Circulating Antiangiogenic Factors and Myocardial Dysfunction in Hypertensive Disorders of Pregnancy

Sajid Shahul, Diego Medvedofsky, Julia B. Wenger, Junaid Nizamuddin, Samuel M. Brown, Surichhaya Bajrcharya, Saira Salahuddin, Ravi Thadhani, Ariel Mueller, Avery Tung, Roberto M. Lang, Zoltan Arany, Daniel Talmor, S. Ananth Karumanchi, Sarosh Rana

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Abstract—Hypertensive disorders of pregnancy (HDP) are associated with subclinical changes in cardiac function. Although the mechanism underlying this finding is unknown, elevated levels of soluble antiangiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt1) and soluble endoglin (sEng) are associated with myocardial dysfunction and may play a role. We hypothesized that these antiangiogenic proteins may contribute to the development of cardiac dysfunction in HDP. We prospectively studied 207 pregnant women with HDP and nonhypertensive controls and evaluated whether changes in global longitudinal strain (GLS) observed on echocardiography is specific for HDP and whether these changes correlate with HDP biomarkers, sFlt1 and sEng. A total of 62 (30%) patients were diagnosed with preeclampsia (group A), 105 (51%) did not have an HDP (group B), and 40 (19%) were diagnosed with chronic or gestational hypertension (group C). Blood was drawn and sFlt1 and sEng levels measured using enzyme-linked immunosorbent assay. Comprehensive echocardiograms, including measurement of GLS, were performed on all patients. Overall, GLS was worse in women in group A (preeclampsia) than those in group B or C. Increasing sFlt1 and sEng levels correlated with worsening GLS (r=0.44 for sFlt1 and r=0.46 for sEng, both P<0.001), which remained significant after multivariable analysis (r=0.18 and r=0.22, both P≤0.01). Increasing levels also correlated with increasing left ventricular mass index, which also remained significant after multivariable analysis (r=0.20 for sFlt1 and 0.19 for sEng, both P=0.01). Elevated circulating levels of antiangiogenic proteins in HDP correlate with and may contribute to myocardial dysfunction as measured by GLS. (Hypertension. 2016;67:1273-1280. DOI: 10.1161/HYPERTENSIONAHA.116.07252.)

Key Words: biomarkers ■ echocardiography ■ hypertension ■ preeclampsia ■ pregnancy

Hypertensive disorders of pregnancy (HDP) affect 5% to 10% of pregnant women, are the most common medical complication of pregnancy in developed countries, and are a leading cause of maternal and fetal death worldwide. HDP include preeclampsia, gestational hypertension, chronic hypertension, and superimposed preeclampsia. Preeclampsia targets the vascular endothelium causing widespread maternal vascular endothelial dysfunction. Antiangiogenic proteins have been implicated as being pathogenic in the development of the observed vascular endothelial dysfunction.

Overexpression of soluble fms-like tyrosine kinase-1 (sFlt1), an endogenous vascular endothelial growth factor inhibitor, is associated with preeclampsia-like phenotypes in a rodent model and symptoms diminish with the addition of vascular endothelial growth factor or placental growth factor. Multiple human clinical studies have established that levels of the sFlt1 and soluble endoglin (sEng) increase in the circulation of pregnant women with preeclampsia. sFlt1 and sEng levels are elevated weeks before the clinical onset of preeclampsia, and the degree of elevation correlates with adverse maternal and fetal outcomes. Few adverse outcomes occur in the absence of angiogenic factor abnormalities.

Although previous studies have detected changes in myocardial function in HDP, a direct association between preeclampsia biomarkers, including sFlt1 and sEng, has not been described. In other abnormal cardiovascular states such as congestive heart failure, increased circulating levels of antiangiogenic proteins have been associated with development of endothelial vascular dysfunction, myocardial dysfunction, and adverse cardiovascular outcomes.

