Preeclampsia is a pregnancy disorder, characterized by new-onset elevation in blood pressure and proteinuria that occurs in 5% to 8% of pregnancies.¹ Both maternal and fetal complications occur with this condition, including high rates of preterm delivery and intrauterine growth restriction.² Most of the pathological conditions associated with preeclampsia seem to resolve after delivery. However, there is growing evidence that there are differences during the postpartum period between subjects with previous preeclampsia and those with previous uncomplicated pregnancy.

Women with a history of preeclampsia are more likely to develop cardiovascular disease later in life.³⁻¹⁰ Some studies have looked at general hemodynamic parameters (eg, blood pressure, cardiac output, and heart rate), whereas others have measured biochemical markers of dysfunction (eg, endothelial dysfunction, dyslipidemia, oxidative stress, and glucose homeostasis). The objective of this study was to provide a comprehensive cardiovascular and biochemical characterization of women with a history of preeclampsia versus women with an uncomplicated first pregnancy. Specifically, systemic arterial hemodynamic and global and regional mechanical properties, left ventricular structure, endothelial function, and several biochemical markers were examined. We hypothesized that, in subjects with a history of preeclampsia, there are differences in many of these parameters during the nonpregnant state and that a simultaneous assessment of multiple derived indices will better differentiate between the 2 groups of women.

Methods

Study Subjects

The study protocol was approved by the University of Pittsburgh Institutional Review Board, and all of the subjects provided written consent. The Institutional Review Board, and all of the subjects provided written consent.


Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.111.173278
informed consent to participate. This cross-sectional study recruited study subjects from a list of women at the Magee-Womens Hospital central repository, which created a list of names and addresses of women who had delivered a baby in the past 36 months. More than 6400 women were sent study fliers and given a telephone number to call if interested in participating. Of these, >760 women were screened over the telephone for eligibility. To participate in the study, subjects must meet the following inclusion criteria: (1) have delivered a singleton pregnancy 6 to 36 months before test date; (2) be premenopausal and nonsmoking; and (3) currently not be breast-feeding. Potential subjects were excluded for underlying medical conditions, specifically, preexisting cardiac disease, diabetes mellitus, renal disease, systemic lupus, or a known disorder of lipid metabolism. Of the large pool of women screened over the telephone, 71 women were invited to participate and scheduled study visits.

Once enrolled, 2 additional criteria had to be met before obtaining cardiovascular measurements. Subjects were excluded if they were currently pregnant or had >1+ protein detected on urine analysis. Two women were excluded for high protein; another woman was excluded because of pregnancy. Sixty-eight healthy women (18 with previous preeclampsia and 50 with previous uncomplicated pregnancies) between the ages of 18 and 40 years were enrolled in the study. Subjects were evaluated in the Magee-Womens Hospital Clinical Research Center in a quiet, temperature-controlled room.

Preeclampsia during the first pregnancy was confirmed by the presence of gestational hypertension, proteinuria, and hyperuricemia beginning after the 20th week of pregnancy, with resolution of gestational hypertension and proteinuria postpartum. We include hyperuricemia in our classification of preeclampsia because it identifies women with a greater frequency of unfavorable pregnancy outcomes, including preterm birth and small for gestational age infants.11 Gestational hypertension was defined as a new-onset increased blood pressure to an absolute blood pressure ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic after 20 weeks of gestation. Proteinuria was defined as ≥300 mg per 24-hour urine collection, ≥2+ protein on voided urine sample, ≥1+ protein on catheterized urine specimen, or a protein/creatinine ratio of >0.3. Hyperuricemia was defined as plasma uric acid concentration ≥1 SD above reference values at the gestational age the sample was obtained (eg, term, >5.5 mg/dL).12 Diagnosis of preeclampsia was determined retrospectively based on medical chart review by a jury of research and clinical investigators.

