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Differences in cardiovascular function comparing prior preeclampsics with nulliparous controls

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Abstract

Objective—The objective of the current study was to evaluate cardiovascular function; including blood pressure, cardiac output, pulse wave velocity and vascular compliance in nonpregnant nulliparous women compared to women with a history of preterm preeclampsia.

Study design—This was a case control study. Blood pressure was measured using the Finapres Pro. Baseline cardiac output was determined by echocardiography. Pulse wave velocity was estimated using simultaneous electrocardiographic tracings and ultrasound determined arterial flow waveforms and calculated as estimated distance divided by the time interval between EKG r-wave peak and ultrasound derived peak popliteal artery flow. During volume challenge, 500 mL of lactated Ringers solution was infused through an indwelling antecubital catheter over 10 min. Cardiac output and blood pressure during and 15 min after the infusion were estimated using the Finapres Pro.

Main outcome measures—Indices of arterial stiffness and vascular compliance.

Results: Previous preeclampsics exhibited a significant increase in pulse pressure and cardiac output in response to volume challenge when compared with nulliparous controls. Prior preeclampsics had a strong positive correlation between blood pressure indices ($r = 0.50$ – 0.68 , $p < 0.01$) and pulse pressure ($r = 0.58$, $P = 0.008$) with pulse wave velocity that was not evident in control women.

Conclusions—In women with prior preterm preeclampsia a relationship between blood pressure, intravascular volume and arterial stiffness, is evident in the nonpregnant state and in the absence of hypertension or overt cardiovascular disease. This supports an overarching hypothesis that nonpregnant physiology is an important contributor to pregnancy adaptations.

Keywords

Hypertension; Arterial stiffness; Vascular compliance; Pregnancy; Preeclampsia

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Conflicts of interest
None.

1. Introduction

Preeclampsia is a pregnancy-specific disorder that affects 3–8% of pregnancies.

Preeclampsia has recently been recognized as a maternal risk factor for future cardiovascular disease and likely has etiology based in cardiovascular derangement as the primary clinical hallmark of the disorder is hypertension [1]. Other cardiovascular manifestations that are often associated with preeclampsia, though not routinely recognized clinically, include increased vascular resistance, endothelial dysfunction and decreased vascular compliance [2–4]. Vascular compliance is a key physiologic feature that facilitates appropriate accommodation to the volume expansion of pregnancy. In this regard, increased compliance and decreased vascular resistance during pregnancy ultimately contribute to normal pregnancy outcomes. Likewise, the failure to reduce vascular resistance and increase compliance during pregnancy is associated with abnormal pregnancy outcomes including preeclampsia and low birth weight [3,5,6].

Cardiovascular adaptations to pregnancy, manifest as structural remodeling, appear to persist postpartum, in both women with uncomplicated previous pregnancies, and those who have had previous preeclamptic pregnancies [7–11]. Emerging research focused on postpartum observations in previous preeclampsics has suggested that differences in cardiac function, arterial stiffness, endothelial dysfunction and venous compliance are evident from six to twenty-four months following delivery, as compared to those with previous uncomplicated pregnancies [8–11]. Taken together, this research suggests that differences exist in the nonpregnant state in those who manifest preeclampsia during pregnancy.

While cardiovascular differences can be identified between women with previous uncomplicated pregnancies compared with previous preeclampsics blood pressure generally returns to the normal range within a few months postpartum for women with hypertensive disorders of pregnancy [12,13]. Despite the normalization of blood pressure a relationship between blood pressure and arterial stiffness may persist, highlighting an underlying cardiovascular physiology exposed as volume sensitivity during pregnancy; consistent with a maternal hemodynamic system manifesting reduced compliance. Evaluation of nonpregnant cardiovascular dynamics may thereby illuminate disease mechanisms of preeclampsia. Our laboratory has hypothesized that some women are destined to develop preeclampsia due to decreased prepregnancy vascular compliance that manifests during pregnancy resulting in an inability to properly accommodate the normal and physiologic volume expansion of pregnancy [14].