Women with HDP have abnormalities in both systolic and diastolic cardiac function that seem before clinical symptoms. Despite preservation of left ventricular ejection fraction (LVEF), longitudinal muscle fiber shortening is decreased, suggesting the presence of subclinical left ventricular systolic dysfunction. This finding suggests a
potential vascular endothelial pathogenesis because longitudinal muscle fibers are especially vulnerable to ischemia or changes in wall stress because of their subendocardial location. Subclinical myocardial dysfunction can be assessed by measuring global longitudinal strain (GLS), which describes shortening of longitudinal myocardial fibers during systole. As a measure of shortening, GLS values are normally negative, and values closer to zero are worse. Manifestations of diastolic dysfunction in HDP include also impaired myocardial relaxation, an increase in left atrial filling pressures and increases in LV mass index (LVMI).19

We hypothesized that GLS measurement using speckle-tracking echocardiography would detect early cardiac dysfunction in HDP, and that changes in GLS would correlate with increased circulating levels of sFlt1 and sEng. Our prespecified primary analysis assessed the correlation between angiogenic factors levels and GLS. We also evaluated in an exploratory analysis the relationship between angiogenic factors and LVMI, a measure of myocardial remodeling.

Methods

Study Design and Oversight

This prospective case-control study was performed at Beth Israel Deaconess Medical Center (Boston, MA) in accordance with all institutional policies and was approved by the Institutional Review Board. All patients provided written informed consent.

Human Subjects

Pregnant women who delivered at the Beth Israel Deaconess Medical Center were enrolled from July 2013 through November 2014. Eligibility criteria included women at least 18 years of age with a singleton pregnancy of <41 weeks and with a diagnosis of preeclampsia (herein referred to as group A), without any HDP (group B), or gestational or chronic hypertension (group C) as classified in previous studies.25 Exclusion criteria included pre-existing ischemic or valvular heart disease, pulmonary disease, diabetes mellitus, or labor. Participants were recruited on admission to labor and delivery, the antepartum floor, or during a routine prenatal visit. All clinical data were abstracted from medical records.

The diagnoses of preeclampsia, gestational hypertension, and chronic hypertension were based on modified American College of Obstetricians and Gynecologists criteria. Preeclampsia was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg occurring after 20 weeks of gestation with proteinuria. The blood pressure readings were documented on at least 2 occasions 4 hours to 2 weeks apart. Proteinuria, defined as urinary excretion of ≥0.3 g protein in a 24-hour urine specimen or urine protein (mg/dL)/creatinine (mg/dL) ratio of ≥0.3. Superimposed preeclampsia was defined as a patient with chronic hypertension who developed one of the following features of new-onset proteinuria (as described above), sudden increase in proteinuria if already present in early gestation, sudden increase in hypertension, development of hemolysis, elevated liver enzymes, and low platelets syndrome or development of headache, scotoma or epigastric pain.

Women in group C had either gestational or chronic hypertension. Gestational hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg occurring after 20 weeks of gestation with no proteinuria. The blood pressure readings were documented on at least 2 occasions 4 hours to 2 weeks apart. Chronic hypertension was defined as a diagnosis of hypertension before pregnancy or development of systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg on at least 2 occasions before 20 weeks of gestation. An obstetrician (S.R.) unaware of the study results confirmed the clinical diagnosis for all patients.

Echocardiography

Transthoracic echocardiograms were performed at enrollment using a Philips CX-50 (Andover, MA) machine by an experienced sonographer blinded to the subject’s diagnosis and to the levels of angiogenic proteins. Images were obtained with the patient lying in the supine or left lateral decubitus position and reported according to American Society of Echocardiography guidelines. Images were stored in a cine-loop format of 3 cardiac cycles of noncompressed data with associated ECG information. The sonographer performed a comprehensive examination including a complete 2-dimensional and color-flow Doppler valvular assessment along with measurement of indices of diastolic function (E/A, DT, and E’). Ejection fraction and left atrial volume were calculated using the Simpson biplane disc method. LVMI was calculated using the area length method. GLS measurement was performed using fully automated Tomtec software (AutoStrain, Tomtec Image Arena 1.2, Unterschleissheim, Germany), a vendor independent software that uses a computer learning algorithm to facilitate endocardial border detection. This software has recently been validated with good correlation and agreement observed between manual and automated strain measurements. Unlike manual analysis of GLS, analysis with automated software results in no variability with repeated measurements thus minimizing inter- and intraobserver variability.