Experimental Measurements
At the study visit, the subject’s demographic information (eg, height, weight, age, and previous pregnancy information) was recorded, and urine and fasting blood samples were collected. The following experimental measurements were obtained with the woman supine: (1) vascular segment lengths were measured along the body surface, using the sternal notch as a landmark (heart-to-carcotid, heart-to-femoral, and heart-to-brachial); (2) brachial artery blood pressure and heart rate by oscillometric sphygmomanometry (Sphygmocor, AtCor Medical, Itasca, IL); (3) pressure waveforms at various vascular sites (carotid, femoral, and brachial) by applanation tonometry (SphygmoCor, AtCor Medical, Itasca, IL); (4) 2D, M-mode, and Doppler echocardiographic assessment of the left ventricle (GE Vivid 7, GE Healthcare); and (5) endothelial function by venous occlusion plethysmography (D. E. Hokanson, Bellevue, WA). Biochemical analyses of blood included markers of endothelial dysfunction (cellular fibronectin and E-selectin), dyslipidemia (triglycerides, apolipoprotein B, free fatty acids, total cholesterol, high-density lipoprotein, and glycerol), oxidative stress (malondialdehyde), and glucose homeostasis (insulin and glucose). Additional methodologic details (including a specific protocol for obtaining blood pressure measurements) can be found in the online Data Supplement, available at http://hyper.ahajournals.org.

Calculated Variables
Systemic hemodynamic variables (various mean pressures and flows) and steady (total vascular resistance [TVR]) and pulsatile (global arterial compliance) components of systemic arterial load were calculated from measured data (carotid pressure waveform, Table 1. Demographic Findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Previous Uncomplicated Pregnancy (n=50)</th>
<th>Previous Preeclamptic Pregnancy (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29.9±0.6</td>
<td>28.1±1.3</td>
<td>0.176</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>46</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±1</td>
<td>161±2</td>
<td>0.004*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.3±2.3</td>
<td>68.7±4.8</td>
<td>0.331</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>26.3±0.8</td>
<td>26.4±1.7</td>
<td>0.959</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.52±0.06</td>
<td>2.35±0.12</td>
<td>0.407</td>
</tr>
<tr>
<td>Postpartum, mo</td>
<td>16.5±0.6</td>
<td>16.5±1.1</td>
<td>0.964</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BSA, body surface area. Data are mean±SEM. *P<0.05, previous preeclamptic vs previous uncomplicated pregnancy by univariate logistic regression.

brachial artery cuff blood pressures, and aortic blood flow). Pulse wave velocity (PWV) was used to characterize regional vascular stiffness. Echocardiography-based assessment of the left ventricle included measurements of systolic and diastolic chamber diameters and wall thicknesses and the calculation of muscle mass. Endothelial function was quantified using forearm blood flow (FBF) measurements at baseline and under mental stress.

Statistical Analysis
All of the statistical analyses were performed using the SPSS software (IBM Corporation, Somers, NY). Data are presented as mean±SEM. Univariate (simple) logistic models were used to assess differences in individual variables, with P<0.10 denoting marginal significance and P<0.05 statistical significance. Multiple logistic regression was performed via both a forward selection algorithm and inclusion of all of the terms selected a priori to discriminate between the 2 groups on the basis of multiple variables. A forward selection approach was implemented to include only variables that were independently associated with outcome after adjusting for other variables (beginning with the most significant on a univariate level) and to avoid colinearity. The receiver operating characteristic (ROC) curve was constructed to judge the performance of the various logistic models.

Results
Demographic data are presented in Table 1. There were no significant differences between the 2 groups in terms of age, body size, and time since delivery. Although subjects in the previous uncomplicated pregnancy group tended to be taller (P<0.01), there were no statistically significant differences in the calculated values of body mass index or body surface area (BSA).

Data regarding systemic arterial hemodynamics and mechanical properties are presented in Table 2. Compared with the previous uncomplicated pregnancy group, women with previous preeclampsia had elevated mean arterial pressure (MAP) mostly because of a rise in diastolic blood pressure (both of which were significant at P=0.04). Systolic blood pressure was also higher in the previous preeclamptic group, but this was not significant (P=0.07). There were no significant differences in heart rate and cardiac output between the 2 groups. TVR was significantly elevated (P=0.03) in the previous preeclamptic group; however, 2 measures of global arterial compliance (stroke volume to pulse pressure and area method) were not significantly different. Regional vascular
stiffness, as quantified by PWV, was not different for large vessels (no significant difference in heart-to-femoral or heart-to-carotid PWV). Heart-to-brachial PWV tended to be higher (P = 0.06) in women with a history of preeclampsia, which suggests that smaller vessels may be stiffer in this group.