The current study aimed to evaluate the relationship between blood pressure and arterial stiffness in normotensive previous preeclampsics compared to nonpregnant nulliparous women. To evaluate vascular compliance in these women, we assessed their cardiovascular response to a physiologic volume challenge in the nonpregnant state. We hypothesized that despite the fact that the previous preeclampsics were normotensive at time of study, the relationship between intravascular volume and pressure would be altered compared to women who have never been pregnant. Specifically, we believed that the prior preeclampsics

would exhibit physiology consistent with decreased vascular compliance in the nonpregnant state.

2. Study design

The research protocols were approved by the University of Vermont Human Investigational Committees. All seventy-seven women studied provided written informed consent. Women were recruited through an open regional advertisement as well as advertisement through the Preeclampsia Foundation. Sixteen women were lost to follow up or conceived prior to their scheduled study visit. Eight women had incomplete data sets due to technical difficulties. Fifty-three women remain and comprise the following report. Thirty women were nulliparous, without recent pregnancies, and 23 had classically defined preeclampsia diagnosed prior to 37 weeks of gestation according to American College of Obstetrics and Gynecology criteria. Self-reporting of prior preeclampsia was confirmed by direct chart review. One nulliparous woman had type 1 diabetes, 1 previous preeclamptic had type 2 diabetes mellitus and 1 previous preeclamptic had neurocardiogenic syncope. We identified no additional chronic medical conditions. None of the women were using hormonal contraception for at least 6 weeks prior to study. Some of the prior preeclamptics had more than one pregnancy. In these cases all prior pregnancies were required to be complicated by preeclampsia for study enrollment. Subjects were enrolled consecutively over a 20 month period, from November 2010 through July 2012. Each subject was a nonsmoker and asked to abstain from alcohol and caffeine beginning at least 24 h before the study and to avoid the use of decongestants and nonsteroidal medications beginning at least 48 h before the study. Compliance with this request was confirmed orally on the day of study. All women were placed on a fully provided sodium/potassium and calorie standardized diet for 3 days prior to study evaluations or, if this was not possible due to geographical access, recorded a 3 day dietary diary for evaluation of sodium, potassium and calorie content. All dietary records and food intake were reviewed and evaluated by a certified dietician. All subjects were normotensive at time of assessment and all assessments were performed during the follicular phase of the menstrual cycle.

Subjects were evaluated after an overnight fast in the University of Vermont and Fletcher Allen Hospital Clinical Research Center between 7 AM and 11 AM, in a quiet, temperature controlled room. First-void urine was obtained to confirm nonpregnant status.

3. Physiologic measures

At the study visit, the subject's demographic information including age, previous pregnancy information and current health information was recorded. Height and weight were measured. A blood sample was obtained from an indwelling antecubital venous catheter for glucose analysis after 15 min of supine rest. Doppler echocardiography determined baseline cardiac output (GE Vivid 7, GE Healthcare, Milwaukee, WI). Popliteal pulse wave forms were obtained by Doppler ultrasound using a 10 MHz linear transducer (GE Vivid 7, GE Healthcare). Time from EKG R wave to peak systolic flow in the popliteal artery was used to determine pulse wave velocity (pPWV), relative to the distance from the heart to popliteal artery (distance from heart to popliteal artery was calculated post hoc as height * 0.45).

Plasma volume was assessed using the Evans blue dye dilution method prior to the volume challenge [15]. Blood pressure measurements, heart rate and change in cardiac output during the volume challenge were obtained using the Finometer Pro (Finapres, Amsterdam, Netherlands). After obtaining baseline supine blood pressure, heart rate and cardiac output measurements, subjects received 500 mL of lactated ringers through an indwelling catheter placed antecubitally. The lactated Ringers was infused over 10 min using a pressure bag. Blood pressure and cardiac output continued to be measured for an additional 15 min following completion of the infusion.