Measurement of Antepartum Circulating Angiogenic Proteins

Venous blood samples were collected on admission to labor and delivery or the antepartum floor, or during a routine prenatal visit. All samples were drawn within 24 hours of the echocardiogram. Blood samples were centrifuged at 1449 g for 8 minutes at −4°C, after which the plasma was aliquoted, labeled with a study ID and stored at −70°C. A single operator blinded to clinical information performed quantitative sandwich enzyme-linked immunosorbent assay for both sFlt1 and sEng biomarkers on each participant’s plasma sample in duplicate using commercially available kits (R&D Systems, Inc, Minneapolis, MN) as described elsewhere. All assays were performed after delivery in all patients and the treating physicians were unaware of the results.

Statistical Analysis

Antepartum, delivery, and echocardiography measurements are presented as means±SDs, median (25th percentile and 75th percentile) or numbers and percentages depending on the variable type and distribution. Characteristics were compared between groups using independent sample t tests, Wilcoxon Mann–Whitney tests or χ² tests, as appropriate. Angiogenic factors were log-transformed to meet assumptions of parametric testing. Pearson correlation coefficients were calculated to determine the degree of association between log-transformed antepartum angiogenic factors and global GLS (prespecified) or LVMI (exploratory). Univariate and multivariable linear regression models were constructed to test the association between angiogenic factor and GLS, LVMI, and LVEF. Multivariable models were adjusted for clinically relevant confounders: maternal age, body mass index, parity, smoking status, gestational age, and mean arterial pressure. Statistical analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, NC). Two-tailed P values of <0.05 were considered statistically significant.

Power Analysis

On the basis of previous studies and assuming a 2-sided α=0.05, we estimated that 40 participants per group would provide 90% power to detect a true difference in sFlt1 levels.

Results

We enrolled 215 patients, of whom 207 were included in the analysis. Of the 8 patients excluded, 3 participants withdrew from the study, 3 had twins, and 2 patients had gestational diabetes mellitus.
Patient Demographics

Patient characteristics are shown in Table 1. Sixty-two (30%) patients were diagnosed with preeclampsia (group A), 105 (51%) did not have an HDP (group B), and 40 (19%) were diagnosed with gestational or chronic hypertension (group C). Groups did not differ in race or ethnicity. Most women were of white descent reflecting the population seen at the center. Preeclamptic women, when compared with women without any HDP, had significantly higher prepregnancy body mass index \( (P=0.02) \) and a slightly higher gestational age at the time of the echocardiographic recording \( (P=0.003) \). As expected, we found higher systolic \( (P<0.001) \), diastolic \( (P<0.001) \), and mean arterial pressures \( (P<0.001) \) in preeclamptic women (group A) when compared with women without any HDP. Women in group A also had higher systolic, diastolic, and mean arterial pressures (all \( P<0.003 \)) than women in group C. One third of women in group A or C had chronic hypertension, when compared with none in the normal group (group B). Of the women diagnosed with chronic/gestational hypertension, 27.5% (11 of 40) were taking antihypertensives (9 of 11 with chronic hypertension and 2 of 27 with gestational hypertension).

### Angiogenic Factor Measurements

Women with preeclampsia (group A) had higher levels of sFlt1 and sEng (all \( P<0.001 \)) when compared with women without preeclampsia.

