4.0 ± 2.4 and 8.7 ± 7.0 mm Hg^2, respectively) than in LPV (10.5 ± 5.6 and 11.2 ± 7.7 $mmHg^2$, respectively),

Table 1. Patient Demographics and Baseline Hemodynamics

	Controls	LPV	*P* Value
n	7	11	
Age, y	32 (28-38)	31 (26-34)	NS
BMI, kg/m^2	22 (20-30)	23 (20-28)	NS
GA, d	281 (259-287)	239 (185-287)	.01
Birth weight, g	3200 (3000-3900)	2100 (500-2800)	.001
Follicular phase			
MAP, mm Hg	89 (73-94)	86 (68-96)	NS
PI, ms^{-1}	992 (848-1296)	934 (878-1024)	.01*
Luteal phase			
MAP, mm Hg	84 (78-86)	84 (67-96)	NS
PI, ms^{-1}	1037 (804-1339)	878 (638-986)	.01*

Values are presented as median (range). The hemodynamic values listed were obtained in supine position. LPV = low plasma volume; NS = not significant; BMI = body mass index; GA = gestational age at previous delivery; MAP = mean arterial pressure; PI = pulse interval.
*Difference between controls and LPV statistically significant by 3-way analysis of variance with the factors subgroups (controls/LPV), menstrual phases (follicular/luteal), and position (supine/standing).

the observed intergroup difference did not reach statistical significance. Upon standing, LF power of SBP had increased in all women (3-way ANOVA, $P < .001$) without, however, appreciable intergroup difference in either phase of the menstrual cycle (Figure 2). Figure 2 also illustrates the impact of standing on the HF power of SBP and on the LF and HF power of PI. Both the HF power of SBP and PI had changed significantly in response to standing (3-way ANOVA, $P < .001$). Probably because of differences in baseline PI, changes in HF power of PI tended to be smaller in the LPV than in the control group. However, neither in FP nor in LP did this difference reach statistical significance.

In line with our previous observations made in a larger population,[15] we noticed that in supine position, BRS tended to be lower in LPV than in controls. However, possibly because of the limited group sizes, the difference did not reach statistical significance ($P = .07$). The 2 subgroups were comparable with respect to the absence of an effect of the menstrual cycle on the BRS as well as with respect to the magnitude of the decline in BRS gain in response to standing in the FP and LP (Figure 3).

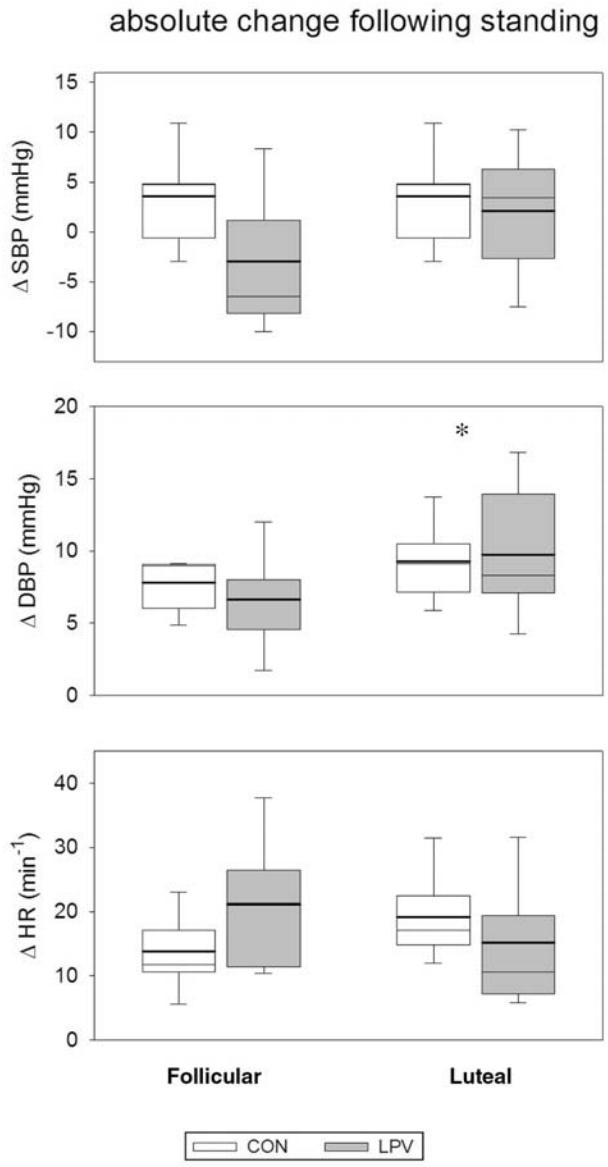

Figure 1. Comparison of absolute changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in response to standing in the control group (CON) and in women with low plasma volumes (LPV) during the follicular and luteal phases of the menstrual cycle. Values are presented as box plots with the mean value (thick line), median (thin line), 25%/75% (bottom/top of box), and 5%/95% (error bars). Data were analyzed by 2-way analysis of variance. The observed changes in these variables were comparable in the 2 subgroups, including the consistently larger change in DBP in the luteal phase than in the follicular phase (*$P < .05$).

