Pulmonary and Systemic Vascular Dysfunction in Young Offspring of Mothers With Preeclampsia

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Background—Adverse events in utero may predispose to cardiovascular disease in adulthood. The underlying mechanisms are unknown. During preeclampsia, vasculotoxic factors are released into the maternal circulation by the diseased placenta. We speculated that these factors pass the placental barrier and leave a defect in the circulation of the offspring that predisposes to a pathological response later in life. The hypoxia associated with high-altitude exposure is expected to facilitate the detection of this problem.

Methods and Results—We assessed pulmonary artery pressure (by Doppler echocardiography) and flow-mediated dilation of the brachial artery in 48 offspring of women with preeclampsia and 90 offspring of women with normal pregnancies born and permanently living at the same high-altitude location (3600 m). Pulmonary artery pressure was roughly 30% higher (mean±SD, 32.1±5.6 versus 25.3±4.7 mm Hg; P<0.001) and flow-mediated dilation was 30% smaller (6.3±1.2% versus 8.3±1.4%; P<0.0001) in offspring of mothers with preeclampsia than in control subjects. A strong inverse relationship existed between flow-mediated dilation and pulmonary artery pressure (r=−0.61, P<0.001). The vascular dysfunction was related to preeclampsia itself because siblings of offspring of mothers with preeclampsia who were born after a normal pregnancy had normal vascular function. Augmented oxidative stress may represent an underlying mechanism because thiobarbituric acid–reactive substances plasma concentration was increased in offspring of mothers with preeclampsia.

Conclusions—Preeclampsia leaves a persistent defect in the systemic and the pulmonary circulation of the offspring. This defect predisposes to exaggerated hypoxic pulmonary hypertension already during childhood and may contribute to premature cardiovascular disease in the systemic circulation later in life. (Circulation. 2010;122:488-494.)

Key Words: endothelium ■ hypertension, pulmonary ■ hypoxia ■ peripheral vascular disease ■ preeclampsia

Epidemiological studies suggest that adverse events in utero may predispose to systemic cardiovascular disease in adulthood, but the underlying mechanisms are unknown, and there is no information with regard to the pulmonary circulation. Preeclampsia is the most frequent complication of pregnancy. It is associated with endothelial dysfunction in the mother, which is related to the release of circulating vasculotoxic factors and the induction of augmented oxidative stress by the diseased placenta.2-5 We speculated that these circulating factors may pass the placental barrier and leave a persistent defect in the circulation of the offspring that may predispose to a pathological response later in life. The hypoxia associated with high-altitude exposure is expected to facilitate the detection of this problem because it induces exaggerated pulmonary hypertension and vascular dysfunction in the systemic circulation in persons displaying endothelial dysfunction.6

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We therefore measured pulmonary artery pressure and flow-mediated dilation (FMD) of the brachial artery in apparently healthy offspring of mothers with preeclampsia and normal control subjects who were born and permanently living at high altitude (3600 to 4000 m). We found that pulmonary artery pressure was higher and FMD was smaller in offspring of mothers with preeclampsia than in control subjects. To examine whether this problem was related to preeclampsia per se or to a genetic abnormality that predisposes the mother to preeclampsia and the offspring to vascular dysfunction, we studied vascular function in siblings of offspring of preeclampsia who were born...
after a normal pregnancy. Finally, oxidative stress is increased in experimental animal models mimicking preeclampsia and facilitates hypoxic pulmonary hypertension in rodents. To test for this potential mechanism, we assessed oxidative stress in the 2 groups.

Methods

Study Subjects and Protocol

Between August 2004 and September 2009, 56 offspring of late-onset, mild to moderate preeclampsia were recruited by contacting obstetricians practicing in the city of La Paz, Bolivia. The diagnosis of preeclampsia was based on the following criteria: new-onset, persistent elevation of systolic and/or diastolic blood pressure >140/90 mm Hg or a rise in blood pressure of 30/15 mm Hg from the baseline level that occurred after 20 weeks of gestation; proteinuria on consecutive dipstick measurements; and normalization of blood pressure and disappearance of proteinuria after delivery. Eight subjects were excluded because of preterm or postterm birth (ie, <37 or >42 weeks of gestation), perinatal hypoxemia, or cardiac or pulmonary malformation. Forty-eight offspring of mothers with preeclampsia (24 girls and 24 boys, mean ± SD age, 14 ± 7 years) who were born after a normal pregnancy so that we could examine whether the suspected vascular abnormality that predisposes the mother to preeclampsia and the offspring to vascular dysfunction was related to preeclampsia per se or to a genetic abnormality that predisposes the mother to preeclampsia and the offspring to vascular dysfunction. All participants were born and had been permanently living in La Paz or its surroundings. All had typical Aymara surnames and self-identified themselves as Aymaras. All studies were performed at the Instituto Boliviano de Biología de Altura in La Paz (altitude, 3600 m). The experimental protocol was approved by the institutional review boards on human investigation of the University of San Andres, La Paz, Bolivia, and the University of Lausanne, Switzerland. All participants (or the parents of those who were <16 years of age) provided written informed consent.