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**Table 1. Participant Characteristics by Diagnosis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=62)</th>
<th>Group B (n=105)</th>
<th>( P ) Value†</th>
<th>Group C (n=40)</th>
<th>( P ) Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.6±5.7</td>
<td>30.7±6.1</td>
<td>0.003*</td>
<td>32.1±5.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2 (1, 3)</td>
<td>2 (2, 4)</td>
<td>0.003*</td>
<td>2 (2, 3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Parity</td>
<td>0 (0, 1)</td>
<td>1 (0, 1)</td>
<td>0.01*</td>
<td>0 (0, 1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Prepregnancy BMI, kg/m²</td>
<td>27.6±7.0</td>
<td>25.0±6.4</td>
<td>0.02*</td>
<td>30.7±8.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Race/Ethnicity%</td>
<td>0.32</td>
<td></td>
<td></td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39 (62.9)</td>
<td>65 (61.9)</td>
<td></td>
<td>27 (67.5)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>8 (12.9)</td>
<td>11 (10.5)</td>
<td></td>
<td>7 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Asian§</td>
<td>10 (16.1)</td>
<td>11 (10.5)</td>
<td></td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>5 (8.1)</td>
<td>18 (17.1)</td>
<td></td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>History of chronic hypertension (%)</td>
<td>20 (32.3)</td>
<td>0 (0.0)</td>
<td>0.01*</td>
<td>13 (32.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td>0.01*</td>
<td></td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>49 (81.7)</td>
<td>64 (61.5)</td>
<td></td>
<td>29 (74.4)</td>
<td></td>
</tr>
<tr>
<td>Past/ Quit before pregnancy</td>
<td>10 (16.7)</td>
<td>22 (21.2)</td>
<td></td>
<td>8 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Quit early pregnancy</td>
<td>1 (1.7)</td>
<td>11 (10.6)</td>
<td></td>
<td>2 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>0 (0.0)</td>
<td>7 (6.7)</td>
<td></td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>GA at ECHO (wk)</td>
<td>32.8±3.7</td>
<td>30.7±4.3</td>
<td>0.003*</td>
<td>34.4±5.2</td>
<td>0.11</td>
</tr>
<tr>
<td>BP at time of ECHO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP at assessment</td>
<td>138.8±13.4</td>
<td>104.8±9.7</td>
<td>&lt;0.001*</td>
<td>126.6±16.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diastolic BP at assessment</td>
<td>81.5±10.4</td>
<td>61.5±7.6</td>
<td>&lt;0.001*</td>
<td>74.3±13.4</td>
<td>0.003*</td>
</tr>
<tr>
<td>MAP at assessment</td>
<td>100.6±9.7</td>
<td>75.9±7.1</td>
<td>&lt;0.001*</td>
<td>91.8±13.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BP on day of ECHO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>150.1±12.0</td>
<td>110.0±9.5</td>
<td>&lt;0.001*</td>
<td>135.0±15.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>89.1±8.8</td>
<td>66.0±8.1</td>
<td>&lt;0.001*</td>
<td>81.6±12.1</td>
<td>0.001*</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2077±901</td>
<td>2431±901</td>
<td>0.02*</td>
<td>2895±717</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>GA at delivery, wk</td>
<td>34.1±3.7</td>
<td>35.1±4.1</td>
<td>0.13</td>
<td>37.5±2.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Angiogenic factors at ECHO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sFlt1 (pg/mL)</td>
<td>18873 (10364, 25965)</td>
<td>2003 (1191, 3951)</td>
<td>&lt;0.001*</td>
<td>4680 (1500, 10977)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Endoglin (ng/mL)</td>
<td>37.3 (22.4, 62.4)</td>
<td>8.2 (5.7, 11.9)</td>
<td>&lt;0.001*</td>
<td>11.6 (7.9, 22.0)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Group A=women with preeclampsia; Group B=normal women; Group C=women with gestational or chronic hypertension. Data are presented as mean±SD, median (quartile 1, quartile 3), or number (percentage). BMI indicates body mass index; BP, blood pressure; ECHO, echocardiogram; GA, gestational age; MAP, mean arterial pressure; and sFlt1, soluble fms-like tyrosine kinase-1.

*Significant at \( P<0.05 \).
†Comparison is between women in groups A and B.
‡Comparison is between women in groups A and C.
§All Asian women (with the exception of one) were East Asian.
any HDP (group B). Similar differences in biomarker levels were also found between groups A and C (all $P$≤0.001; Table 1).

