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Low Plasma Volume Coincides With Sympathetic Hyperactivity and Reduced Baroreflex Sensitivity In Formerly Preeclamptic Patients

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BACKGROUND: *Preeclampsia is associated with enhanced sympathetic activity as well as subnormal plasma volume. Meanwhile, in over 50% of these complicated pregnancies, the subnormal plasma volume has been found to persist for a prolonged period after pregnancy. The objective of this study is to test the hypothesis that in normotensive formerly-preeclamptic women, persistence of a subnormal plasma volume coincides with enhanced sympathetic activity and with it, an altered autonomic control of blood pressure.*

METHODS: *Forty-eight formerly-preeclamptic women participated in this study. After measurement of their plasma volume by iodine 125-albumin indicator dilution, they were subdivided into a group with a normal plasma volume (plasma volume >48 ml/kg lean body mass) and a group with a subnormal plasma volume (≤48 ml/kg lean body mass). We performed spectral analysis on their beat-to-beat blood pressure and heart rate recordings and compared both groups using non-parametric tests.*

RESULTS: *Formerly-preeclamptic women with a subnormal plasma volume had a higher sympathetic activity (*P = *.001) and a lower baroreflex sensitivity (*P = *.04) than their counterparts with a normal plasma volume.*

CONCLUSION: *In normotensive formerly-preeclamptic women, a subnormal plasma volume coincides with a higher sympathetic activity in the blood pressure regulation and lower baroreflex sensitivity. Whether these alterations in the autonomic control mechanisms are a cause or effect of the subnormal plasma volume remains to be elucidated. (J Soc Gynecol Investig 2006;13:48–52) Copyright © 2006 by the Society for Gynecologic Investigation.*

KEY WORDS: Plasma volume, autonomic function, blood pressure, preeclampsia, spectral analysis.

Preeclampsia complicates almost 5% of all pregnancies.[1] It is one of the most common causes of maternal mortality.[2] It is also an important cause of perinatal mortality and morbidity, as it predisposes to fetal growth restriction and iatrogenic preterm birth.

Subnormal plasma volume and cardiovascular sympathetic hyperactivity are common features of preeclampsia.[3,4] Meanwhile, in more than half of formerly preeclamptic patients a subnormal plasma volume persists after pregnancy.[5,6] Recently, evidence has been provided for the concept that subnormal plasma volume in formerly preeclamptic women is consistent with a reduced venous capacitance.[7] However, the functional meaning of a subnormal venous capacitance in these women is unclear: either it reflects a subnormal size of a *normally* functioning venous compartment or, alternatively, it indicates a normal-sized venous compartment functioning *abnormally* in conjunction with a reduced venous compliance or a raised sympathetic tone. This question is clinically relevant as the first option is resistant to any intervention, whereas in the case of the second option it may be possible to enlarge the venous compartment and with it, improve the function of the venous compartment by removing the trigger responsible for the elevated cardiovascular sympathetic tone.[6,8–10]

This study was designed to test the hypothesis that in normotensive formerly preeclamptic women, a subnormal plasma volume is associated with elevated sympathetic control of blood pressure and heart rate and altered baroreflex function. To this end plasma volume was measured using standard isotope dilution techniques while sympathetic tone and baroreflex sensitivity (BRS) were assessed noninvasively by analyzing spontaneous variations in blood pressure and heart rate according to validated computerized methods.[11]

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METHODS

Patient Selection

Forty-eight normotensive formerly preeclamptic women participated in this study. Data acquisition was initiated at least 6 months postpartum. Formerly preeclamptic women were recruited from our outpatient clinic at the postpartum follow-up. All patient charts were studied for the following inclusion criteria: diastolic blood pressure ≥90 mm Hg measured on two separate occasions in combination with a significant proteinuria (3+ dipstick or >0.3 mg albumin per milliliter urine). Patients with a history of pregnancy-induced hypertension or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome were excluded. Preeclampsia was defined according to the criteria of the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy.[1] Quantification of the 24-hour urinary sodium output on the day prior to the experiment was performed to estimate average sodium intake. Participants were instructed not to use vitamin supplements or any other medication in the weeks prior to measurement. After an overnight fast, participants were tested for hemodynamic and autonomic function. All subjects were Caucasian and gave written informed consent. The study was approved by the hospital's medical-ethical board, (Medisch Ethische Commissie [MEC]).