Pulmonary Artery Pressure

Transcatheter Doppler echocardiography was performed in all children to rule out structural heart disease. To estimate systolic pulmonary artery pressure, echocardiographic recordings were obtained with a real-time, phased-array sector scanner (Acuson Cypress or Acuson Sequoia C512, Acuson Siemens, Mountain View, Calif) with an integrated color Doppler system and transducers containing crystal sets for 2-dimensional imaging (3.6 or 6.0 MHz) and for continuous-wave Doppler recording (2.15 or 3.6 MHz) after 15 minutes of supine rest. The recordings were stored on magneto-optical disks for offline analysis by 3 investigators (T.S., C.S.S., and Y.A.). All reported values represent the mean of at least 3 measurements. After tricuspid regurgitation had been localized with Doppler color flow imaging, the peak flow velocity of the tricuspid jet was measured with the use of continuous-wave Doppler, and the pressure gradient between the right ventricle and the right atrium was calculated by use of the modified Bernoulli equation. Right ventricular to right atrial pressure gradient measurements, the standard method for the noninvasive estimation of pulmonary artery pressure, have been validated against invasive measurements at high altitude. In 6 subjects of each group, tricuspid regurgitation could not be detected and pulmonary artery pressure could not be measured. The intraobserver variability and interobserver variability for the right ventricular to right atrial pressure gradient measurements were 5.1 ± 4.6% and 6.0 ± 8.6%, respectively (n = 30).

Vascular Function in the Systemic Circulation

In a representative subgroup of 24 offspring of mothers with preeclampsia and 27 control subjects (Table 2), we assessed systemic conduit artery endothelial function by determining the increase of the brachial artery diameter evoked by reactive hyperemia using high-resolution ultrasound and automatic wall tracking software according to the recommended guidelines. Briefly, the brachial artery was identified ~5 cm above the antecubital fossa with a high-resolution ultrasound device (Acuson Sequoia C512 or Essaote MyLab25 Gold, Genova, Italy) and a high-frequency (7 to 10 MHz) linear-array probe. The ultrasound probe was then fixed in a stereotactic clamp with micrometer movement capabilities (AMC Vascular Imaging, Amsterdam, the Netherlands), and the Doppler flow was recorded continuously throughout the study. After 1 minute of baseline measurements, a pressure cuff placed around the forearm was inflated to 250 mm Hg for 5 minutes. After deflation of the cuff, the...
Switzerland).

diffusing capacity (DLCO)\textsuperscript{16} with a Sensor-Medics 2200 pulmonary
reduced size of the pulmonary microcirculation, we assessed lung
To examine whether pulmonary hypertension was related to a
Monoxide–Diffusing Capacity
analyzed with a system for automatic real-time measurement of the
were measured for 3 minutes. B-mode ultrasound images were
blinded reviewers. We found that at this altitude, the mean difference
in FMD between 2 consecutive measurements taken 24 hours apart
in vessel diameter from baseline. All studies were interpreted by
Pisa, Italy). FMD was expressed as the maximal percentage change
in vessel diameter evoked by nitroglycerin (250 \textmu g orally, UCB-Pharma, Bulle,
Switzerland).

Pulmonary Function and Carbon Monoxide–Diffusing Capacity
To examine whether pulmonary hypertension was related to a
reduced size of the pulmonary microcirculation, we assessed lung
function (FEV\textsubscript{1}, FVC, FEV\textsubscript{1}/FVC, and VA) and carbon monoxide–
diffusing capacity (DLCO)\textsuperscript{16} with a Sensor-Medics 2200 pulmonary
function system (Bilthoven, the Netherlands). DLCO was measured
with the single-breath technique following standard guidelines.\textsuperscript{16} To
adjust for hemoglobin (Hb), the following equations were used: for adolescent boys (>15 years of age): Hb-adjusted DLCO= observed DLCO×(10.22+Hb)/1.7 Hb; for children <15 years of age and women: Hb-adjusted DLCO=observed DLCO×(9.38+Hb)/1.7 Hb. To adjust for altitude, the following equation was used: altitude-adjusted DLCO=measured DLCO×(1.0+0.0035[(PaO\textsubscript{2}−120)]. To calculate the car-
bon monoxide transfer coefficient, DLCO was divided by the alveolar
volume and expressed as DLCO/VA (L min\textsuperscript{-1} mm Hg\textsuperscript{-1} L\textsuperscript{-1}).