DISCUSSION

LP differs from FP by a slightly higher PV, most likely triggered by mild systemic vasorelaxation, a phenomenon accompanied by compensatory changes in the hemodynamic function. In a previous study, we found this cyclic pattern to be preserved in formerly preeclamptic women with a subnormal PV,[4] which raised the question as to whether the subnormal PV—and with it, a subnormal venous capacitance[6]—affects the response to the orthostatic

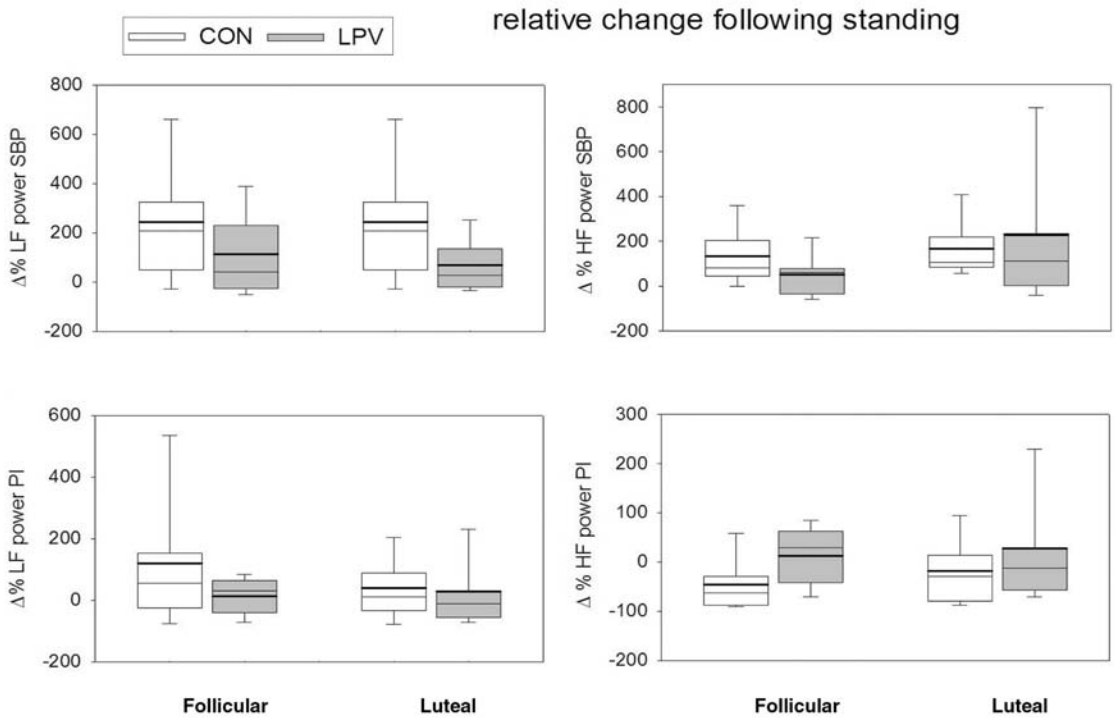

Figure 2. Comparison of relative changes in spectral power in response to standing in the follicular and luteal phases of the menstrual cycle. Data are presented in box plots (see legend of Figure 1). None of the changes in response to standing differed significantly (2-way analysis of variance) between the controls (CON) and low-plasma-volume (LPV) subgroup. PI = pulse interval; SBP = systolic blood pressure; LF = low-frequency power; HF = high-frequency power.

challenges of normal daily life, particularly in LP. In this study, we found comparable changes in BP and HR, as well as in the autonomic responses to the orthostatic challenges of normal life, in both former patients with a subnormal PV and normal parous controls. Therefore, we reject our hypothesis that in both phases of the menstrual cycle, the autonomic responsiveness to orthostatic stress in formerly preeclamptic women with a subnormal PV differs from that in healthy parous women. Nevertheless, the sympathetic contribution to the autonomic cardiovascular control appears to be larger in former patients with a subnormal PV as suggested by a higher baseline HR as previously observed in LPV women. We speculate that in formerly preeclamptic women with a subnormal PV, rapid adjustments to orthostatic changes are preserved at the expense of a slightly higher basal sympathetic tone in the autonomic control of the circulation.

