Uterine Vascular Function in a Transgenic Preeclampsia Rat Model

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Abstract—We investigated intrauterine growth restriction, endothelial function, and uterine artery blood flow characteristics in a transgenic preeclampsia rat model with an activated renin-angiotensin system. We compared preeclamptic Sprague-Dawley (SD-PE) rats with normal pregnant Sprague-Dawley and nonpregnant Sprague-Dawley rats. We used transabdominal ultrasound and found that SD-PE rat embryos developed intrauterine growth restriction. Isolated uterine arteries from SD-PE rats incubated with phenylephrine exhibited an increased contractile response, whereas a single high dose of acetylcholine resulted in an impaired vasorelaxation compared with controls. Incremental acetylcholine doses increased relaxation of SD-PE vessels at low acetylcholine doses but caused a paradoxical contraction at higher acetylcholine doses. Indomethacin and a thromboxane-receptor antagonist (SQ 29,548) blocked this effect, suggesting maternal prostanooid-dependent endothelial dysfunction. SD-PE rats had a decreased prostacyclin (6-keto-prostaglandin F1α):thromboxane ratio in the serum compared with normal pregnant Sprague-Dawley rats or nonpregnant Sprague-Dawley. Surprisingly, the Doppler resistance index decreased during pregnancy in SD-PE compared with normal pregnant Sprague-Dawley rats, suggesting unimpaired uteroplacental flow in the uterine artery. Umbilical flow was unchanged with absent end-diastolic flow in all of the groups. Renin-angiotensin system activation–induced preeclampsia is associated with altered placentaion, modified resistance index, and endothelial dysfunction. A disturbed prostacyclin:thromboxane ratio could be an important mediator. (Hypertension. 2008;51[part 2]:547-553.)

Key Words: preeclampsia ■ uterine artery ■ rat ■ endothelial dysfunction ■ intrauterine growth restriction ■ Doppler ultrasound

Preeclampsia affects 3% to 5% of all pregnant women and remains one of the major causes of maternal and fetal morbidity and mortality.¹ The maternal syndrome involves endothelial dysfunction with a disturbed endothelial prostanooid balance, oxidative stress, and inflammation. The pathophysiology involves insufficient trophoblast invasion, incomplete placental spiral artery remodeling, and increased blood flow impedance in the maternal uterine vessels.² Placental insufficiency leads to fetal intrauterine growth restriction (IUGR). Modeling preeclampsia in experimental animals is difficult. We described a transgenic preeclampsia rat model earlier.³ Rat dams transgenic for the human angiotensinogen gene (hAogen) develop proteinuria and hypertension in the second half of pregnancy when mated with sires transgenic for the human renin gene (female hAogen transgenic rat [TGR]×male hRen TGR). The reverse mating (female hRen TGR×male hAogen TGR) and other controls do not show these features. Human plasma renin concentration increased from 0 to ~900 ng of angiotensin (Ang) I per milliliter per hour in late gestation, and the plasma hAogen concentration was 50- to 100-fold higher than controls.³ Activating AT1 receptor antibodies (AT1-AA) were also detected in the model.⁴ A similar transgenic mouse model has been described in which Takimoto-Ohnishi et al⁵ showed that hRen is produced in trophoblast giant cells and secreted into the maternal circulation, whereas hAogen, produced in chorionic trophoblasts and epithelium, was undetectable in the maternal plasma. Spiral arteries of pregnant rats are similar to those in human pregnancy, although the trophoblast invasion pattern differs from that seen in humans.⁶ We studied embryo development and performed in vivo and in vitro studies of uterine vessels in our transgenic renin-angiotensin system (RAS)–activated model. We show a contribution of altered prostaglandin (PG):thromboxane ratio downstream of RAS activation in preeclampsia. The model resembles important hallmarks of PE and may have use in elucidating human preeclampsia-related mechanisms.
**Methods**

Details on the TGR model have been published previously. Local authorities approved the studies along American Physiological Society guidelines. Mean blood pressure, heart rate, and ambulatory activity were continuously recorded by radiotelemetry (Data Sciences International). Female hAogen TGR rats, when mated with an hRen TGR male, develop hypertension and proteinuria in the second half of pregnancy (preeclamptic Sprague-Dawley [SD-PE]). Sprague-Dawley females were mated with an Sprague-Dawley male as controls (pregnant Sprague-Dawley [SD-P]). SD-PE rat blood pressure was 174±4/138±5 mm Hg, and proteinuria was 4.3±0.6 mg/d, whereas blood pressure was 107±7/75±5 mm Hg and proteinuria 0.19±0.13 mg/d in the SD-P group. For some experiments, nonpregnant Sprague-Dawley (SD-NP) rats were used as additional controls.

