Maternal vascular responses to hypoxia in a rat model of intrauterine growth restriction

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1Department of Obstetrics and Gynecology, University of Alberta, Alberta, Edmonton, Canada; 2Department of Physiology, University of Alberta, Alberta, Edmonton, Canada; and 3Women and Children’s Health Research Institute and the Cardiovascular Research Centre, Edmonton, Alberta, Canada

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Aljunaidy MM, Morton JS, Cooke CL, Davidge ST. Maternal vascular responses to hypoxia in a rat model of intrauterine growth restriction. Am J Physiol Regul Integr Comp Physiol 311: R1068–R1075, 2016. First published October 19, 2016; doi:10.1152/ajpregu.00119.2016.—Intrauterine growth restriction (IUGR) is a common pregnancy complication and is a leading cause of fetal morbidity and mortality. Placental hypoxia contributes to adverse fetal consequences, such as IUGR. Exposing pregnant rats to hypoxia may lead to IUGR; however, assessment of maternal vascular function in a rat model of hypoxia, and the mechanisms that may contribute to adverse pregnancy outcomes, has not been extensively studied. We hypothesized that exposing pregnant rats to hypoxia may affect maternal systemic vascular function and increase the uterine artery resistance index (RI), which will be associated with IUGR. To test this hypothesis, pregnant rats were kept in normoxia (21% O2) or hypoxia (11% O2) from gestational day (GD) 6 to 20. Maternal blood pressure, uteroplacental resistance index (RI) (ultrasound biomicroscopy), and vascular function (wire myography) were assessed in uterine and mesenteric arteries. Fetal weight was significantly reduced (P < 0.001), while maternal blood pressure was increased (P < 0.05) in rats exposed to hypoxia. Maternal vascular function was also affected after exposure to hypoxia, including impaired endothelium-dependent vasodilation responses to methacholine in isolated uterine arteries (pEC50, normoxia: 6.55 ± 0.23 vs. hypoxia: 5.02 ± 0.35, P < 0.01) and a reduced uterine artery RI in vivo (normoxia: 0.53 ± 0.01 vs. hypoxia: 0.53 ± 0.01, P < 0.05); associated with an increase in umbilical vein RI (normoxia: 0.35 ± 0.02 vs. hypoxia: 0.45 ± 0.04, P < 0.05). These data demonstrate maternal and fetal alterations in vascular function due to prenatal exposure to hypoxia. Further, although there was a compensatory reduction in uterine artery RI in the hypoxia groups, this was not sufficient to prevent IUGR.

IUGR; intrauterine growth restriction; uterine artery; wire myography; ultrasonography

INTRAUTERINE GROWTH RESTRICTION (IUGR) is a common pregnancy complication that occurs when a fetus does not reach its genetic growth potential during gestation. IUGR prevalence is ~15% for all pregnancies, and it is one of the leading causes of neonatal morbidity and mortality worldwide (13, 31). Further, IUGR offspring are at increased risk of cardiovascular disease later in life (2, 17). Because of this significant global impact, there is a critical need to understand the factors involved in the pathophysiology of IUGR to develop therapeutic strategies.

A common feature of IUGR is low oxygen availability/hypoxia (5, 9, 26). Studies in our laboratory have shown that exposing pregnant rats to hypoxia (11–12% O2, gestational day (GD) 15–21) can lead to fetal growth restriction (24, 28, 34). Other laboratories have also demonstrated fetal growth restriction resulting from maternal hypoxia in rats (9% O2, GD 14.5–17.5), mice (12% O2, GD 15.5–18.5), as well as in guinea pigs, sheep, and women at high altitude (6, 10, 11, 20, 23, 30). Hypoxia during pregnancy has been shown to affect the maternal cardiovascular system. For example, hypoxia increased maternal blood pressure by increasing plasma levels of endothelin-1 in pregnant rats (37), increased uterine artery myogenic tone in pregnant sheep (35), and impaired proliferation of uterine artery vascular smooth muscle cells and impaired uterine vascular growth in pregnant guinea pigs (22, 23). Gestational hypoxia can also increase uterine artery vasodilator responses to AMPK through both nitric oxide (NO)-dependent and -independent mechanisms in pregnant mice (29). Further, hypoxia during pregnancy diminished the effects of NO inhibition in uterine arteries and enhanced basal NO activity in mesenteric arteries in pregnant guinea pigs (32, 33). The effect on uterine artery vascular function in response to hypoxia may also involve alterations in uteroplacental blood flow. For example, the umbilical artery shows an increased resistance index (RI) in pregnant wild-type mice exposed to hypoxia (25). Furthermore, in normotensive pregnant women living at high altitude, uterine artery diameter and blood flow were lower than those women living at low altitude, resulting in lower birth-weight offspring (7, 36). In Andean women, however, increased uterine artery blood flow and oxygen delivery to the fetus prevented altitude-associated IUGR (8).