Total peripheral vascular resistance (TPVR) was calculated using the following formula: $TPVR = 80 \times \text{mean arterial pressure (MAP)} / \text{cardiac output (CO)}$ [16]. Left ventricular work (LVW), was calculated using the following formula: $LVW = 80 \times \text{MAP} \times \text{CO}$ [16].

4. Statistical analyses

Nulliparous women and those with a history of preterm preeclampsia were compared on baseline characteristics using *t*-tests or Mann–Whitney tests for continuous measures and chi square tests for categorical variables. *T*-tests were also used to compare groups on area under the curve (AUC) values for computed for cardiac output, pulse pressure, mean arterial pressure and heart rate in response to the volume challenge procedure. AUC was calculated as change from baseline. Spearman's rank correlation and regression analyses were used to examine the relationship between blood pressure and pPWV and the association between plasma volume and subjects' response to the volume challenge. Spearman's rank correlation was also used to examine the relationship between cardiovascular measures and length of gestation in previous preeclampsics. All statistical analyses were performed using SAS statistical software Version 9.3 (SAS Institute, Cary, NC). Statistical significance determined based on $\alpha = 0.05$.

5. Results

Demographic information is presented in Table 1. Subjects were predominately Caucasian. There were no significant differences between preeclamptic and nulliparous women in mean age or average menstrual cycle day studied. Previous preeclamptics had significantly higher body mass indices compared to nulliparous women ($p < 0.05$).

Baseline comparisons of physiologic variables, including blood pressure, are presented in Table 2. Compared to the nulliparous group, mean arterial pressure was increased in the previous preeclamptic group due to both elevated systolic and diastolic pressure ($p < 0.01$). LVW was significantly greater in the previous preeclamptics than in the nulliparous women ($p = 0.049$). Additionally, serum glucose levels were significantly lower in the nulliparous women than the previous preeclamptics ($p = 0.01$).

6. Vessel stiffness

The relationship between blood pressure and pPWV in nulliparous and previous preeclamptics women are presented in Fig. 1. There was no correlation between pulse pressure and pPWV in the nulliparous women, however, in the previous preeclamptics, pulse

pressure and pPWV were positively correlated ($r = 0.54$, $p = 0.008$). Similarly, there was no significant correlation between systolic blood pressure and pPWV in the nulliparous women while a significant correlation was seen in previous preeclampsics ($r = 0.68$, $p < 0.001$). In addition, diastolic blood pressure and pPWV were positively correlated in preeclampsics ($r = 0.50$, $p = 0.01$). To control for the potential influence of prior pregnancy on this relationship we used data from a previous study that examined 15 young healthy nonsmoking women after uncomplicated gestations [17]. Women with a previous uncomplicated pregnancy did not exhibit any significant relationships between PWV and any measure of blood pressure. Pulse pressure and PWV ($r = -0.11$, $p = 0.71$), systolic blood pressure and PWV ($r = -0.06$, $p = 0.83$), diastolic blood pressure and PWV ($r = 0.02$, $p = 0.94$) (data not shown).

Stepwise linear regression was used to evaluate the potential confounding effect of BMI and cardiac output in describing the relationship between pPWV and blood pressure. Neither pPWV, BMI nor cardiac output were significant predictors of pulse pressure in the nulliparous group. In the previous preeclamptic group, pPWV was the only significant predictor of pulse pressure ($R^2 = 0.29$, $p = 0.008$). BMI was the only significant predictor of systolic blood pressure in the nulliparous group ($R^2 = 0.19$, $p = 0.014$); while pPWV was the only significant predictor of systolic blood pressure in the previous preeclampsics ($R^2 = 0.46$, $p < 0.001$). Cardiac output was the only independent predictor of diastolic blood pressure in prior preeclampsics ($R^2 = 0.31$, $p = 0.005$) while BMI was the only predictor of diastolic blood pressure in the nulliparous group ($R^2 = 0.14$, $p = 0.04$).