Rats were euthanized under ether and decapitated. The bifurcation of the iliac artery into the main branch of the uterine artery was prepared, and uterine arteries from both sides were excised. The arteries were transferred to cold (4°C) oxygenated (95% O2/5% CO2) physiological salt solution and dissected into 2-mm rings. Each ring was dispensed between 2 stainless-steel wires in a 5-mL organ bath and connected to a force transducer (Small Vessel Myograph, Danish Myo Technology). A standard pretension was applied to the vessels after equilibration using the software PowerLab Chart5 (ADInstruments). After equilibration, the arteries were exposed to isomolar 60 mmol/L of KCl-containing solution. Thereafter, rings were rinsed with saline 3 times until baseline tone was restored.

Blood was collected in sterile, cold 10-mL tubes containing 2% EDTA in 0.8% sodium chloride and 0.35 mg of the cyclooxygenase (COX) inhibitor indomethacin and immediately centrifuged at 3000 rpm for 10 minutes at 4°C for high-performance liquid chromatography and mass spectrometry (MS) for measuring 6-keto-PGF1α and thromboxane (TxB2). High-performance liquid chromatography was conducted using the Agilent 1200 system with Column Zorbax Eclipse Plus-C18 4.6×150 mm×1.8 μm, operating at 40°C. The buffer solution used was acetonitrile/ammonium acetate (0.01 mol/L, [pH=7.0], Gradient from 15% to 90% Aceto-nitrile in 10 minutes, 0.6 mL/min). For mass spectroscopy, the Triple Quadrupole MS/MS Agilent 6410 was used. The detection limit for TxB2 was 0.1 ng/mL for 6-keto-PGF1α at 0.5 ng/mL. The 6-keto-PGF1α/TxB2 ratio was calculated. Rat sFlt-1 and rat vascular endothelial growth factor (VEGF) were measured using commercially available ELISA kits and were performed according to the manufacturer’s instructions (R&D SYSTEMS).

Doppler studies were performed on separate groups. The animals were anesthetized with 1.5% isoflurane via an oxygen mask. Maternal heart rates and rectal temperatures were monitored (Model THM100, Indus Instruments). Rectal temperature was maintained at 36°C to 38°C. All of the hair was removed from the abdomen, and prewarmed gel was used as an ultrasound-coupling medium. The pregnant rats were imaged at embryonic days 9.5, 12.5, 15.5, and 18.5, and 21.5 with an ultrasound biomicroscope and a 30-MHz or 40-MHz transducer at 30 frames per second (Model Vevo 660, VisualSonics Inc.). In Doppler mode, the high-pass filter was set at 6 Hz, and the pulsed repetition frequency was set between 4 and 48 kHz to detect low to high blood flow velocities, respectively. A 0.2- to 0.5-mm pulsed Doppler gate was used, and the angle between the Doppler beam and the vessel was recorded and was <30°. Waveforms were saved for later offline analysis. The Doppler waveforms were obtained in the proximal uterine artery, the arcuate artery, distal of the main branch of the uterine artery between 2 embryonic implantation sites, and the embryonic umbilical artery. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured from 3 consecutive cardiac cycles that were not affected by motion caused by maternal breathing, and the results were averaged. The resistance index (RI=[PSV−EDV]/PSV) was calculated when EDV was >0 to quantify the pulsatile arterial blood velocity waveforms. For biometric measurements, abdominal and head transversal and longitudinal diameters were measured, and the circumference was calculated. Measurements were made on embryonic days 15.5, 18.5, and 21.5.

All of the values are given as means±SEMs. Student's t tests or ANOVA were used as appropriate. A value of P<0.05 was considered statistically significant; n represents the number of arterial rings studied. Terms such as greater or lesser than are used only when P value is <0.05.