Nitric Oxide Inhalation
To examine whether pulmonary hypertension was reversible, partic-
ipants were asked to take part in a study in which we assessed the
effects of nitric oxide inhalation on pulmonary artery pressure. A
representative subgroup of subjects (17 offspring of preeclampsia
and 51 control subjects; Table 3) agreed to participate. For nitric
oxide inhalation (40 ppm for 20 minutes), the subject wore a face
mask connected to a nonbreathing circuit consisting of a gas
delivery system with a 50-L reservoir bag.

Oxygen Saturation
Transcutaneous arterial oxygen saturation and heart rate were mea-
sured in a fingertip with a pulse oximeter (OxiMax N-595, Nellcor,
Pleasanton, Calif).

Analytic Methods
Blood samples were taken on heparin and immediately centrifuged at
4°C, and the plasma was frozen at −80°C. To assess lipid peroxi-

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n=27)</th>
<th>Preeclampsia (n=24)</th>
<th>( \Delta ) Mean (CI 95%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>11 (41)</td>
<td>14 (58)</td>
<td>...</td>
<td>0.27</td>
</tr>
<tr>
<td>Age, y</td>
<td>17 (6)</td>
<td>14 (6)</td>
<td>3.0 (−1.0–6.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3345 (539)</td>
<td>2961 (412)</td>
<td>384 (80–690)</td>
<td>0.01</td>
</tr>
<tr>
<td>SaO\textsubscript{2}, %</td>
<td>91 (3)</td>
<td>92 (2)</td>
<td>−1.0 (−2.0–0.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>74 (16)</td>
<td>75 (13)</td>
<td>−1 (−10–7)</td>
<td>0.73</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>110 (12)</td>
<td>108 (9)</td>
<td>−2 (−4–8)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>72 (5)</td>
<td>73 (7)</td>
<td>−1 (−4–3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Artery diameter, mm</td>
<td>3.3 (0.5)</td>
<td>3.1 (0.5)</td>
<td>0.2 (−0.1–0.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Blood flow, mL/min</td>
<td>9.6 (4.0)</td>
<td>8.2 (3.1)</td>
<td>1.4 (−5.0–2.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>FMD, %</td>
<td>8.3 (1.6)</td>
<td>6.3 (1.2)</td>
<td>2.0 (1.2–2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperemia, %</td>
<td>680 (270)</td>
<td>620 (250)</td>
<td>60 (−193–318)</td>
<td>0.61</td>
</tr>
<tr>
<td>GTN, %</td>
<td>15.8 (3.5)</td>
<td>16.8 (2.7)</td>
<td>−1.0 (−3.9–2.0)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

\( \Delta \) Mean indicates between-group difference in means; CI, confidence interval; SaO\textsubscript{2}, arterial oxygen saturation; HR, heart rate; BP, blood pressure; FMD, flow-mediated dilation; and GTN, glycerin trinitrate–induced endothelium-independent vasodilation. Data are presented as mean (SD).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n=51)</th>
<th>Preeclampsia (n=17)</th>
<th>( \Delta ) Mean (CI 95%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>19 (37)</td>
<td>8 (47)</td>
<td>...</td>
<td>0.57</td>
</tr>
<tr>
<td>Age, y</td>
<td>15 (6)</td>
<td>14 (6)</td>
<td>1 (−2–5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3217 (370)</td>
<td>2756 (533)</td>
<td>461 (181–471)</td>
<td>0.002</td>
</tr>
<tr>
<td>SaO\textsubscript{2}, %</td>
<td>93 (3)</td>
<td>93 (2)</td>
<td>0.1 (−1.4–1.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>71 (11)</td>
<td>74 (14)</td>
<td>3 (−9–4)</td>
<td>0.48</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.8 (1)</td>
<td>3.4 (1)</td>
<td>0.4 (−0.2–1.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>RV-RA before NO, mm Hg</td>
<td>26.0 (4.7)</td>
<td>34.2 (4.4)</td>
<td>−8.2 (−10.0–−5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV-RA during NO, mm Hg</td>
<td>21.2 (4.0)</td>
<td>26.4 (4.2)</td>
<td>−5.2 (−7.4–−2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \Delta ) RV-RA, mm Hg</td>
<td>−4.8 (2.1)</td>
<td>−7.8 (3.2)</td>
<td>3.0 (1.6–4.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( \Delta \) Mean indicates between-group difference in means; CI, confidence interval; SaO\textsubscript{2}, arterial oxygen saturation; HR, heart rate; CO, cardiac output; RV-RA, right ventricular to right atrial pressure gradient; \( \Delta \) RV-RA, nitric oxide-induced changes in RV-RA; and NO, nitric oxide. Data are presented as mean (SD).
Statistical Analysis