As previously demonstrated, sFlt1 correlated with increasing gestational age in our normal group (group B). In our overall cohort, gestational age correlated with sEng levels ($P$=0.004), but not with sFlt1 ($P$=0.17). In our overall cohort, body mass index did not correlate with either sFlt1 or sEng levels.

**Echocardiography Measurements**

GLS was worse in women with preeclampsia (group A) than in women with gestational or chronic hypertension (group C, $P$=0.002) or those without a hypertensive disorder (group B, $P$>0.001). Indices of diastolic function (E/A and E′) were also depressed in women with preeclampsia when compared with group B ($P$<0.01). We found higher LVMI, greater septal wall thickness, and higher left ventricular filling pressures (E/E′, all $P$<0.0001) in women with preeclampsia (group A) than in women without an HDP. We found higher LVMI and higher left ventricular filling pressures (E/E′, all $P$<0.05) in women with preeclampsia (group A) than in women without an HDP (group B) or women with gestational or chronic hypertension (group C). Septal wall thickness was greater in women with preeclampsia (group A) compared with women without an HDP (group B) (Table 2).

In the multivariable regression analyses, we found no correlation between GLS ($P$=0.18) or lateral E′ to septal wall thickness ($P$=0.49). Similarly, we found no correlation between GLS ($P$=0.18) or lateral E′($P$=0.94) to LVMI.

**Correlation Between Angiogenic Factors and Echocardiography Measurements**

Across the entire study population increased sFlt1 levels correlated with worsened GLS ($r$=0.44, $P$<0.001; Figure A). A similar correlation was also observed between increasing sEng levels and worsened GLS ($r$=0.46, $P$<0.001; Figure B). Higher sFlt1 and sEng levels also correlated independently with increasing LVMI ($r$=0.27 and $r$=0.28, both $P$<0.01; Table 3). We found no correlation between LVEF and LAVI (data not shown) and either sFlt1 or sEng ($P$>0.05). Levels of sFlt1 and sEng both correlated with mean arterial pressure (data not shown) similar to previous studies. Levels of sFlt1 and sEng both correlated with mean arterial pressure (data not shown) similar to previous studies. When diastolic function was calculated using the definition used by Melchiorre et al., we found significant higher sFlt1 and sEng levels and a worse GLS in the pathological group defined as lateral E′ <14 cm/s (all $P$<0.001).

In multivariable regression, correlations between sFlt1 levels and worsening GLS persisted after adjusting for maternal age, parity, body mass index, smoking status, gestational age, and mean arterial pressure ($P$=0.01). Similar correlations were also found between increasing levels of sEng and worsening GLS ($P$<0.001), and between LVMI and both sFlt1 and sEng ($P$=0.01) (Table 3).

**Discussion**

In this prospective study of cardiac function in patients with various forms of HDP and nonhypertensive controls, we demonstrate worsening changes in GLS in women with preeclampsia. We further demonstrate that these changes in GLS correlate with circulating levels of preeclampsia biomarkers, sFlt1 and sEng. Circulating levels of sFlt1 also correlated with LVMI, an index of cardiac remodeling. These findings remained robust after adjustment for relevant confounders, including mean arterial pressure.

Our data are consistent with previous work on cardiac function in preeclampsia. We have previously observed changes in GLS, despite a concurrently normal ejection fraction...
fraction in women with preeclampsia.^{20} We have now identified biomarkers that correlate with these changes, suggesting a possible mechanistic link. Increased circulating levels of sFlt1 are associated with systemic vasoconstriction and elevated blood pressures.^{6} However, the association of these biomarkers with worse left ventricular strain persisted after adjusting for mean arterial pressure, thus indicating a role for sFlt1 or sEng independent of blood pressure. One possible mechanism is that elevated sFlt1 levels cause intense small vessel coronary vasoconstriction leading to myocardial ischemia and the changes in cardiac function we observed.^{21,34} The role of sEng is even less clear. Mechanistically, sEng may work through interrupting transforming growth factor-β1 signaling, a pathway that has been previously linked with cardiac fibrosis.^{35} Whether sEng is synergistic with sFlt1 in its effects on myocardial function or whether this is an adaptive response is unknown. Placental growth factor levels (a proangiogenic protein) in this cohort did not correlate with cardiac dysfunction (data not shown), suggesting that the driver of the cardiac dysfunction in preeclampsia is likely mediated by antiangiogenic factors.