7. Measures of compliance

Pulse pressure and cardiac output response to the volume challenge are displayed in Fig. 2 for nulliparous and previous preeclampsics. Area under the curve (AUC) was computed for the measures pulse pressure, cardiac output, mean arterial pressure and pulse to compare overall response to the volume challenge between the nulliparous and previous preeclampsics. AUC was defined from initiation of the infusion to the end of the monitoring period expressed in terms of change from baseline. The total monitoring period was 25 min, 10 min during infusion and 15 min post-infusion. While pulse pressure of both groups increased in response to the infusion, pulse pressure of the previous preeclampsics increased by approximately 2.5-fold above that of the nulliparous women in response to the volume challenge ($p = 0.01$). Cardiac output increased in both groups in response to the volume challenge, however, cardiac output response in the women who had previous preeclampsia increased approximately 3-fold more than the nulliparous women and remained elevated throughout the monitoring period ($p = 0.04$). This difference in response persisted when the results were controlled for BMI. There were no significant differences in AUC for mean arterial pressure ($p = 0.31$) or heart rate ($p = 0.44$).

We were further interested in evaluating the pressure-volume relationship in the nonpregnant state using the volume challenge, a simulated physiologic stress of volume expansion. Fig. 3 shows Spearman rank correlations between baseline plasma volume, corrected for BMI (PV/BMI), and area under the curve (AUC) for pulse pressure and cardiac output. There was no significant relationship between pulse pressure AUC and PV/BMI in nulliparous women while there was, however, a significant negative correlation in women who had previous

preeclampsia ($r = -0.59$, $p = 0.003$). Similarly, there was no significant relationship in the nulliparous women between cardiac output AUC and baseline PV/BMI whereas previous preeclampsia had a significant negative association ($r = -0.71$, $p < 0.001$).

8. Discussion

Our laboratory has hypothesized that some women are destined to develop preeclampsia due to decreased preexisting, prepregnancy, arterial compliance when faced with pregnancy induced volume expansion. Further, that an intravascular high pressure-low volume relationship exists in a subclinical state prior to pregnancy and that this physiologic state is volume sensitive. This cross-sectional study of blood pressure and vascular dynamics in prior preeclampsia demonstrates a significant alteration in the relationship between blood pressure and vascular stiffness, as compared to nulliparous women, that becomes evident upon volume challenge. This specific cardiovascular adaptation, apparent in the previous preeclampsia, responds to acute saline loading with increased cardiac output and pulse pressure and is likely accompanied by a lower plasma volume in the basal state [11,16].

While most previous preeclamptic women will return to a normal blood pressure range postpartum, studies show that their blood pressure remains elevated above parous women without a previous preeclamptic pregnancy [8–10,18]. Consistent with earlier literature, we also observed a higher blood pressure in previous preeclampsia as compared to our nulliparous population. Interestingly, neither pulse pressure nor pulse wave velocity, in our previous preeclamptic group, were significantly different than the nulliparous group. Some studies performing postpartum pulse wave analysis in previous preeclampsia show no difference in PWV, others show increased PWV as compared to those women with previous uncomplicated pregnancies [8,19,20].

Recent research has suggested that arterial stiffness precedes changes in blood pressure and is an independent predictor of future blood pressure [21]. In our current study, the correlation between blood pressure and arterial stiffness was only evident in the previous preeclampsia, and not identifiable in either the nulliparous or women with previous uncomplicated pregnancies. We have previously published data suggesting preexistence of increased arterial stiffness prior to pregnancy in women who subsequently developed preeclampsia [22,23]. Taken together, these observations strongly suggest increased arterial stiffness, in the nonpregnant state, as an antecedent to increased blood pressure, especially in the context of a cardiovascular stress such as pregnancy. As the two largest contributors to systolic blood pressure are stroke volume and vascular stiffness, it is not surprising that both PWV and cardiac output had large and confounding contributions to systolic blood pressure accounting for 76% of the variability of systolic blood pressure [24,25].