**Results**

SD-PE offspring developed IUGR compared with SD-P offspring (Figure 1). Transabdominal ultrasound showed progressive decrease in abdominal circumference during pregnancy (embryonic days 15.5, 18.5, and 21.5). Whereas at embryonic day 15.5 SD-PE and SD-P rats were not different (n=20 embryos per group), a smaller abdominal circumference was measured in the SD-PE embryos at embryonic days 18.5 and 21.5 (Figure 1A; n=20; P<0.05). The head circumference was not different on embryonic days 15.5 and 18.5...
but showed smaller values on embryonic day 21.1 (Figure 1B; n=18; P<0.05). When calculating the head:abdomen ratio, an increase was visible from embryonic days 15.5 to 18.5 to 21.5 in the SD-PE embryos compared with SD-P embryos (data not shown). The body weights of the SD-PE embryos were reduced (Figure 1C; n=30; P<0.05). The offspring also had lighter livers and brains (Figure 1D). The ratio of brain:liver weight documented asymmetrical growth in these offspring, with more pronounced growth retardation in the livers than in the brains (n=30; P<0.05). These data underscore the resemblance of this animal model to human IUGR.

We exposed isolated uterine artery segments (Figure 2A) to 10 μmol/L of phenylephrine (Phe), which resulted in increased maximal tension in the SD-PE compared with SD-P and SD-NP rats. The comparison is to maximal 60 mmol/L of KCl contraction. Dose-response curves to incremental Phe (Figure 2B) revealed a stronger contractile response in the SD-PE rat vessels compared with the 2 control groups. The SD-P vessels showed a decreased contractile response, in line with normal pregnancy adaptation. Acetylcholine (ACh; 10 μmol/L) resulted in a blunted endothelium-dependent relaxation in SD-PE vessel rings (Figure 2C). SD-P rings instead showed significant relaxation compared with SD-PE or SD-NP rings. Incremental ACh doses (Figure 2D) resulted in a biphasic response in the SD-PE rings, with a pronounced relaxation to low doses of ACh (1×10⁻⁸ to 1×10⁻⁶ mol/L) and a paradoxical contractile response to higher doses (3×10⁻⁶ to 1×10⁻⁵ mol/L) of ACh. This contractile response was absent in SD-P and SD-NP rats. The comparison is to maximal 60 mmol/L of KCl contraction. Dose-response curves to incremental Phe (Figure 2B) revealed a stronger contractile response in the SD-PE rat vessels compared with the 2 control groups. The SD-P vessels showed a decreased contractile response, in line with normal pregnancy adaptation. Acetylcholine (ACh; 10 μmol/L) resulted in a blunted endothelium-dependent relaxation in SD-PE vessel rings (Figure 2C). SD-P rings instead showed significant relaxation compared with SD-PE or SD-NP rings. Incremental ACh doses (Figure 2D) resulted in a biphasic response in the SD-PE rings, with a pronounced relaxation to low doses of ACh (1×10⁻⁸ to 1×10⁻⁶ mol/L) and a paradoxical contractile response to higher doses (3×10⁻⁶ to 1×10⁻⁵ mol/L) of ACh. This contractile response was absent in SD-P and SD-NP rats. The comparison is to maximal 60 mmol/L of KCl contraction. Dose-response curves to incremental Phe (Figure 2B) revealed a stronger contractile response in the SD-PE rat vessels compared with the 2 control groups. The SD-P vessels showed a decreased contractile response, in line with normal pregnancy adaptation. Acetylcholine (ACh; 10 μmol/L) resulted in a blunted endothelium-dependent relaxation in SD-PE vessel rings (Figure 2C). SD-P rings instead showed significant relaxation compared with SD-PE or SD-NP rings. Incremental ACh doses (Figure 2D) resulted in a biphasic response in the SD-PE rings, with a pronounced relaxation to low doses of ACh (1×10⁻⁸ to 1×10⁻⁶ mol/L) and a paradoxical contractile response to higher doses (3×10⁻⁶ to 1×10⁻⁵ mol/L) of ACh. This contractile response was absent in SD-P and SD-NP rats.
rings. Each series is mean±SEM of 18 to 20 uterine artery rings. These experiments showed that the SD-PE uterine artery rings were hyperresponsive to Phe and relaxed with low-dose ACh but exhibited paradoxical vasoconstriction at high-dose ACh.