Results for endothelial function testing by venous occlusion plethysmography are presented in Figure 1. Baseline FBF was comparable between the 2 groups. The mental stress test led to a similar increase in heart rate and blood pressure in the 2 groups, with blood pressure higher in the previous preeclamptic group (data not shown). Stress-induced blood flow is characterized by 3 measurements: (1) stress FBF; (2) excess FBF (ie, difference between stress FBF and baseline FBF); and (3) percentage increase in FBF (ie, excess FBF divided by baseline FBF). Stress and excess FBF were significantly lower in the previous preeclamptic group compared with the uncomplicated pregnancy group (stress FBF 6.0 ± 0.6 versus 8.3 ± 0.5 mL·100 mL−1·min−1; P = 0.02 and excess FBF 3.4 ± 0.5 versus 5.7 ± 0.5 mL·100 mL−1·min−1; P = 0.01). Percentage increase in FBF was significantly attenuated in the previous preeclamptic group (245% ± 21% versus 136% ± 22%; P = 0.01). These data suggest impaired endothelial function in the previous preeclamptic group.

No differences in left ventricular properties were observed. These data are presented in the online Data Supplement (Table S1, supplementary material).

The values of the biochemical markers are presented in Table 3. No differences were detected in the 2 markers for endothelial dysfunction (cellular fibronectin or E-selectin), dyslipidemia (triglycerides, apolipoprotein B, free fatty acids, total cholesterol, high-density lipoprotein, and glycerol), or oxidative stress (malondialdehyde). Circulating concentrations of insulin were similar between the 2 groups, but glucose levels tended to be elevated in previous preeclampsia (245% ± 21% versus 136% ± 22%; P = 0.01). These data suggest impaired endothelial function in the previous preeclamptic group.

Odds ratios and P values for logistic regression modeling are shown in Table 4. The specific variables listed in Table 4 were selected based on physiological relevance; in cases where multiple variables represented the same or similar construct (eg, body mass index and BSA), we considered both physiological and statistical significances. Multiple logistic regression models were run with and without a forward selection approach. The purpose of this step was to build a model that could discriminate between the 2 groups of women. The 3 variables selected from the forward selection process were then specified as predictors of preeclampsia (BSA, MAP, and excess FBF). Although not significant on the univariate level, BSA got included in the final multiple logistic regression model based on having the highest level of

### Table 2. Systemic Arterial Hemodynamic and Mechanical Properties

<table>
<thead>
<tr>
<th>Variable</th>
<th>Previous Uncomplicated Pregnancy</th>
<th>Previous Preeclamptic Pregnancy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>65 ± 1</td>
<td>68 ± 3</td>
<td>0.292</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>99 ± 2</td>
<td>107 ± 4</td>
<td>0.069</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>64 ± 1</td>
<td>68 ± 2</td>
<td>0.037*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>80 ± 1</td>
<td>86 ± 3</td>
<td>0.038*</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>36 ± 1</td>
<td>39 ± 3</td>
<td>0.240</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.2 ± 0.1</td>
<td>4.1 ± 0.2</td>
<td>0.491</td>
</tr>
<tr>
<td>SV, mL</td>
<td>66 ± 2</td>
<td>62 ± 4</td>
<td>0.251</td>
</tr>
<tr>
<td>TVR, dyne · s/cm²</td>
<td>1562 ± 37</td>
<td>1784 ± 114</td>
<td>0.027*</td>
</tr>
<tr>
<td>ACp, area method, mL/mm Hg</td>
<td>1.7 ± 0.1</td>
<td>1.5 ± 0.2</td>
<td>0.410</td>
</tr>
<tr>
<td>ACp, SV-to-PP ratio, mL/mm Hg</td>
<td>2.0 ± 0.1</td>
<td>1.8 ± 0.2</td>
<td>0.258</td>
</tr>
<tr>
<td>Heart-to-carotid PWV, cm/s</td>
<td>326 ± 14</td>
<td>343 ± 31</td>
<td>0.561</td>
</tr>
<tr>
<td>Heart-to-femoral PWV, cm/s</td>
<td>254 ± 7</td>
<td>239 ± 8</td>
<td>0.255</td>
</tr>
<tr>
<td>Heart-to-brachial PWV, cm/s</td>
<td>374 ± 8</td>
<td>405 ± 20</td>
<td>0.061</td>
</tr>
</tbody>
</table>

HR indicates heart rate; BP, blood pressure; MAP, mean arterial pressure; CO, cardiac output; SV, stroke volume; PP, pulse pressure; ACp, global arterial compliance; TVR, total vascular resistance; PWV, pulse wave velocity. Data are mean ± SEM.