Our observations are unique in that we identified that blood pressure is highly associated with arterial stiffness and that this relationship is exclusive to the previous preeclamptic group, in the absence of current hypertension. There is clearly interplay between cardiac output, blood pressure and arterial stiffness that is apparent in the previous preeclamptic group and absent in the nulliparous group. In those with subclinical cardiovascular disease, these relationships may indicate a tightly coupled dialogue between peripheral vasculature

and central hemodynamics which manifests as hypertension with specific cardiovascular stress.

Arterial compliance is the measure of the change in pressure relative to a change in volume such that a very compliant cardiovascular system will not change much in pressure with great volume changes. Arterial compliance and stiffness are inversely related such that as arterial stiffness increases, compliance generally decreases. It is well established that increased arterial compliance must accompany pregnancy to ensure appropriate accommodation of pregnancy induced volume expansion. Though controversial, some studies show increased cardiac output during pregnancy in those who subsequently develop preeclampsia and after clinical diagnosis [26–28]. One study demonstrated increased cardiac output postpartum existing in previous preeclamptics who remain hypertensive [16]. Increased cardiac output may be reflective of a physiology that exhibits decreased compliance, particularly if this reduction is manifested in both the arterial and, perhaps more importantly, venous compartments, thus increasing preload. Indeed, venous compliance is likely lower in previous preeclamptics [11,29]. Our observations of increased cardiac output and pulse pressure in the previous preeclamptics under the cardiovascular stress of an acute volume load echo these previous studies and support the hypothesis that women who develop preeclampsia have decreased arterial and venous compliance thus increasing preload and causing an increase in cardiac output above that of the nulliparous women.

Volume challenge via intravenous volume infusion is associated with increased left ventricular diastolic filling pressures and has been shown to unmask left ventricular diastolic dysfunction [30,31]. Evidence suggests that up to 40% of previous preterm preeclamptics exhibit some degree of left ventricular altered geometry up to a year postpartum that is reflective of past left ventricular diastolic dysfunction evident in pregnancy, and absent by two years postpartum [10]. Consistent with previous studies, the previous preeclamptics in our study were approximately 2 years postpartum and showed increased LVW [16]. Though we did not measure left ventricular diastolic dysfunction or left ventricular geometry, our evidence of increased LVW in the previous preeclamptics may be suggestive of lingering left ventricular diastolic dysfunction. Further, these observations suggest that both decreased compliance and cardiac dysfunction affect hemodynamics, especially in the context of cardiovascular stress such as a volume load, for up to two years postpartum and these responses may well be present prior to a first pregnancy representing underlying predisposition.

A limitation of the current study is that we did not have a group of women with previous uncomplicated deliveries for comparison for all of our observations and physiologic challenges. Nevertheless, our prior examinations have suggested that the effect of prior pregnancy on postpartum vascular function is to reduce vessel stiffness and increase compliance [17,32]. This effect appears to persist for several years following pregnancy. If this pregnancy induced effect was active in our cohort of postpartum preeclamptics, it would bias the results away from the observed associations. Additionally, we cannot rule out the possibility that while the previous preeclamptic group in the studied cohort is normotensive by standard criteria, the significantly higher blood pressures, when compared with the nulliparous group, may account for the physiologic relationships observed.

We believe that the observations noted above, which identify hemodynamic differences in the nonpregnant state in women with prior preeclampsia, but in the absence of current clinical hypertension or cardiovascular disease, supports the overarching hypothesis that nonpregnant physiology is an important contributor to pregnancy physiology. These findings point to the potential value of evaluating cardiovascular health prior to pregnancy, in the context of understanding subsequent pregnancy outcome. This hypothesis, that prepregnancy maternal hemodynamics contribute centrally to the clinical manifestation of hypertensive complications of pregnancy, diverts sharply from our current conceptualization of preeclampsia pathogenesis. Where we are currently focused on variations of placental implantation and its pathophysiologic consequences the current findings support a hypothesis that highlights the normal, placentally driven, physiologic challenge of pregnancy associated volume expansion, as a primary driver of pregnancy associated hypertension.

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Fig. 1.