Subtle changes in longitudinal strain with preserved EF have been increasingly detectable in conditions predisposing to heart failure include increasing age, hypertension, diabetes mellitus, renal dysfunction, stable angina, and obesity.^{36–39} These observations suggest that remodeling may occur in the absence of changes in EF. Therapeutic vascular endothelial growth factor signaling inhibitors that resemble sFlt1 when used in humans as part of cancer chemotherapy have been associated with new-onset cardiac dysfunction similar to that in women with preeclampsia.^{40} Taken together with the findings reported here, these data raise the possibility that elevated antiangiogenic proteins may contribute directly to the cardiac dysfunction noted during HDP.

Previous work performed by our group and others have found that GLS measurement is a more sensitive marker than LVEF to identify LV dysfunction in preeclampsia.^{19,20,23} Advantages of GLS measurement over LVEF include excellent reproducibility, independence from tethering, and a lack of requirement for geometric assumptions required for ejection fraction measurement.^{41} Previous work performed by Stanton et al^{22} has demonstrated in patients with suspected LV dysfunction, GLS better predicts all-cause mortality than LVEF measurement, especially when LVEF is preserved.

Preeclampsia and accompanying elevated sFlt1 levels are, to date, the strongest known risk factors for the development of peripartum cardiomyopathy, and sFlt1 administration in pregnant animals causes cardiac dysfunction similar to what is observed in patients with preeclampsia.^{31,43} Our work adds to

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**Table 3. Unadjusted and Adjusted Correlation Coefficients Between Angiogenic Factors† and ECHO Parameters**

| Angiogenic Factors | Unadjusted | | | Adjusted‡ | | |
|-------------------|------------|----------------|----------------|----------------|----------------|
|                   | GLS        | LVMi           | LVEF           | GLS        | LVMi           | LVEF           |
|                   | R          | P Value        | r              | P Value        | r              | P Value        |
| sFlt1             | 0.44       | <0.001*        | 0.27           | <0.001*        | −0.14          | 0.16           |
| Endoglin          | 0.46       | <0.001*        | 0.28           | <0.001*        | −0.17          | 0.08           |

GLS indicates global longitudinal strain; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; and sFlt1, soluble fms-like tyrosine kinase-1.

*Significant at P<0.05.

†Natural log transformed.

‡Adjusted for maternal age, parity, body mass index, smoking status, gestational age, and mean arterial pressure.

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**Figure.** Correlation between angiogenic factors soluble fms-like tyrosine kinase-1 (sFlt1, A) and soluble endoglin (B) with global longitudinal strain (GLS) among all patients. Plasma angiogenic factors were measured within 24 hours of echocardiogram analyses.
those findings by correlating circulating levels of sFlt1 to early subclinical cardiac dysfunction and remodeling. These results suggest that sFlt1 may be toxic to the heart, and may trigger changes leading to full-blown peripartum cardiomyopathy among susceptible women. Whether other markers of inflammation such as endothelin-1 or reactive oxygen species could also contribute to cardiac dysfunction in preeclampsia remains to be studied in the future.

Our work may also be clinically relevant to preserving cardiac function in women with preeclampsia. Recent work has demonstrated persistent subclinical cardiac dysfunction on echocardiography in asymptomatic women with a history of preeclampsia that antedates subsequent hypertension in the postpartum period. In addition, these changes allow for early identification of women at highest risk of recurrent preeclampsia in their next pregnancy and, therefore may also provide an opportunity for intervention to mitigate future cardiovascular disease. Once detected, subclinical changes in cardiac function may be amenable to cardioprotective therapies, such as β-blocker use. Previous work has demonstrated that in patients receiving cardiotoxic chemotherapy, β-blocker administration reversed worsening of longitudinal strain. Recently, extracorporeal removal of sFlt1 has been shown to improve pregnancy outcomes in women with preeclampsia. Whether such therapies have a protective effect on the heart remains unknown.