P < 0.05, previous preeclampsia vs previous uncomplicated pregnancy by univariate logistic regression.

### Table 3. Biochemical Markers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Previous Uncomplicated Pregnancy</th>
<th>Previous Preeclamptic Pregnancy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular fibronectin, µg/mL</td>
<td>21 ± 2</td>
<td>24 ± 3</td>
<td>0.337</td>
</tr>
<tr>
<td>E-selectin, ng/mL</td>
<td>29 ± 2</td>
<td>34 ± 4</td>
<td>0.241</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>84 ± 6</td>
<td>73 ± 10</td>
<td>0.363</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>79 ± 3</td>
<td>80 ± 5</td>
<td>0.824</td>
</tr>
<tr>
<td>Free fatty acids, mEq/L</td>
<td>0.29 ± 0.03</td>
<td>0.36 ± 0.04</td>
<td>0.201</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>180 ± 5</td>
<td>176 ± 12</td>
<td>0.726</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>52 ± 2</td>
<td>54 ± 3</td>
<td>0.449</td>
</tr>
<tr>
<td>Glycerol, mg/dL</td>
<td>7.6 ± 0.6</td>
<td>5.9 ± 0.8</td>
<td>0.144</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>5.9 ± 0.5</td>
<td>6.5 ± 1.2</td>
<td>0.636</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>86 ± 2</td>
<td>95 ± 5</td>
<td>0.056</td>
</tr>
<tr>
<td>HOMA index</td>
<td>1.28 ± 0.13</td>
<td>1.65 ± 0.47</td>
<td>0.312</td>
</tr>
<tr>
<td>Malondialdehyde, µM</td>
<td>0.57 ± 0.03</td>
<td>0.55 ± 0.05</td>
<td>0.700</td>
</tr>
</tbody>
</table>

HOMA indicates homeostatic model assessment. Data are mean ± SEM.

In the 2 groups, with blood pressure higher in the previous preeclamptic group (data not shown). Stress-induced blood flow is characterized by 3 measurements: (1) stress FBF; (2) excess FBF (ie, difference between stress FBF and baseline FBF); and (3) percentage increase in FBF (ie, excess FBF divided by baseline FBF). Stress and excess FBF were significantly lower in the previous preeclamptic group compared with the uncomplicated pregnancy group (stress FBF 6.0 ± 0.6 versus 8.3 ± 0.5 mL·100 mL−1·min−1; P = 0.02 and excess FBF 3.4 ± 0.5 versus 5.7 ± 0.5 mL·100 mL−1·min−1; P = 0.01). Percentage increase in FBF was significantly attenuated in the previous preeclamptic group (245% ± 21% versus 136% ± 22%; P = 0.01). These data suggest impaired endothelial function in the previous preeclamptic group.

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No differences in left ventricular properties were observed. These data are presented in the online Data Supplement (Table S1, supplementary material).

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Table 4. Logistic Regression Modeling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Logistic Regression Univariate</th>
<th>Multiple Regression Forward Selection</th>
<th>Multiple Regression Without Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>TVR, dyne - s/cm⁵</td>
<td>1.002</td>
<td>0.027</td>
<td>. . .</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.925</td>
<td>0.176</td>
<td>. . .</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>0.177</td>
<td>0.407</td>
<td>0.139</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>1.094</td>
<td>0.037</td>
<td>. . .</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>1.065</td>
<td>0.038</td>
<td>1.152</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>1.029</td>
<td>0.240</td>
<td>. . .</td>
</tr>
<tr>
<td>ACg, mL/mm Hg</td>
<td>1.000</td>
<td>0.410</td>
<td>. . .</td>
</tr>
<tr>
<td>H-B PWV, cm/s</td>
<td>1.008</td>
<td>0.061</td>
<td>. . .</td>
</tr>
<tr>
<td>CFn, µg/mL</td>
<td>1.022</td>
<td>0.337</td>
<td>. . .</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.884</td>
<td>0.144</td>
<td>. . .</td>
</tr>
<tr>
<td>Glycerol, mg/dL</td>
<td>1.036</td>
<td>0.056</td>
<td>. . .</td>
</tr>
<tr>
<td>Excess FBF, mL - 100</td>
<td>0.695</td>
<td>0.007</td>
<td>0.576</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; TVR, total vascular resistance; BSA, body surface area; BP, blood pressure; MAP, mean arterial pressure; PP, pulse pressure; ACg, global arterial compliance (area method); H-B PWV, heart-to-brachial pulse wave velocity; CFn, cellular fibronectin; FBF, forearm blood flow.