Correlations of blood pressure with popliteal pulse wave velocity (PWV) in nulliparous women (left panels) as compared to previous preeclamptics (right panels). Spearman's correlation coefficient was used to evaluate relationships between blood pressure and PWV. A, B: Pulse pressure correlates with PWV. C, D: Systolic blood pressure correlates with PWV. E, F: Diastolic blood pressure correlates with PWV.

Fig. 2.

Change in pulse pressure (A) and cardiac output (B) in response to volume challenge. Pulse pressure and cardiac output were adjusted for baseline values and changes are relative to adjusted baseline values. Volume challenge was initiated after obtaining two minutes of baseline supine values. Lactated ringers infusion occurred over 10 min and beat-to-beat blood pressure monitoring continued for 15 min post-infusion. Pulse pressure and cardiac output area under the curve in previous preeclampsia was significantly higher than nulliparous women ($p = 0.01$ and 0.03 , respectively).

Fig. 3. Pulse pressure (PP, A and B) and cardiac output (CO, C and D) response to volume challenge (area under the curve of beat-to-beat blood pressure monitoring initiated at the start of the volume challenge through the 15 min post-infusion blood pressure monitoring time period) correlates with baseline plasma volume corrected for BMI (PV/BMI) previous preeclamptic (right panels) women but not in nulliparous subjects (left panels).

Table 1

Demographic information.

Characteristic	Nulliparous (n = 30)	Previous preeclamptic (n = 23)	P
Age, y	31 ± 0.8	31.5 ± 1.1	0.68
Race			0.23 [*]
White	25	20	
Non-white	5	3	
Height, cm	165 ± 8	162 ± 1.6	0.17
Weight, kg	67.4 ± 3.0	76.5 ± 3.8	0.06
BMI, kg m ⁻²	25.2 ± 1.0	29.1 ± 1.4	0.02
Menstrual cycle day	10.3 ± 0.7	9 ± 0.9	0.45
Postpartum, y	-	2.3 ± 0.2	-
Gestational age at last delivery, w	-	32.0 ± 1.2	-
Parity	-	1.7 ± 0.2	-

BMI indicates body mass index.

Data are expressed as mean ± SEM, unless otherwise specified. Significance based on *Student's t-test (2-tailed)*, unless otherwise specified.^{*}Significance based on chi square test.

Table 2

Baseline comparisons of physiologic variables.

Characteristic	Nulliparous (n = 30)	Previous preeclamptic (n = 23)	P
CO, L/min	4.5 ± 0.2	4.9 ± 0.3	0.15
CI, L/min/m ²	2.5 ± 0.1	2.7 ± 0.1	0.37
SV, mL/beat	71.2 ± 3.1	71.5 ± 3.8	0.78
HR, beats/min	66.5 ± 1.8	70.3 ± 1.5	0.12
PP, mmHg	46.5 ± 1.2	47.7 ± 1.5	0.51
MAP, mmHg	88.3 ± 1.3	95.8 ± 2.2	0.004
Systolic BP, mmHg	116.0 ± 1.5	123.8 ± 2.6	0.008
Diastolic BP, mmHg	69.5 ± 1.3	76.1 ± 1.9	0.005
TPVR, ×10 ³ dyne·s·cm ⁻⁵	1.7 ± 0.4	1.6 ± 0.4	0.82
LVW, ×10 ³ mmHg·L·min ⁻¹	32 ± 2	38 ± 3	0.049 [#]
PV/BMI, mL/kg·m ⁻²	110.6 ± 3.7	98.8 ± 5.2	0.06
Glucose, mg/dL	84.6 ± 6.0	91.3 ± 6.7	0.01 [#]

CO, cardiac output; CI, cardiac index; SV, stroke volume; HR, heart rate; MAP indicates mean arterial pressure; PP, pulse pressure; BP, blood pressure; TPVR, total peripheral vascular resistance; LVW, left ventricular work; PV, plasma volume.

Data are expressed as mean ± SEM.

Significance based on Student's t-test (2 tailed) unless otherwise specified.

[#] Mann-Whitney statistical test used to assess statistical differences.