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Differences in cardiovascular function comparing prior preeclamptics 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 preeclamptics exhibited a significant increase in pulse pressure and cardiac output in response to volume challenge when compared with nulliparous controls. Prior preeclamptics had a strong positive correlation between blood pressure indices ($r = 0.50–0.68$, $p \leqslant 0.01$) 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.

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 preeclamptics 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.

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While cardiovascular differences can be identified between women with previous uncomplicated pregnancies compared with previous preeclamptics 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 preeclamptics 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 preeclamptics 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 preeclamptics 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.

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.

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

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, x10^3 dyne·s·cm^{-5}	1.7 ± 0.4	1.6 ± 0.4	0.82
LVW, x10^3 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.