Figure 2. Receiver operating characteristic (ROC) curves for various logistic regression analyses. The multiple logistic regression equation used to construct the ROC curve (solid line) was logit(y) = −5.56 + (−0.531 · excess FBF) + (0.141 · MAP) + (−1.972 · BSA), with the area under the curve of 0.82. MAP indicates mean arterial pressure; BSA, body surface area. Univariate logistic regression equation used to construct the ROC curve for excess FBF (dashed line) was logit(y) = 0.573 + (−0.364 · excess FBF), with the area under the curve of 0.71. Univariate logistic regression equation used to construct the ROC curve for MAP (dash line) was logit(y) = −6.269 + (0.063 · MAP), with the area under the curve of 0.66.

Discussion

The present study provides a comprehensive functional and biochemical assessment of the cardiovascular status of women with previous preeclamptic and uncomplicated pregnancies. At ~16 months postpartum, we found differences between these 2 groups, with previous preeclamptics having higher MAP and diastolic blood pressure, higher TVR, tendency toward higher peripheral (small vessel) vascular stiffness, endothelial dysfunction, and marginal insulin resistance. A simultaneous consideration of multiple measures resulted in better discrimination between the 2 groups.

Arterial Hemodynamic and Mechanical Properties

During pregnancy, blood pressure decreases slightly, increasing toward nonpregnant values as pregnancy progresses. A hallmark of preeclampsia is new onset elevation of blood pressure during the gestational period, which is expected to fall after delivery. We observed higher blood pressures in previous preeclamptics during the postpartum period, consistent with other studies. Higher blood pressure in previous preeclamptics, although still well within the normal range, may precede development of hypertension later in life.

TVR rapidly decreases during the first trimester of uncomplicated (normal) pregnancy, and this decrease is maintained until the end of pregnancy. A common feature of preeclamptic pregnancy is the significantly higher TVR during late gestation (third trimester) as compared with that in uncomplicated pregnancies. Our data indicate that TVR is also higher in women with a history of preeclampsia during the postpartum state, consistent with other published data.

If TVR remains elevated over time, the risk for developing heart disease also increases.

In uncomplicated pregnancy, vasodilation (ie, reduced TVR) is accompanied by an increase in global arterial compliance (ie, reduced vascular stiffness). This increased global arterial compliance is adaptive from multiple perspectives: it accommodates greater intravascular volume without increasing MAP, helps maintain the efficiency of left ventricular-to-arterial system mechanical energy transfer, and helps preserve coronary perfusion pressure by reducing aortic diastolic pressure decay. Global arterial compliance is significantly lower during late gestation in preeclamptic subjects, even after adjusting for higher blood pressures. The current data show no difference in global arterial compliance between women with previous preeclampsia and uncomplicated pregnancies, indicating that, unlike TVR, the gestational differences in global compliance do not persist into the postpartum period.

PWV has been used to quantify regional vascular stiffness: the higher the PWV higher the stiffness and vice versa. A longitudinal study has reported that both central and peripheral PWVs drop between the first and second trimesters of uncomplicated pregnancy, returning back to control values 1 month after delivery. Cross-sectional studies indicate that both central and peripheral PWVs are elevated in the preeclamptic pregnancy as compared with the uncomplicated pregnancy. Regarding the postpartum period, some studies have reported no differences in central PWV. However, a recent report indicates increased central PWV in the previous preeclamptic group. In our study population, we observed no
difference in central PWV between the groups; however, heart-to-brachial PWV tended to be higher, suggesting that peripheral vessels may continue to be stiffer during the postpartum state in women with previous preeclampsia.

Arterial Endothelial Function
During pregnancy, endothelial function is improved such that forearm plethysmography-based indices are increased.\textsuperscript{25} Endothelial dysfunction appears to be a central component of the pathophysiology of preeclampsia,\textsuperscript{26} and flow mediated dilation has also been shown to be reduced during early pregnancy in women who later develop preeclampsia.\textsuperscript{25} In our study, endothelial function was significantly lower postpartum in women with a history of preeclampsia. This is consistent with previous reports\textsuperscript{17,27} and indicates that preeclampsia-associated endothelial dysfunction persists after pregnancy.