We next studied contraction and relaxation in the presence of N^o-nitro-L-arginine methyl ester (L-NAME; 100 μmol/L; Figure 3, top) and indomethacin (Figure 3, bottom; 5 μmol/L). L-NAME (100 μmol/L) resulted in no further increase in SD-PE or SD-P ring tension (Figure 3A). Relaxation was nearly abolished after L-NAME in both SD-PE and SD-P ring groups (Figure 3B). Indomethacin (5 μmol/L) caused no change in the contractile response in both groups (Figure 3C). The paradoxical contractile SD-PE ring response to ACh was abolished by indomethacin (Figure 3D). Each series was the mean±SEM of 7 to 8 uterine artery rings. These experiments showed the NO dependency of ACh responses in uterine rings exposed to Phe. They also suggest that the paradoxical SD-PE ring response to high-dose ACh was COX product dependent.

We then incubated the rings with the specific thromboxane-receptor antagonist SQ 29,548 (1 μmol/L). This maneuver did not alter the Phe-evoked contractile response (Figure 4A). However, the paradoxical ACh contraction was abolished in the SD-PE vessels (Figure 4B; n=8; P<0.05). The relaxation in response to ACh was unchanged in SD-P vessels. High-performance liquid chromatography/MS/MS analysis of the maternal blood showed a significantly diminished PGF1α:TXB2 ratio in SD-PE rats (Figure 4C). The mean PGF1α concentration was 1.44±0.65 ng/mL in SD-PE compared with 2.78±0.05 ng/mL in SD-P rats. The mean TXB2 concentrations were 8.10±2.06 and 9.34±1.19 ng/mL. No significant differences between the groups were detected when measuring sFlt-1 and VEGF in the maternal blood using ELISA (Figure 4D). The sFlt-1 concentration in the SD-PE was 242.10±33.82 pg/mL compared with 245.40±35.34 pg/mL in the SD-P rats. The values for total unbound VEGF were 974.5±75.36 pg/mL in SD-PE and 1202.00±68.83 pg/mL in SD-P rats.

Uterine and arcuate artery B-mode ultrasound was performed (Figure 5A and 5B). PSV and EDV were traced, and the RI (RI=PSV/EDV/PSV) was calculated. SD-PE rats showed a decreased RI during pregnancy starting between embryonic days 12.5 and 15.5 in the uterine artery (n=7; P<0.05), whereas the RI remained stable in pregnant SD at embryonic days 9.5 to 18.5 (Figure 5C). Uterine PSV velocities showed a tendency to increase in the uterine arteries of SD-P and did not increase in the SD-PE. The arcuate arteries, located closer to the embryonic implantation sites, showed a lower RI in both groups compared with the uterine artery. In SD-PE rats, a decreased RI was observed between embryonic days 15.5 and 18.5 (Figure 5D). In the arcuate arteries, there was a decreased PSV in SD-PE in late gestation, whereas there were unchanged values in SD-P. Contrary to our expectations, these data showed a decrease RI in the SD-PE rats, although the disease worsens to the point of delivery. We also measured the umbilical artery of SD-PE and SD-P embryos. PSV was detectable at embryonic days 12.5, 15.5, and 18.5, whereas EDV was not detectable at all of the time points. No differences were observed (n=20; data not shown).

**Discussion**

The RAS-activated, transgenic SD-PE rat model features fetal IUGR similar to the human disease. The vascular response to ACh showed an initial adequate relaxation at low doses but a paradoxical failure to relax at higher doses. This vasocontractile response could be blocked with a COX inhibitor or thromboxane receptor antagonist. Furthermore, the PGF1α:TXB2 ratio was diminished in preeclamptic SD, compared with pregnant SD rats, whereas sFlt-1 and VEGF were not altered in this model. We had expected a decrease in Doppler uterine blood flow related to an increase in uterine blood flow RI; however, the
opposite proved to be the case. In addition to the unexpected findings of the SD-PE was the lack of the expected changes in RI of the normal pregnant rat.