Our observational study has limitations. First, as we did not measure echocardiograms or angiogenic biomarker levels in the postpartum period, we cannot say whether the changes in strain and biomarker levels are persistent or whether the correlations we observed continue after delivery. Second, for this study echocardiograms and blood draws were performed on study enrollment usually in the third trimester. This was not a longitudinal study so we do not know whether these patients had abnormal echocardiograms in the first trimester and before angiogenic factor abnormalities. Thus, no causal inference can be drawn about relationship between angiogenic factors and cardiac dysfunction among this patient cohort. Third, it is possible that chronic hypertension itself may have affected GLS independent of the effect of sFlt1 and sEng. We found, however, in our cohort no significant differences in GLS between patients with chronic and gestational hypertension. After adding chronic hypertension to our multivariate model, GLS remained strongly correlated with both sFlt1 and sEng. In addition, when patients with chronic hypertension were excluded from our analysis, significant differences in biomarker levels and GLS between normal and preeclamptic patients persisted. Thus, our work strengthens the link between antiangiogenic proteins and myocardial dysfunction demonstrated by worsening GLS on echocardiography in women with HDP by establishing an independent correlation between antiangiogenic biomarker levels and myocardial dysfunction.

Perspectives

In this study, we demonstrate a direct association between elevated levels of angiogenic proteins, sFlt1 and sEng, and myocardial dysfunction demonstrated by worsening GLS on echocardiography. These findings have broad implications. HDP are a leading cause of maternal morbidity and mortality, and myocardial dysfunction, both subclinical and clinically overt, are often noted in these patients. By demonstrating this direct association, we are revealing a group of targets for potential therapies to treat the myocardial dysfunction. Furthermore, future work may focus on monitoring levels of angiogenic proteins during such targeted therapies to monitor physiological responses and determine whether myocardial function has improved. In addition, future directions also include determining whether such alterations in angiogenic protein levels are persistent and contribute to cardiovascular disease in the long term.

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Disclosures
S.A. Karumanchi and R. Thadhani are coinventors on patents related to preeclampsia biomarkers that are held at Harvard Hospitals. S.A. Karumanchi has financial interest in Aggamin LLC, and reports serving as a consultant to Siemens, Roche Diagnostics, and Thermofisher Scientific. S. Rana reports serving as consultant to Roche Diagnostics. R. Thadhani has a financial interest in Aggamin LLC and reports serving as a consultant for Roche Diagnostics. The other authors report no conflicts.

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What Is New?

- We demonstrate a direct association between plasma antiangiogenic protein levels and myocardial dysfunction as demonstrated by abnormal global longitudinal strain in women with hypertensive disorders of pregnancy.

What Is Relevant?

- Hypertensive disorders of pregnancy are among the leading causes of maternal morbidity and mortality in developed countries.
- In this study, we demonstrate that plasma antiangiogenic factor levels identify patients at risk for recurrent preeclampsia. Hypertension. 2016;67:748–753. doi: 10.1161/HYPERTENSIONAHA.115.06674.

Novelty and Significance

Elevated circulating levels of antiangiogenic proteins in preeclampsia are correlated with and may contribute to myocardial dysfunction as measured by myocardial strain imaging.

Summary

- We demonstrate a direct association between plasma antiangiogenic protein levels and myocardial dysfunction as demonstrated by abnormal global longitudinal strain in women with hypertensive disorders of pregnancy.
Circulating Antiangiogenic Factors and Myocardial Dysfunction in Hypertensive Disorders of Pregnancy

Sajid Shahul, Diego Medvedofsky, Julia B. Wenger, Junaid Nizamuddin, Samuel M. Brown, Surichhya Bajracharya, Saira Salahuddin, Ravi Thadhani, Ariel Mueller, Avery Tung, Roberto M. Lang, Zoltan Arany, Daniel Talmor, S. Ananth Karumanchi and Sarosh Rana

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