Biochemical Markers
Several biochemical markers were examined, all having important physiological significance in pregnancy and preeclampsia. Markers of endothelial dysfunction (eg, cellular fibronectin and E-selectin) and oxidative stress (malondialdehyde and uric acid) are elevated during preeclamptic pregnancy.\textsuperscript{28–30} Lipid metabolism changes dramatically during pregnancy,\textsuperscript{31} with increases in circulating concentrations of triglycerides and cholesterol; and these are even greater during preeclamptic pregnancy.\textsuperscript{30,32} Free fatty acid levels are elevated before the onset of clinical findings of preeclampsia and contribute to endothelial dysfunction.\textsuperscript{33} In the current study, endothelial dysfunction, dyslipidemia, and oxidative stress markers were not different, consistent with other postpartum studies.\textsuperscript{34–37} There are, however, several studies demonstrating differences in these parameters. It is possible that the population of previous preeclampsics studied may not have been homogeneous.

Pregnancy is associated with minimal changes in glucose homeostasis during early to middle gestation, with maternal insulin resistance developing in the third trimester.\textsuperscript{38,39} Insulin resistance occurs in preeclamptic pregnancies much earlier in gestation.\textsuperscript{38,39} Most but not all studies have reported that insulin resistance is also present during the postpartum period in women with a history of preeclampsia.\textsuperscript{2,4,15,17,34,35,37} Our results are somewhat difficult to interpret with regard to insulin resistance. The hallmark of insulin resistance is elevated insulin in relationship to glucose. This is usually assessed, as we did, in fasting samples. In our study, only glucose seemed to be elevated, but this did not reach statistical significance ($P=0.06$). Although homeostatic model assessment and insulin values were in the direction of insulin resistance, the differences with respect to preeclampsia were small.

Left Ventricular Structure
During middle to late gestation in uncomplicated pregnancy, the left ventricular end-diastolic diameter, muscle mass, and outflow tract diameter are higher than values during the postpartum period.\textsuperscript{13} Similar changes are observed in preeclamptic pregnancy.\textsuperscript{40} We did not observe any differences in the indices of left ventricular structure during the postpartum state between the 2 groups (previous uncomplicated pregnancy and previous preeclampsics).

Utility of the Multivariate Characterization
A number of variables seem to be different for the previous preeclamptic group, with some reaching statistical significance based on the univariate analysis. We conducted the multiple logistic regression analysis to examine whether the 2 groups can be better discriminated when several variables are considered simultaneously. As discussed in the Results section, the logistic regression model containing BSA, excess FBF, and MAP provided the best discrimination (area under the ROC curve=$0.82$). The discrimination based on a single variable was not as good, for example, the area under the ROC curve using excess FBF alone was 0.71 and based on MAP alone was 0.66 (Figure 2). Because of the relatively small number of observations (total observations: 68; 50 for previous uncomplicated pregnancies and 18 for previous preeclampsia), we did not test the predictive ability of the regression model on an independent data set. In addition, it is likely that a larger sample size will yield a different, and larger, set of variables in the model. However, the current multiple regression model makes physical sense: the odds ratio of having had a previous preeclamptic pregnancy increases with BSA and MAP and decreases with excess FBF. Thus, we emphasize the point that the previous preeclamptic group is best discriminated from the previous uncomplicated pregnancy group during the postpartum state when multiple variables are considered simultaneously; the definitive identification of these discriminatory variables and unbiased prediction in an independent test set should be investigated further.

Preeclampsia and Cardiovascular Risk Later in Life
Several studies have demonstrated that having preeclampsia is associated with an increased risk of cardiovascular disease later in life.\textsuperscript{3,4,8,10,36,37} Preeclamptic pregnancy is associated with characteristic cardiovascular and biochemical alterations, including vasomotor dysfunction, hypertension, endothelial damage, inflammation, and metabolic disturbances (oxidative stress, dyslipidemia, and insulin resistance). These alterations are known predictors of cardiovascular risk later in life. We observed that some of these alterations continue during the postpartum state in previous preeclamptic women. Whether these are the previous preeclamptic women at a higher risk of cardiovascular disease later in life compared with women with preeclamptic pregnancy without these differences postpartum is not known.