Measurement of Central Hemodynamic Function

The measurement session started at 9 AM. Participants were instructed not to drink caffeine- or alcohol-containing beverages and to refrain from smoking and eating for at least 10 hours prior to the experiment. Furthermore, all participants were instructed to empty their bladder before starting with the experiment. We took effort in explaining to all participants the importance of these measures as it would affect the results.[11] They were also assured a meal after the measurement. During the measurements, subjects were placed in supine position. Arterial blood pressure and heart rate were recorded intermittently by a semi-automatic oscillometric device (Dinamap Vital Signs Monitor 1846, Critikon, Tampa, FL). Urinary sodium concentration was measured from a 24-hour urine sample, collected on the day prior to the measurement session and quantified by standard chemical procedures.

Assessment of Plasma Volume

Plasma volume was measured using the iodine 125–albumin (^{125}I-HSA) indicator dilution method and expressed in ml per kilogram lean body mass (LBM).[5] Data for normal values were derived from plasma volume measurements in healthy parous controls as reported previously.[8] The cut-off level for normal plasma volume was defined as the mean plasma volume minus two standard deviations in the control group.[8] This level corresponded with 48 mL per kilogram lean body weight. A plasma volume ≤48 mL · kg LBM^{-1} was defined as being a subnormal plasma volume (LPV), whereas a plasma volume greater than 48 mL · kg^{-1} LBM was defined as being a normal plasma volume (NPV).

Sympathetic Activity and Baroreflex Sensitivity

Spontaneous fluctuations in systolic blood pressure (SBP) and heart rate 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 supine position in a quiet dimmed room with an average temperature set at 23C to optimize finger blood flow (prevent cold fingers). A period of 15 minutes acclimatization time was adopted to attain steady state. Subsequently, an interval of at least 5 minutes containing more than 256 beats was recorded. Beat-to-beat signals of SBP (in mmHg) and the respective interbeat interval (PI = pulse interval in milliseconds) were stored on a personal computer for off-line analysis. All traces were individually screened and inspected for irregularities. If more than 5% of the data showed artifacts or missing values the recording was excluded. Each valid recording was then processed using computerized algorithms (so-called fast Fourier transform [FFT]) that extract indices of sympathetic tone and baroreflex sensitivity from these spontaneous variations in SBP and PI. These procedures have been described in detail by Laude et al.[12] In short, each valid recording was subdivided into multiple data segments of 100 seconds that were 50% overlapping. Because the FFT procedure is based on regularly (in time) sampled 2^n data points, these 100-seconds beat-to-beat segments were resampled at 5.12 Hz. resulting in a 51.2-seconds long equidistantly spaced data segment. The FFT procedure searches for regular variations in each segment. In fact, the algorithm quantifies for each regular fluctuation within the 0 and 2.56 Hz frequency range its amplitude and expresses this as power in mm Hg^2 for SBP and ms^2 for PI. The greater the spectral power, the greater the contribution of that specific frequency component to the total variation of SBP or PI. Total spectral power, ie, the cumulative power in all frequency bands, is by definition equal to the SD^2 of each data segment in the time domain. Spectral powers of SBP and PI are most frequently found at about 0.1 Hz and 0.25 Hz. The first component is mostly known as the low frequency (LF) component; the latter as the high frequency (HF) component. LF oscillations in SBP and PI are mainly determined by fluctuations in autonomic nervous activity. HF fluctuations in SBP and PI are coherent with the respiratory frequency. In many conditions the amplitude of LF oscillations in SBP has been shown to reflect sympathetic tone,[13,14] while the amplitude of HF fluctuations of PI mainly reflects vagal modulation of PI. Because the frequency range of the LF and HF variations vary over time and between subjects frequency ranges have been defined for these LF (0.04 to 0.15 Hz) and HF (0.15 to 0.4 Hz) fluctuations. Powers are therefore given as the cumulative power within the indicated frequency range. The ratio between these values of LF and HF power of PI is a measure of cardiac autonomic balance between the sympathetic and vagal system.[13] Besides spectral powers, the FFT