We showed that SD-PE embryos had a decelerated growth slope compared with SD-P embryos. When we euthanized the embryos on embryonic day 21.5, these noninvasive findings were substantiated. These results are similar to human IUGR.9 The abdominal circumference thus proved to be a reliable parameter for embryonic growth development in rat pregnancy. The method can be applied to monitor changes in embryonic growth after pharmacological or surgical interventions and could also have use in other investigations of rat pregnancy and embryonic growth. We have shown previously that AT1-AAs are present in SD-PE rats.4 AT1-AAs are also present in the fetuses of preeclamptic mothers.10 We focused on the uterine artery and found a significantly increased contractile response to incremental doses of the pure α-adrenergic agonist Phe in SD-PE rat vessels. Pregnant Sprague-Dawley rats showed a markedly reduced contractile response to Phe stimulation. These data are in line with several studies investigating isolated arteries from humans and animals. Normal pregnancy is associated with a reduced response to vasoconstricting agents, such as norepinephrine, Phe, and Ang II.11 In omental arteries from preeclamptic women, Pascoal et al8 found an increased vascular response to arginine vasopressin. In the reduced uterine perfusion pressure model, a significantly greater contractile response was observed in the aorta, as well as in mesenteric and uterine arteries, compared with the sham-operated controls.12 We next challenged the uterine artery endothelium with 10 μmol/L of ACh. This maneuver resulted in a reduced vasodilatory response in the SD-PE vessels compared with SD-NP or SD-P vessels, which relaxed best. This observation is in line with observations in humans. Vascular smooth muscle relaxation is influenced by endothelium-derived relaxing factors such as NO, prostacyclin (PGI2), endothelium-derived hyperpolarizing factor, and substances derived from the perivascular adipose tissue.7 On the other hand, the endothelium may produce contracting factors, such as endothelin I and thromboxaneA2 (TxA2).13 In preeclampsia, endothelial dysfunction or inappropriate cell activation, as well as alterations in endothelium-dependent vascular contractile properties, is part of the maternal syndrome.14 Studies on isolated vessels from preeclampsia models have revealed inconsistent results. In isolated vessels, normal pregnancy is associated with an increased vascular relaxation in response to ACh.15 In the reduced uterine perfusion pressure model, the preeclamptic animals exhibited a reduced vasorelaxation to ACh in the uterine and mesenteric arteries. In vitro studies on isolated microvessels from patients with preeclampsia showed an absence of ACh-mediated vasodilatation in omental microvessels.8 Uterine artery rings from SD-PE rats relaxed at low ACh doses, whereas at higher doses increased resistance was observed. Our data suggest that a COX derivative is responsible. Endothelial-derived constrictors include TxA2 and its immediate precursor PGH2. Both are involved in hypertension, diabetes, and cerebral ischemia.16 In our study, the endothelium-dependent contractions were blocked by indomethacin and by a TxA2 receptor blocker, suggesting that ACh may facilitate the release of endothelial vasoconstrictor prostanoids. A similar ACh-mediated response has been observed in obese mice.17 Virdis et al18 showed that chronic Ang II infusion in mice led to endothelial dysfunction by an interaction with COX. Francois et al19 used gene-deletion mouse experiments and showed that, in thromboxane receptor–deficient and in COX-deficient mice, Ang II–induced hypertension was attenuated. Their data suggest a major role for thromboxane receptor activation in Ang II–related hypertension. Our data direct attention to possibly similar mechanisms in preeclampsia.

We also found a reduced PGF1α:TxB2 ratio in SD-PE compared with SD-P rats. The absolute values of Pgf1α were markedly reduced in preeclamptic SD rats. The balance of endothelial production/release and/or the smooth muscular
action of PGI₂ and TxA₂ is disturbed in preeclamptic women. In normal pregnancy, the endothelial production and smooth muscle response to vasodilutative agents, such as NO or PGI₂, is enhanced, whereas the urinary PGI₂ excretion is increased. In preeclampsia, plasma and urine levels of TxA₂ are elevated, whereas PGI₂ synthesis is reduced. The TxA₂ production may exceed the PGI₂ production in preeclampsia, which was the rationale for the introduction of low-dose aspirin therapy. The fact that TxA₂ receptor overexpression in murine vessels resulted in IUGR further emphasizes the importance of endothelium-derived contracting factors in preeclampsia.