Perspectives
There are cardiovascular functional differences \textless 16 months postpartum among women with previous preeclampsia compared with women with previous uncomplicated pregnancies. The observed differences in the previous preeclamptic group are in the direction associated with greater cardiovascular disease risk later in life. It is presently unclear whether these differences are the remnants of the changes attributed to the preeclamptic pregnancy or whether they were present before pregnancy.
Acknowledgments

We thank Dr Patricia Agatisa (Research Coordinator, Department of Bioethics, Cleveland Clinic, Cleveland, OH) for assistance with analyzing and interpreting the plethysmography data.

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Disclosures

None.

References

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Short Title: Cardiovascular system in prior preeclamptic women

CARDIOVASCULAR SYSTEM DURING THE POST PARTUM STATE IN WOMEN WITH A HISTORY OF PREECLAMPSIA

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Additional Methodological Details

Systemic Arterial Hemodynamics and Mechanical Properties

With subjects in supine position, heart rate and blood pressure were measured in the non-dominant brachial artery using oscillometric sphygmomanometry (Critikon Dinamap, GE Healthcare, Wakesha, WI USA). Three separate blood pressure values were obtained and averaged. A custom Matlab® program (The Mathworks Inc., Natick, MA USA) was used to calculate hemodynamic variables from measured carotid pressure waveform (tonometry, see below), mean and diastolic brachial artery blood pressures (oscillometric sphygmomanometry), and cardiac output (echocardiography, see below) data. The carotid pressure waveform was assumed to be a surrogate for the aortic pressure waveform and was calibrated by equating mean and diastolic pressures at this site to those measured at the brachial site using oscillometric sphygmomanometry.\(^1\) Total vascular resistance (TVR), calculated from the mean arterial pressure and cardiac output, was used to quantify the steady component of systemic arterial load. The pulsatile component systemic arterial load was characterized by global arterial compliance (AC\(_G\)). Two methods were used to estimate AC\(_G\): analysis of the diastolic decay of the carotid pressure waveform using the area method\(^2\) and as the ratio of stroke volume and carotid pulse pressure.\(^3\)

Pulse Wave Velocity (PWV)

All measurements were made with subjects in supine position. ECG leads were placed on the subject and three vascular segment lengths were measured (heart-to-carotid, heart-to-femoral, and heart-to-brachial). A tonometer (Sphygmocor, AtCor Medical, Itasca, IL USA) was used to obtain pressure waveforms at three vascular sites (carotid, femoral, and brachial). Using the Sphygmocor machine, ECG and pressure waveform data were simultaneously recorded for 30 seconds (100 Hz sampling rate) at each of the three sites. These data were analyzed off-line by a custom Matlab® program. Specifically, transit time for the pressure wave to travel from the heart to a given vascular site was calculated as the time difference between the peak of the QRS wave on ECG and the foot of the pressure waveform at that site. The foot of the pressure waveform was identified using the intersecting tangent algorithm.\(^4\) Heart-to-vascular site PWV was calculated as the ratio of the vascular segment length and pulse transit time.

Echocardiographic Assessment

All echocardiographic measurements were performed with subjects in left lateral decubitus position (GE Vivid 7, GE Healthcare, Wakesha, WI USA). Specifically, the following data were recorded: left ventricular dimensions in parasternal short axis (2D-directed M-mode) and apical and four chamber long axis (2D) views, left ventricular outflow tract diameter (D\(_{LVOT}\)) in parasternal long axis view, and aortic blood velocity obtained by continuous and pulsed wave Doppler from the apical window.\(^6\) D\(_{LVOT}\) was measured during systole at the base of the aortic valve leaflets and aortic annular cross-sectional area was calculated assuming a circular orifice of diameter D\(_{LVOT}\). Stroke volume was calculated as the product of aortic velocity-time integral and aortic annular cross-sectional area. Cardiac output was determined as the product of stroke volume and heart rate. Left ventricular mass was calculated using images at end-diastole and the area-length method as recommended by the American Society of Echocardiography.\(^7\) End-diastolic and end-systolic left ventricular wall thickness (septal
and posterior) and chamber diameter were measured from M-mode, short-axis images. Left ventricular fractional shortening was calculated as the difference between end-diastolic and end-systolic chamber diameters divided by end-diastolic chamber diameter.

