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Reprod Sci. Author manuscript; available in PMC 2010 May 24.

Published in final edited form as:
Reprod Sci. 2009 October ; 16(10): 980–985. doi:10.1177/1933719109338876.

The Relationship of Plasma Volume, Sympathetic Tone and Pro-Inflammatory Cytokines in Young Healthy Nonpregnant Women

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Abstract

Objective—Preeclampsia has been associated with elevated pro-inflammatory markers, increased sympathetic activity and decreased plasma volume. We hypothesized that these associations would be identified in women prior to a first pregnancy.

Methods—We studied 76 healthy nulligravid subjects measuring the pro-inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha. Plasma volume (PV) was measured in supine position and corrected for body mass index (BMI). We examined supine plasma levels of epinephrine and norepinephrine and blood pressure response to Valsalva's maneuver to quantify sympathetic activation. We then examined the association of plasma volume and sympathetic activity with pro-inflammatory cytokines with $P < 0.05$ accepted for significance.

Results—CRP was significantly increased in subjects with lowest PV/BMI quartile when compared to middle two quartiles and highest quartile (ANOVA, $p = 0.037$). We found no significant association of PV/BMI with either interleukin 6 or tumor necrosis factor alpha. Both plasma epinephrine concentration ($r = 0.29$, $P = 0.02$) and the phase II_L blood pressure response to Valsalva's maneuver ($r = 0.44$, $P < 0.0001$) were associated with serum IL-6 concentrations.

Conclusions—Low plasma volume is associated with increased CRP levels and increased sympathetic tone is linked to elevated IL-6 concentration in young non-pregnant women. These findings represent elements of a non-pregnancy phenotype that parallels the findings observed in preeclampsia and in women at risk for ischemic cardiovascular disease. This suggests that the relationships observed during preeclampsia, which have been associated with placental pathology, may predate pregnancy and be independent of placental activity.

Introduction

Preeclampsia is a pregnancy-specific disorder characterized by hypertension and proteinuria that occurs in the second half of pregnancy (1). It is a leading cause of maternal and fetal morbidity and mortality and occurs most often in nulliparous patients. The exact etiology is unclear, but the disorder has been associated with decreased maternal plasma volume and increased sympathetic tone (2–8). In addition, there is evidence to support an association between preeclampsia and inflammatory cytokines (9–10).

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Patients who develop preeclampsia during pregnancy are at increased risk of long-term cardiovascular complications, such as ischemic cardiovascular disease, thromboembolic disease, and chronic hypertension (11–14). These diseases, most specifically ischemic cardiovascular disease, appear to be associated with elevations of inflammatory cytokines (15,16). This suggests a common thread of underlying physiologic factors that may predispose to the development of these diseases.

We have hypothesized that preeclampsia can result from an intolerance to the normal volume expansion of pregnancy in some women with a specific prepregnancy phenotype (17). We have suggested that reduced plasma volume is at the core of this prepregnancy phenotype and we have demonstrated, in young healthy women who have never been pregnant, that low plasma volume is associated with increased sympathetic tone and exaggerated platelet activation (18,19), findings that are associated with both preeclampsia and long term cardiovascular risk (20,21). In strong support of this hypothesis a group of investigators from Maastricht has recently demonstrated that plasma volume between pregnancies, in women who had preeclampsia in their first pregnancy, is a predictor of pregnancy complications in future pregnancies (22,23). Most recently their results suggest that inter-pregnancy plasma volume in those with prior preeclampsia completely discriminated future pregnancy hypertensive complications of pregnancy (24). In their observations all women with low inter-pregnancy plasma volume went on to develop recurrent hypertensive disease of pregnancy, while those with higher inter-pregnancy plasma volumes did not.

In this study we sought to determine the relationship between levels of the inflammatory cytokines C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), all of which are increased in women with preeclampsia, with sympathetic tone and plasma volume in nulligravid women of reproductive age. We hypothesized that the association between low plasma volume, elevated sympathetic tone and increased inflammatory cytokines observed in women with preeclampsia would exist as a cohort phenotype prior to pregnancy supporting an expanded view of prepregnancy phenotypes and their relationship to the clinical laboratory associations observed in women with preeclampsia.