Table 1. Demography of the Two Groups of Formerly Preeclamptic Women

	Normal PV (*N* = 22)	Low PV (*N* = 26)	*P*
Age (y)	31 (23–36)	31 (19–39)	NS
BMI ($kg \cdot m^{-2}$)	22 (18–29)	24 (16–29)	NS
Parity	1 (1–2)	1 (1–2)	NS
Sodium excretion ($mmol \cdot 24\ h^{-1}$)	136 (37–258)	137 (52–320)	NS
Mean arterial blood pressure (mm Hg)	84 (72–107)	92 (75–106)	NS
Heart rate (bpm)	70 (55–97)	71 (48–96)	NS
Plasma volume ($mL \cdot kg^{-1}lbm$)	52 (48–60)	42 (30–47)	<.0001
Gestational age at delivery (wk)	34 (28–42)	34 (26–39)	NS

NS = not significant; BMI = body mass index.

method allows also the calculation of transfer functions between SBP (regarded as the input signal) and PI (regarded as the output signal). The gain of the transfer function is calculated at each frequency and is a measure for the extent the magnitude of the PI fluctuation depends on the magnitude of the SBP fluctuation. The transfer gain between PI and SBP is expressed as ms/mmHg and is a measure for the baroreflex sensitivity (BRS). A hemodynamic state with a low BRS is often characterized by small variation in PI with relatively enhanced SBP fluctuations. A hemodynamic state with a high BRS usually displays significant PI fluctuations with a very stable blood pressure.[14] The phase of the transfer function provides information on the time lag (in seconds) between the PI and SBP variations, while the coherence is a value between 0 and 1 indicating the significance of the relation between PI and SBP. A coherence of 1 indicates a full linear dependence of PI on SBP at that given frequency, whereas a value of zero signifies that there is no correlation at all. Generally, coherence values above 0.4 and 0.5 are taken as being physiologically significant.

Very low frequency components (VLF <0.04 Hz) were not evaluated because of the relatively short recording period and with it, the lack of spectral resolution in this frequency band.

Statistical Analysis

Data are presented as median and range unless otherwise specified. We evaluated the differences between the two groups using the Mann-Whitney *U* test. A *P* value of less than .05 was considered statistically significant.

RESULTS

The study group was subdivided into a LPV group (*N* = 26) and a NPV group (*N* = 22). Both groups were comparable with respect to age, body mass index, parity, urinary sodium output, average blood pressure, and gestational age at previous childbirth (Table 1). Obviously, the women in the LPV group had a lower plasma volume than those in the NPV group.

Table 2 lists the data obtained from the spectral analysis of SBP and PI variations in supine position. Average spectral curves are illustrated in Figure 1. The spectral power in the LF

Table 2. Spectral Powers of SBP and RR Interval From the Two Subgroups of Formerly Preeclamptic Women

	Normal PV (*N* = 22)	Low PV (*N* = 26)	*P*
LF SBP	3.44 (0.26–13.7)	7.58 (1.03–74.39)	0.001
HF SBP	2.65 (0.50–14.5)	3.60 (0.42–17.4)	NS
LF RR	641 (119–2453)	854 (59–6614)	NS
HF RR	858 (82–3953)	661 (67–8251)	NS
LF/HF ratio RR	0.57 (0.26–2.96)	0.99 (0.43–35.0)	.002
BRS	13.8 (5.7–24.5)	10.3 (3.9–33.3)	.04
Phase	−3.0 (−4.0–0.04)	−1.78 (−3.6–−0.6)	NS
Coherence	0.89 (0.27–0.98)	0.91 (0.14–0.98)	NS

VLF = very low frequency (Hz); LF = low frequency power of SBP (mm Hg^2); HF = high frequency of SBP (mm Hg^2); LF-RR = low frequency of RR interval (ms^2); HF-RR = high frequency of RR interval (ms^2); LF/HF = ratio represents autonomic balance; BRS = Baroreflex sensitivity; transfer gain, TF ($ms \cdot mm\ Hg^{-1}$); SBP = Systolic blood pressure (mm Hg); RR-I = RR interval (reciprocal of heart rate).