The rise in venous return generated by a given venous constriction increases with venous capacitance.[16] Conversely, at similar venous driving pressures, the degree of venous constriction needed to generate a given rise in venous return will be inversely related to venous capacitance. In a previous study in formerly preeclamptic women with a subnormal PV and parous controls with a normal PV, we noticed a comparable acute rise in HR and SV in response to exercise; however, in only former patients did these variables decline in the course of ongoing exercise.[5] Apparently, a subnormal PV and thus also reduced venous capacitance has no consequences for acute adjustments but does limit the cardiac ability to sustain these adjustments for a prolonged period, a feature that could explain the observed chronically raised basal sympathetic tone in the circulation in these women.

In neither group did we find an appreciable difference in BRS and the response of the BRS gain to standing throughout the menstrual cycle. Also, others reported only minor differences in hemodynamic and volume parameters between both phases of the menstrual cycle.[4,17] Small amplitudes in the cyclic changes are to be considered perfectly normal in healthy women without complaints or constrains. Therefore, we consider the finding of no or only minor intergroup differences, despite meticulous measurement, inherent to the combination of measurement technique and expected small differences.

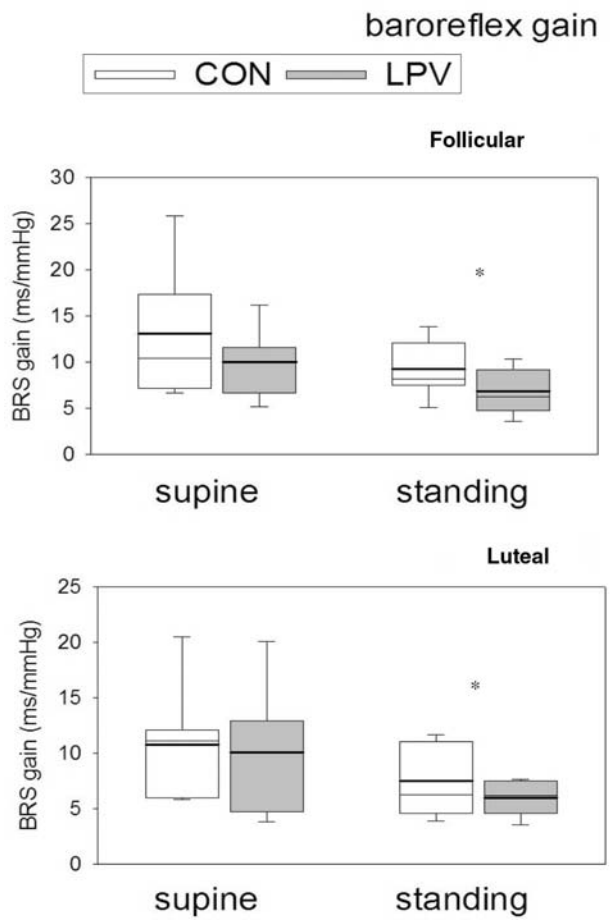

Figure 3. Comparison of baroreflex sensitivity (BRS gain) between the controls (CON) and the low-plasma-volume (LPV) subgroup in the follicular and the luteal phases of the menstrual cycle. Data are presented in box plots (see Figure 1). Data were analyzed by 2-way analysis of variance. * = Significantly smaller BRS gain in both groups in the standing position relative to the supine position ($P < .05$). There were no significant differences between the follicular and luteal phase.

Another possible explanation for the observed minor difference may be that the renin angiotensin aldosterone system is up-regulated during the LP, providing an extra endogenous sympathetic stimulus. Circulating levels of norepinephrine are elevated in the LP,[3] which could have modulated the thresholds for the rapid changes in the autonomic system that we studied. And last but not least, the difference between LP and FP is possibly below the detection level of our methodology.

To conclude, the cyclic change in PV as a function of the menstrual cycle of formerly preeclamptic women with a subnormal PV is comparable to that in healthy parous controls. The compensatory change of the autonomic function is also similar in both groups. Nevertheless, a subnormal PV is associated with a higher basal sympathetic tone. These phenomena may well reflect a diminished circulatory reserve capacity in patients at risk for hypertensive complications in pregnancy.

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