Material and Methods

Seventy-six women of reproductive age were recruited for participation in this study through an open enrollment. The study subjects were between the ages of 18 and 40 years, nonsmokers, free from major medical illness including cardiovascular disease or diabetes mellitus and taking no regular drugs or medications other than thyroid replacement. All subjects were studied in the fasting state. They were asked to abstain from alcohol and caffeine for at least 24 hours prior to the study, and to avoid the use of decongestants and non-steroidal medications for at least 48 hours prior to the study. All studies were performed during the follicular phase of the menstrual cycle. On the morning of study women were questioned and were free of either recent (72 hours) or current illness and all women were afebrile and had normal vital signs at admission

Each study began at about 7:00 am. Subjects were admitted to the University of Vermont General Clinical Research Center following an overnight fast. A first-void urine was obtained for a pregnancy test. In addition, height and weight were obtained to calculate body mass index (BMI). The subject was placed in supine position. An 18-gauge intravenous saline lock was placed in the antecubital vein for blood draws and administration of dye. After 30 minutes at rest in supine position a discard blood sample was drawn to clear the indwelling line and the blood immediately surrounding the catheter. Blood was then drawn without venous constriction for measurement of C-reactive protein (mg/L), interleukin-6 (pg/mL), and tumor necrosis factor alpha (pg/mL) concentrations. In addition a superficial forearm vein was

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catheterized and the hand and forearm placed in a warming box set at 50 degrees Celsius to "arterialize" the venous samples (25). After at least 15 minutes in the warming box blood samples for plasma catecholamine assessment were obtained from the indwelling catheter without occlusion. Blood samples were collected in pre-iced tubes and immediately spun with plasma analyzed for free catecholamines (epinephrine, norepinephrine) using a two-step chromatographic purification method that results in a highly purified and concentrated final eluate (26). The purified amines were then quantified using high-pressure liquid chromatography with electrochemical detection. C-reactive protein was measured using the BNII nephelometer from Dade Behring utilizing a particle enhanced immunonepholometric assay. Polystyrene particles are coated with monoclonal antibodies to CRP, which, in the presence of antigen (CRP) agglutinate to cause an increase in the intensity of scattered light. The assay range is 0.16 – 1100 ug/mL. Inter-assay CVs range from 2.1 – 5.7%. Interleukin-6 was measured by ultra-sensitive ELISA (R&D Systems, Minneapolis, MN). The lower detection limit <0.15 pg/mL, detection range 0.156–10.0 pg/mL. We have determined a routine inter-assay CV of 15%. TNF-α is measured by an ultra-sensitive, solid-phase sandwich ELISA using a monoclonal antibody specific for TNF-α (R&D Systems, Minneapolis, MN). The lower detection limit is 0.18 pg/mL with a detection range of 0.5 – 32 pg/mL. Using this method, we have determined a routine inter-assay CV of 18%.

Plasma volume was estimated in supine position using the Evans blue dye dilution test. A 15 mg dose of Evans blue dye was administered, using a pre-weighed syringe, over a one-minute period through the saline lock. The Evans blue dye was prepared as a batched sample for this project. Samples for measurement of baseline plasma values had already been drawn, and additional plasma samples were drawn at ten and thirty minutes after the dye injection to measure disappearance kinetics and calculate plasma volume. Samples were placed in a centrifuge for 30 minutes, and the supernatant plasma was collected. Dye from the samples was absorbed into a sephadex chromatographic column, read with a spectrophotometer at 615 nm absorption, and compared to a standardized solution of Evans blue dye. A log transformed decay line was generated from the ten and thirty minute post-dosing samples, and extrapolated back to calculate plasma volume, a technique described in further detail elsewhere (27,28). The plasma volume was reported in total mL, and as plasma volume per body mass index (PV/BMI), to control for variations in body size.

Continuous non-invasive tonometric radial artery blood pressure monitoring was performed employing the Colin Pilot 9200 device (San Antonio, TX) with auto-standardization to brachial artery measurements. Heart rate/RR interval measurements were obtained by a standard three lead electrocardiogram integrated with blood pressure measurements via the Colin device. Baseline blood pressure and heart rate were estimated following 30 minutes of supine rest by calculating the mean arterial pressure and RR interval from measurements during a sample time window. Sympathetic responsiveness was estimated by measuring the blood pressure response to Valsalva's manuever in the supine position (29). Subjects created a forced expiration for 20 seconds against a non-fixed low flow resistance to a pressure of 40 millimeters of mercury measured with an attached manometer. The calculated difference between the peak mean arterial pressure measured at the end of late phase II response of the Valsalva manuever and the trough mean arterial pressure at the end of the early phase II response is termed the late phase II response (phase II_L) and reflects baroreceptor activity mediated by vascular alpha-adrenergic receptors (29). Additional elements of this technique have been previously outlined (19).