Data were analyzed with the GraphPad Prism 5 software package (GraphPad Software Inc, San Diego, Calif). Statistical analysis was performed with an unpaired 2-tailed Student t test. Bonferroni adjustment for multiple comparisons was used when appropriate. Relations between variables were analyzed by calculating the Pearson product-moment correlation coefficients. Unless otherwise indicated, data are given as mean ± SD. Power calculation was performed before the study based on our pulmonary artery pressure data at this altitude in healthy children and in children with pulmonary hypertension related to a predisposition to high-altitude pulmonary edema (unpublished data), assuming similar pulmonary hypertension in the offspring of mothers with preeclampsia. Assuming a 5-mm Hg difference in pulmonary artery pressure between offspring and control subjects (SD of pulmonary artery pressure in referents, 7 mm Hg; power >0.80; α <0.05), 32 subjects were needed in each group to address this aim. A value of P <0.05 was considered to indicate statistical significance.

Results

The characteristics of the participants are shown in Table 1. Body weight, height, arterial oxygen saturation, heart rate, blood pressure, cardiac output, and pulmonary function were comparable in offspring of mothers with preeclampsia and control subjects; as expected, birth weight was significantly lower in offspring of women with preeclampsia than in control children.

The systolic right ventricular to right atrial pressure gradient was roughly 30% higher in the offspring of women with preeclampsia than in control subjects (32.1 ± 5.6 versus 25.3 ± 4.7 mm Hg; P <0.001; Figure 1A), whereas cardiac output was not different between the 2 groups (3.4 ± 1.0 versus 3.8 ± 1.0 L/min; P = 0.20). Baseline brachial artery diameter and blood flow and the ischemia-induced increase in blood flow were comparable between the 2 groups (Table 2). FMD was >30% smaller (6.3 ± 1.2% versus 8.3 ± 1.6%; P <0.001; Figure 1B) in offspring of mothers with preeclampsia than in control subjects, whereas endothelium-independent vasodilation was similar in the 2 groups (16.8 ± 2.7% versus 15.8 ± 3.5%; P = 0.51; Figure 1C). A strong inverse relationship existed between FMD and pulmonary artery pressure (r = −0.61, P <0.001; Figure 2). There was no relationship between birth weight and pulmonary artery pressure or flow-mediated vasodilation in the 2 groups. FMD and pulmonary artery pressure were normal in siblings of offspring of mothers with preeclampsia who were born after normal pregnancy (Figure 3).

DLCO was comparable in offspring of women with preeclampsia and control subjects (Table 1). The nitric oxide–induced decrease in pulmonary artery pressure was almost twice as large in offspring of mothers with preeclampsia than in control subjects (−7.8 ± 3.2 versus −4.8 ± 2.1 mm Hg; P <0.001; Table 3), but pulmonary artery pressure during nitric oxide inhalation remained significantly higher in offspring of women with preeclampsia than in control subjects (26.4 ± 4.2 versus 21.2 ± 4.0 mm Hg; P <0.001; Table 3). TBARS plasma concentration was roughly 30% higher in offspring of mothers with preeclampsia than in control subjects (130 ± 44 versus 100 ± 24 nmol/L; P = 0.007), and a strong inverse relationship existed between oxidative stress and pulmonary artery pressure (r = 0.38, P = 0.01) and FMD (r = −0.77, P = 0.04).

Discussion

Epidemiological studies suggest that adverse events during early life predispose to cardiovascular disease in adulthood, but the underlying mechanisms are incompletely understood, and there is no information on the pulmonary circulation. Here, we show that young offspring of mothers with preeclampsia display marked vascular dysfunction in the pulmo-
nary and systemic circulations, as evidenced by a roughly 30% higher pulmonary artery pressure and a 30% smaller FMD of the brachial artery than in control subjects. This vascular dysfunction was related to preeclampsia itself because siblings of preeclampsia who were born after a normal pregnancy had normal vascular function. These findings provide the first direct evidence in humans that a pathological event during the fetal period causes pulmonary and systemic vascular dysfunction.