**Endothelial Function**

Forearm blood flow (FBF) was measured in the non-dominant arm by venous occlusion plethysmography (D. E. Hokanson, Bellevue, WA USA). A wrist cuff was inflated to supra-systolic pressure (200 mmHg) to exclude hand circulation while an upper arm cuff cycled between 15 seconds of inflation (50 mmHg) and 5 seconds of deflation during flow measurements. Baseline FBF was determined by the mean of six to eight FBF measurements. Subjects were then given a rest period of 15 minutes, allowing blood flow in the hand to return to normal. Next, the Stroop Color Word Test, a mental stress test that elicits an endothelial dependent vasodilation, was administered over a period of three minutes. FBF was again measured under stressed conditions. Excess FBF was defined as the difference between stress FBF and baseline FBF and percent increase in FBF was calculated as excess FBF divided by baseline FBF. Systolic, diastolic, and mean brachial blood pressures, along with heart rate, were measured (Critikon Dinamap) in the dominant arm every 3 minutes during the rest period and every minute during the data acquisition period.

**Blood Biochemical Analyses**

Participants were asked to fast for at least eight hours prior to their study visit. Venous blood was collected using BD-vacutainer tubes and immediately centrifuged for 15 minutes at 4°C. Resulting plasma or serum samples were then separated and stored at -80°C in 1mL aliquots for later analysis. Testing of samples was segregated into four categories: (1) endothelial function [plasma cellular fibronectin (Millipore, Bedford, MA USA, elisa kit #08-102) and plasma E-selectin (R & D Systems, Minneapolis, MN USA, elisa kit #BBE-2B)], (2) dyslipidemia [serum triglycerides (Sigma, St. Louis, MO USA, diagnostic kit #343-25P), plasma apo B (Sigma, diagnostic kit #357-A), serum free fatty acids (Wako Chemicals, Richmond, VA USA, diagnostic kit #994-75409), plasma total Cholesterol and HDL (Sigma, diagnostic kit #402-20), and serum glycerol (Sigma, reagent #337-A)], (3) glucose homeostasis [plasma insulin and glucose (Sigma, reagent #115-A)], and (4) oxidative stress [plasma malondialdehyde (liquid chromatography)]. Homeostasis model assessment (HOMA) index was calculated as the product of fasting glucose and insulin values divided by 22.5.
References


Table S1. Left Ventricular Properties

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prior Uncomplicated Pregnancy</th>
<th>Prior Preeclamptic Pregnancy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g)</td>
<td>140.7 ± 6.9</td>
<td>142.8 ± 10.2</td>
<td>0.872</td>
</tr>
<tr>
<td>D_{LVOT} (cm)</td>
<td>1.92 ± 0.02</td>
<td>1.91 ± 0.04</td>
<td>0.427</td>
</tr>
<tr>
<td>D_{LV ED} (cm)</td>
<td>4.45 ± 0.07</td>
<td>4.61 ± 0.11</td>
<td>0.230</td>
</tr>
<tr>
<td>D_{LV ES} (cm)</td>
<td>3.08 ± 0.06</td>
<td>2.92 ± 0.08</td>
<td>0.159</td>
</tr>
<tr>
<td>h_{PW ED} (cm)</td>
<td>0.81 ± 0.02</td>
<td>0.79 ± 0.03</td>
<td>0.575</td>
</tr>
<tr>
<td>h_{PW ES} (cm)</td>
<td>1.34 ± 0.03</td>
<td>1.37 ± 0.07</td>
<td>0.657</td>
</tr>
<tr>
<td>h_{S ED} (cm)</td>
<td>0.75 ± 0.02</td>
<td>0.76 ± 0.03</td>
<td>0.934</td>
</tr>
<tr>
<td>h_{S ES} (cm)</td>
<td>1.16 ± 0.02</td>
<td>1.17 ± 0.04</td>
<td>0.866</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>47 ± 1.6</td>
<td>59 ± 1.2</td>
<td>0.486</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; D_{LVOT}, left ventricular outflow tract diameter; D_{LV ED}, D_{LV ES}, left ventricular end-diastolic and end-systolic diameter, respectively; h_{PW ED}, h_{PW ES}, left ventricular end-diastolic and end-systolic posterior wall thickness, respectively; h_{S ED}, h_{S ES}, left ventricular end-diastolic and end-systolic septal wall thickness, respectively. Data are mean ± SEM. *P<0.05, prior preeclampsia versus prior uncomplicated pregnancy by univariate logistic regression.