Data are expressed as mean +/− standard deviation (SD). Regression analyses were performed where appropriate. $P < 0.05$ was considered significant. Statistical analysis was performed using SigmaStat software (Version 2.0, Chicago, IL). The University of Vermont Committee

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on Human Research approved this study. All subjects provided written informed consent prior to participation in this study.

Results

At the time of study, subjects were 26.1 +/− 4.8 years, at menstrual cycle day 10.5 +/− 2.0 days, and the mean BMI was 23.4 +/− 3.2 kg/m^2. Subjects were predominantly Caucasian (73/76, 96%). The mean values for the physiologic observations are presented in Table 1.

For purposes of comparison, the relationship of plasma volume to inflammatory cytokines subjects were divided into quartiles, based upon plasma volume per body mass index (PV/BMI). This data is presented in Table 2. Examining the relationship between plasma volume and inflammatory cytokines using ANOVA, we found a significant difference between quartiles of CRP ($p = 0.037$). The mean CRP from the lowest PV/BMI quartile was significantly elevated when compared to the middle two quartiles ($p < 0.05$). In contrast to this, we identified no significant relationship of IL-6 or TNF-alpha to plasma volume corrected for body mass index. We examined the cross correlation of CRP, IL-6 and TNF–alpha in these samples. CRP was strongly associated with IL-6 ($r = 0.40$, $p<0.001$) but was not associated with TNF-alpha ($r = -0.05$, $p = 0.65$). We observed no association of IL-6 with TNF-alpha ($r = 0.14$, $p = 0.24$). The independent relationship of body mass index to CRP was evaluated to determine whether it was the relationship of body size to CRP that defined the significant association of PV/BMI to CRP. In our relatively fit sample of subjects with an average BMI of approximately 23 there was no significant association of BMI to CRP ($r = 0.12$, $p = 0.29$) We did observe a significant direct association of BMI to plasma volume ($r = 0.23$, $P = 0.04$)

Despite its negative association with plasma volume we found that CRP was not significantly correlated with any index of sympathetic tone (Table 3). However, IL-6 was associated with phase II_L response to Valsalva and there was a trend towards an association with plasma epinephrine concentration. Consistent with these observations there was also an inverse relationship of IL-6 with the cardiac R-R interval, but the strength of this relationship fell short of significant (P=0.06). In support of our prior observations there was a significant negative association of plasma volume to Phase II-L Valsalva response, an index of alpha adrenergic responsiveness, and with heart rate. The R value for this relationship is −0.31, $P = 0.006$ for phase II_L response and $R = 0.35$, $P < 0.002$ for heart rate expressed as r-r interval.

Discussion

We have broadly hypothesized that some women develop preeclampsia based in part on their pre-pregnancy physiology. Specifically, we have suggested that chronic low pre-pregnancy plasma volume results in the inability to accommodate the profound physiologic volume expansion of pregnancy (17). Plasma volume is decreased in women with preeclampsia, and there is strong evidence this reduction in plasma volume precedes the clinical manifestations of disease. Aardenburg has recently demonstrated that plasma volume following a pregnancy complicated by preeclampsia strongly predicts recurrent hypertensive complications of pregnancy (24).

Evidence also suggests that women who develop preeclampsia during pregnancy, particularly those with preterm preeclampsia, appear to be at increased risk for cardiovascular disease later in life (12–14). This raises the intriguing possibility that elements of the preeclampsia syndrome share pathophysiologic characteristics with cardiovascular disease and raises the possibility of a shared physiologic predisposition with reduced plasma volume as a component.

Elevated levels of pro-inflammatory cytokines have been identified in patients with preeclampsia (9,10). These cytokines have been observed to be elevated prior to the onset of

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clinical symptoms of preeclampsia (30). Some have speculated the increased pro-inflammatory cytokine environment contributes to abnormal placentation and plays a role in placental ischemia which results in release of molecules capable of inducing oxidative injury, most specifically endothelial cell damage. However, it is still unclear exactly how early in pregnancy the elevation of inflammatory cytokines observed with preeclampsia occurs, and whether it might even precede the pregnancy. It also remains unclear what role these inflammatory cytokines play as active mediators of placental dysfunction or the pathophysiology of preeclampsia.