In human pregnancy, Doppler waveform analysis is the only available screening tool for preeclampsia. The hemodynamic alterations of normal pregnancy and preeclampsia are well known. The decrease in systemic vascular resistance in normal pregnancy is exceeded by an even higher relative decrease in uterine vascular resistance. In preeclampsia, insufficient spiral artery remodeling by endovascular trophoblasts results in an impaired placental blood flow. The reduction in the uteroplacental blood flow may result in a systemic release of placental factors that further contribute to increased systemic vascular resistance. The reduction of placental perfusion is reflected by an increased resistance to blood flow, measured by Doppler-ultrasound. An increase of vascular resistance is associated with the incidence of preeclampsia and IUGR.

We found an unexpected decreased RI in the uterine and arcuate arteries from SD-PE compared with SD-P rats. The decline began at embryonic days 12.5 and 15.5, respectively. In human preeclampsia, the mal-implanted placenta is believed to release factors that contribute to the disease. Elevated levels of sFlt-1 and decreased levels of VEGF can be used as prognostic markers; however, we did not find such features in our model. High impedances to blood flow and the appearance of a protodiastolic notch identify the increased risk of human preeclampsia. However, in SD-PE rats, RI decreased beginning at embryonic day 12.5 after the appearance of hypertension at embryonic day 11.5, although IUGR occurred.

Mu and Adamson monitored uteroplacental Doppler flow in normal pregnant mice during gestation and reported PSV and EDV increases, as well as an RI decrease. We observed a stable RI in the course of pregnancy in SD-P rats. However, mouse and rat placentation are quite different. Trophoblast invasion occurs in both the decidua and the mesometrial triangle in the rat but is restricted to the decidua in the mouse. Hemberger et al showed that trophoblast invasion in the mouse placenta is restricted to a maximum of 300-μm depth in the decidua. In contrast, we found a trophoblast invasion of several millimeters in the rat placenta, which extends beyond the decidua in the mesometrial triangle. We have investigated the trophoblast invasion in the placenta of SD-PE and SD-P rats. Using histological techniques and a computer-based scoring system, we were able to show a deeper endovascular trophoblast invasion in SD-PE compared with SD-P rats (N. Geusens, S. Verlohren, C. Luyten, L. Vercruysse, M. Hanssens, R. Dechend, and R. Pijnenborg, unpublished observations, 2007). In line with these morphological differences, we observed a significantly decreased RI in the SD-PE rats. However, the discrepancy of the RI in healthy pregnant rats and mice persists and has to be elucidated in future studies. Mouse placenta is different in the histological context with striking morphological differences to the human setting, which has to be taken into account when interpreting Doppler data. The different rodent models will help to investigate the causal relationship among trophoblast invasion, vascular remodeling, and Doppler flow and resistance.

Our model is Ang II driven and, as all animal models, can only resemble human preeclampsia. Nonetheless, in normal human and sheep pregnancy, the uterine artery demonstrates both increased NO and PGI₂ production and attenuated increases in uterine vascular resistance in response to infused Ang II. Ang II has been associated with increases in placental blood flow that are abrogated by indomethacin. These responses are only present in pregnancy, because PGI₂ production is not observed in the uterine artery in the nonpregnant state. In human preeclampsia, the vascular responsiveness to Ang II is markedly increased, whereas the Ang II type 1 receptor is upregulated. Furthermore, the pregnancy-induced increase in PGI₂ production and reduced constrictor responses of uterine arteries to Ang II are disturbed.

Perspectives
We have demonstrated the use of our model. IUGR and impaired maternal endothelial function that we attributed to altered prostanoid metabolism may be responsible. Our model allows various aspects of vascular remodeling to be investigated. Not all aspects of the human syndrome are apparent. Nonetheless, we are convinced that important information can be accrued from this model. The SD-PE model will facilitate studies on placentaion, cytotrophoblast invasion, syncytiotrophoblast conversion, and spiral artery remodeling. Comparison of these processes between animal models and humans will increase our understanding of the human condition.

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Disclosures
None.

References


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