Vascular dysfunction in the pulmonary and systemic circulations was a robust finding because we found a close inverse relationship between pulmonary artery pressure and FMD. This dysfunction was not related to a difference in arterial oxygenation because it was comparable in the 2 groups. Vascular dysfunction in offspring of mothers with preeclampsia could be related to preeclampsia per se or to a genetic abnormality that predisposes the mother to preeclampsia and the offspring to vascular dysfunction. To distinguish between these 2 possibilities, we assessed vascular function in siblings of offspring of mothers with preeclampsia who were born after a normal pregnancy. These siblings had normal pulmonary artery pressure and flow-mediated vasodilation of the brachial artery. This finding suggests that preeclampsia per se, possibly by inducing epigenetic alterations in utero, causes vascular dysfunction in the offspring. In line with this speculation, restrictive-diet pregnancy, a mouse model of preeclampsia, induces vascular dysfunction related to an epigenetic mechanism (E.R., S.F.R., P.N., C.S. and U.S., unpublished observation, 2010). Alternatively, we cannot exclude the possibility of a unique genetic makeup of the preeclampsia sibling that predisposes to vascular dysfunction.

Pulmonary artery pressure in the control children was comparable to that reported in the largest series of healthy children of comparable ethnic and socioeconomic background studied at this altitude. On the basis of these data, a pressure gradient >34.5 mm Hg indicates pulmonary hypertension in children at this altitude. In the present study, 13 of 42 (31%) of the offspring of women with preeclampsia but only 4 of 84 (5%) of the control children fulfilled these criteria (P = 0.002). The difference in pulmonary artery pressure does not appear to be related to a difference in the extent of the pulmonary microcirculation because carbon monoxide–diffusing capacity was similar in offspring of women with preeclampsia and control subjects. The decrease in pulmonary artery pressure induced by nitric oxide inhalation was almost twice as large in offspring of mothers with preeclampsia as in control subjects, indicating that the physiological role of nitric oxide is intact in the offspring and that pulmonary hypertension was related, at least in part, to a functional defect. In experimental animal models, fetal insults are associated with a persistent increase in oxidative stress in the offspring. Here, we found that oxidative stress was increased in offspring of women with preeclampsia and related to pulmonary artery pressure and FMD, suggesting that it may represent an underlying mechanism. Finally, pulmonary artery pressure during nitric oxide inhalation remained significantly higher in offspring of mothers with preeclampsia than in control subjects, suggesting that a structural defect, possibly related to remodeling of the pulmonary vascular wall, also contributes to pulmonary hypertension. We previously found that a perinatal insult predi-
poses to exaggerated hypoxic pulmonary hypertension later in life.\textsuperscript{10} Taken together with the present observations, these data suggest that pathological events in utero and during early life may have similar long-term consequences for the regulation of the pulmonary circulation.

The preeclampsia-induced vascular dysfunction may have clinical consequences. Exaggerated hypoxic pulmonary hypertension is an important underlying mechanism of high-altitude pulmonary edema.\textsuperscript{20,21} Offspring of mothers with preeclampsia appear to be at risk for this problem.\textsuperscript{21} Moreover, offspring of women with preeclampsia living at high altitude or suffering from disease states associated with chronic hypoxemia may be at risk for developing sustained pulmonary hypertension and right heart failure. Finally, defective FMD of the brachial artery in offspring of mothers with preeclampsia was related to endothelial dysfunction because endothelium-independent dilation was normal in these subjects. Endothelial dysfunction in the systemic circulation represents a very early step in the development of cardiovascular disease. In line with this concept, epidemiological data show that the risk of arterial hypertension\textsuperscript{22,23} and stroke\textsuperscript{24} is increased in offspring of mothers with preeclampsia.

Limitations

Some limitations apply to the present study. First, we did not study offspring of mothers with gestational hypertension but not preeclampsia. To the best of our knowledge, there is no epidemiological evidence for an increased cardiovascular morbidity in such subjects. Second, the study was cross-sectional and the sample size was relatively small. However, pulmonary and systemic vascular function differed strikingly between the 2 groups, making a false-positive finding very unlikely.

Conclusion

This study demonstrates for the first time in humans that a pathological event during the fetal period, namely preeclampsia, causes systemic and pulmonary vascular dysfunction in the offspring. The pulmonary vascular defect predisposes to exaggerated hypoxic pulmonary hypertension already during childhood, and it is tempting to speculate that the defect in the systemic circulation may contribute to the increased risk of arterial hypertension and stroke in this population.

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Disclosures

None.

References

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