In this study, we sought to determine if elevated serum pro-inflammatory cytokines, a finding common to both preeclamptic and ischemic cardiovascular syndromes, were linked to either reduced plasma volume or elevated sympathetic tone in young healthy nulligravid women of reproductive age. We have previously demonstrated that prior to pregnancy reduced plasma volume is associated with increased sympathetic tone, an observation which has been confirmed by other investigators (19,31). Our findings demonstrate that CRP levels in the lowest plasma volume quartile were elevated when compared to the middle plasma volume quartiles. Those women with the lowest plasma volume had the highest CRP levels. This suggests there is a biologic subset of nulligravid women with decreased plasma volume and elevated CRP. Elevated levels of CRP are associated with risk for ischemic cardiovascular disease (32–34). CRP levels have even been demonstrated to affect the arteries of children by disrupting endothelial function and promoting early atherosclerotic change (35). Thus, elevated levels of CRP may be a common element found in association with endothelial injury in both the preeclampsia syndrome and atherosclerotic cardiovascular disease.

Sympathetic tone is difficult to quantify and our measures are subject to limitations. The measurement of catecholamines, such as epinephrine, is influenced by synaptic transmitter release and reuptake, neural activity, target receptor density and sensitivity, and blood flow. Regional variations may not be detectable with peripheral blood measurements. Nevertheless we did identify trends associating plasma epinephrine with serum concentration of both tumor necrosis factor alpha and interleukin-6. Valsalva's maneuver provides information about the integration of cardiac and peripheral vascular adrenergic function, but may not be sensitive for the detection of regional variations in cardiovascular adaptation. This may limit information regarding the adaptation in regional beds of interest in preeclampsia including the kidney and uterus. We did however demonstrate a strong association of the phase II_L alpha adrenergically mediated blood pressure response to Valsalva's maneuver with serum levels of IL-6 suggesting a global association of sympathetic responsiveness with the serum concentration of a pro-inflammatory cytokine.

We believe our findings contribute to the hypothesis that a pre-pregnancy phenotype exists that combines many of the sub-clinical elements of the preeclampsia syndrome. These associations support the concept of a common underlying phenotype contributing to both the development of preeclampsia and the long term risks of ischemic cardiovascular disease as the elements of platelet activation, increased sympathetic tone and elevated pro-inflammatory cytokines are common to both and are linked before a first pregnancy (36–37).

Acknowledgments

Supported by NIH R0-1 HL 71944 and GCRC MO-1 RR109

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Table 1

Results of Physiologic Observations (n=76)

Plasma volume (mL)	2638 ± 417
Plasma volume (mL/BMI)	114 ± 20
Hematocrit (%)	36.3 ± 2.2
Cardiac r-r interval (millisecs)	981 ± 165
Epineprine (pg/mL)	23 ± 13
Norepinephrine (pg/mL)	210 ± 79
C-Reactive Protein (mg/L)	1.1 ± 2.5
Interleukin-6 (pg/mL)	1.3 ± 1.7
Tumor necrosis factor alpha (pg/mL)	1.8 ± 1.1

All data are presented as the mean + standard deviation

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Table 2

Values of Inflammatory Cytokines Corresponding to Subject Plasma Volume

Cytokine	Lowest Quartile	Middle Two Quartiles	Highest Quartile	P-value
CRP	0.987 +/− 0.313	0.366 +/− 0.082	0.596 +/− 0.266	0.037
IL-6	1.286 +/− 0.272	1.378 +/− 0.301	0.799 +/− 0.110	0.550
TNF-α	2.076 +/− 0.383	1.786 +/− 0.138	1.685 +/− 0.801	0.550

Plasma volume is defined as mL/BMI. Data are expressed as mean values + standard deviation.

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Table 3

Correlations of Indices of Sympathetic Tone with Inflammatory Cytokines

Comparison	R-value	P-value
[TNF-alpha] vs. [Norepinephrine]	−0.02	0.83
[TNF-alpha] vs. [Epinephrine]	0.24	0.04
[TNF-alpha] vs. Phase II_L Response	0.15	0.21
[TNF-alpha] vs. Cardiac R-R Interval	−0.04	0.72
[IL-6] vs [Norepinephrine]	−0.02	0.84
[IL-6] vs. [Epinephrine]	0.29	0.02
[IL-6] vs. Phase II_L Response	0.44	< 0.0001*
[IL-6] vs. Cardiac R-R Interval	−0.22	0.06
[CRP] vs. [Norepinephrine]	−0.10	0.40
[CRP] vs. [Epinephrine]	0.11	0.33
[CRP] vs. Phase II_L Response	0.13	0.28
[CRP] vs. Cardiac R-R Interval	−0.14	0.24

* designates those associations which reached statistical significance after correction for multiple comparisons.