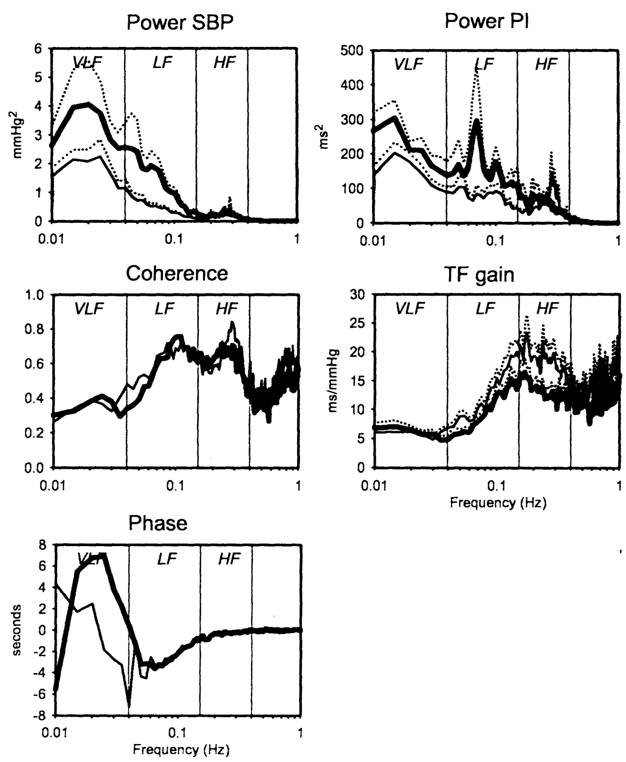

Figure 1. Total power spectrum of SBP and RR interval (PI) in women with LPV (*N* = 26, ***bold line***) and NPV (*N* = 22, *thin line*). *Dashed lines* indicate SEM, displayed only when LPV and NPV were statistically different. (For statistical analysis, see Table 2).

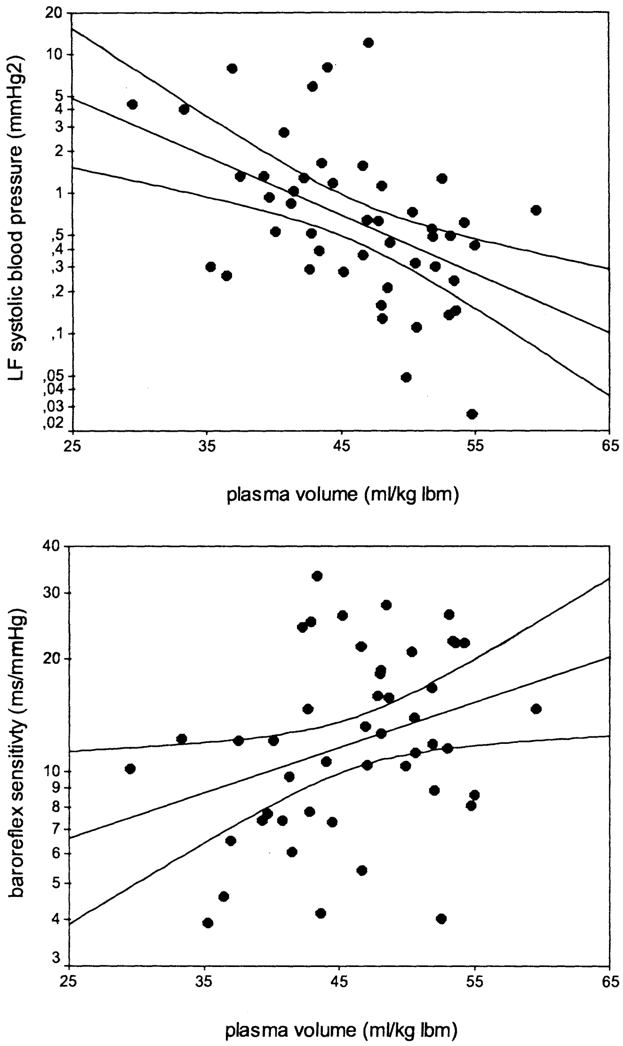

Figure 2. Logistic regression of the total LF power spectrum of systolic blood pressure (upper panel) and baroreflex sensitivity (lower panel) as a function of plasma volume in normotensive formerly preeclamptic women. The *straight line* represents the mean linear regression in the population studied; the *curved lines* represent the 95% confidence interval for the mean predicted line.

bin of SBP, but not in the HF bin, was higher in the LPV group. Although the LF and HF spectral powers of pulse interval power did not differ among subgroups, the LF/HF ratio of the pulse interval was higher in the LPV group. The baroreflex gain was lower in the LPV group, with the phase index and coherence being not appreciably different between the two groups (Figure 1).

We performed logistic regression analyses of LF power of SBP and gain in transfer function with plasma volume. Sympathetic activity of SBP correlated inversely with plasma volume ($r = -0.48$, $P = .001$), while the gain in transfer function was found to correlate positively with plasma volume ($r = 0.34$, $P = .02$, Figure 2).

DISCUSSION

Vascular dysfunction plays a central role in the development of preeclampsia. This disease is also associated with a reduced plasma volume compartment and sympathetic hyperactivity of the peripheral vascular bed.[3,4] The objective of this study was to determine whether the frequently observed combination of sympathetic hyperactivity and a subnormal plasma volume as seen in preeclampsia persists postpartum. In a cohort of apparently healthy, normotensive formerly-preeclamptic women with subnormal plasma volumes, sympathetic activity was indeed higher than in the control group with normal plasma volumes. Autonomic balance, estimated as the LF/HF ratio of heart rate spectrum, was higher in women with a subnormal plasma volume and was accompanied by a lower LF baroreflex gain. Theoretically, the low baroreflex gain in transfer function between PI and SBP is either due to a diminished LF variability of PI, an enhanced LF variability of SBP, or both factors. The present data indicate that in the subgroup of formerly preeclamptic women with LPV, the sympathetic modulation of PI is unaltered while their sympathetic modulation of SBP is rather enhanced. Since blood pressure fluctuations are derived from variations in cardiac output and vascular resistance, and given the fact that sympathetic modulation of PI was not altered (cardiac output is heart rate times stroke volume), it is most likely that the increased magnitude of SBP fluctuations at 0.1 Hz is of a vascular origin and may reflect a vascular sympathetic hyperactive state. The present study was performed 6 to 12 months after the preeclamptic pregnancy. It does not answer whether the enhanced sympathetic activity is a consequence of the former preeclamptic period (and may even resolve over time), or that it is a latent pathophysiological factor contributing to the development of preeclampsia.

In the early stages of chronic hypertension, plasma volume is reduced. Considering the association between a low plasma volume in the pre-pregnant state and subsequent pregnancy-related hypertensive complications, a low plasma volume may represent a condition of "pre-hypertension" or latent hypertension.[5,8] This view is further supported by the association made between preeclampsia and the increased remote risk to develop clinical hypertension and other cardiovascular disorders.[15] A low plasma volume may originate from sympathetic hyperactivity, leading to a higher vascular tone and with it, a compensatory lower intravascular volume.[9,10] Conversely, sympathetic hyperactivity could also be an effect of a primarily reduced plasma volume compartment, and serve to preserve cardiovascular function.[16] The results of this study do not discriminate between these two options.

In a recent study, serial assessment of cardiovascular autonomic modulation during pregnancy displayed a concomitant increased resting sympathetic activity and increased orthostatic stress response in early pregnancy in normotensive women destined to develop preeclampsia.[17] These observations are in line with a reduced circulatory volume in early pregnancy, triggering sympathetic hyperactivity. Therefore, it is possible that the sympathetic hyperactivity as observed during preeclampsia may precede the complicated pregnancy, predisposing for the development of the hypertensive disorder in advanced pregnancy.[3,17]

In both non-pregnant and pregnant humans and animals, impairment of baroreceptor mediated modulation of heart rate has been reported to accompany high blood pressure and low plasma volume conditions.[18–22] Since a reduced pre-pregnant plasma volume predisposes for a blunted increase in vascular compliance and plasma volume during pregnancy, and eventually for a hypertensive complication in pregnancy, the observation of reduced baroreflex sensitivity amongst these normotensive women with a low plasma volume may indicate an already subclinically changed vascular system.[9,10] Structural (ie, vascular remodeling) and/or functional changes (ie, responsiveness to vasoactive stimuli) in the arterial vascular wall as well as a reduction in venous compliance leading to a relative resistance to increase venous return may be responsible for these baroreflex readjustments.[9,10,18,20–22]

In conclusion, the results of this study provide evidence for the concept that low plasma volume in normotensive formerly preeclamptic women coincides with sympathetic hyperactivity along with an altered autonomous control of the cardiovascular system as indicated by reduced baroreflex sensitivity. Whether these alterations in the autonomic control mechanisms is cause or effect of the diminished plasma volume, remains to be elucidated.

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