Because of the complexity of maternal vascular adaptations to hypoxia and some conflicting results in the literature, further assessment of in vivo and ex vivo maternal vascular function is warranted. We hypothesize that exposing pregnant rats to hypoxia will cause maternal systemic vascular dysfunction and increase the uterine artery RI, which will be associated with IUGR. To fully evaluate the effects of disrupted maternal vascular function, assessments of maternal blood pressure, fetal growth, and in vivo assessment of uterine and umbilical vasculature Doppler ultrasonography were performed. In addition, we assessed uterine artery (important for placental blood supply) and mesenteric artery (a representative resistance-sized systemic artery) vascular function ex vivo.

MATERIALS AND METHODS

All of the procedures used were approved by the University of Alberta Animal Policy and Welfare Committee in accordance with the Canadian Council on Animal Care and conformed to the “Guide for the Care and Use of Laboratory Animals.”

Animals and treatments. Female and male Sprague-Dawley (SD) rats were obtained from Charles River, Quebec, Canada at 12 wk of age. All of the procedures used were approved by the University of Alberta Animal Policy and Welfare Committee in accordance with the Canadian Council on Animal Care and conformed to the “Guide for the Care and Use of Laboratory Animals.”
age and were acclimatized for 1 wk within the animal facilities of the University of Alberta. Females were then mated with a young male overnight, and pregnancy was confirmed the following morning via the presence of sperm in a vaginal smear; designated as GD 0 (term 22 days). Throughout the pregnancy period, rats were singly housed in standard rat cages under a 10:14-h light-dark cycle and fed standard rat chow ad libitum. Rats were randomly divided into two groups; in one group rats were kept in normal atmospheric conditions (21% O2; normoxia) throughout pregnancy. In the second group, rats were exposed to hypoxia (11% O2; hypoxia) by placing them in an acrylic chamber (Animal Chamber for Disease Modeling type A, Biospherix, Lacona, New York), which maintained the concentration of oxygen at 11% by regulating nitrogen infusion. Soda lime was placed inside the chamber to absorb excess CO2. The hypoxic exposure was started on GD 6 based on a previous study, which showed that chronic hypoxia before GD 5 can considerably increase the rate of pregnancy loss in rats (21). Rats in both the Normoxia and Hypoxia Group were housed in the same room. On GD 14, rats underwent a rapid clean cage replacement with fresh feed and water, which caused the O2 levels to rise to 15.0 ± 0.6% for less than 5 min. Rats were removed from the hypoxia chamber on GD 20 to perform experimental procedures.

Blood pressure and heart rate measurement. Blood pressure was measured on GD 5 and GD 20 (before and after hypoxia) using tail-cuff plethysmography (CODA, Kent Scientific Corporation, Torrington, CT). Rats were placed in restraint tubes and left for 20 min to warm (tail skin surface temperature ~30°C). An average was taken of at least 10 blood pressure measurements performed over a period of 10 min.

Ultrasound biomicroscopy. Fetal heart rate and uterine artery, umbilical artery and umbilical vein blood flow velocities, and RI were assessed on GD 20, using an ultrasound biomicroscope (model Vevo 2100, VisualSonics, Toronto, ON, Canada) and a previously established protocol (18). Briefly, rats were removed from the hypoxia chamber on GD 20 to perform experimental procedures. Ultrasound was performed at a point when structural vascular remodeling is complete, and any uterine artery changes that may have occurred with hypoxia would be expected to persist in the normoxic environment. One hour of reacclimatization was used before performing ultrasound to avoid acute responses to changing oxygen levels. Rats were anesthetized with inhaled isoflurane (3% induction, 1–3% maintenance). Doppler waveforms were obtained from the uterine artery near the uterocervical junction close to the iliac artery. The highest point of the systolic waveform was considered to be the peak systolic velocity (PSV), and the end point of the diastolic waveform was considered to be the end diastolic velocity (EDV). Both PSV and EDV were measured from at least three consecutive cardiac cycles that were not affected by maternal breathing motion, and the results were averaged per dam. Waveforms were obtained from umbilical arteries and veins near the placental surface of at least three randomly selected fetuses per dam, and the values were averaged to generate a single value per dam. RI was calculated using the equation (PSV − EDV)/PSV (Fig. 1). The pulsatility index (PI) was calculated as (PSV − EDV)/TAV (time-averaged velocity). Fetal heart rate was calculated by averaging the measurements of the distance between the peaks of three consecutive umbilical artery waveforms. To increase the power of our in vivo study (blood pressure and Doppler ultrasound measurements), data from the current study were merged with data from a pilot study, in which rats experienced exactly the same normoxia/hypoxia environments but were given Ensure as a vehicle control (5 ml orally once/day, GD 0–20; Abbott Laboratories, Saint Laurent, QC, Canada). In both normoxia and hypoxia groups, subgroup analysis demonstrated that there were no significant differences in blood pressure or ultrasound parameters among rats that received Ensure and rats that did not; hence, these data could be merged.

Fetal and placental measurements and maternal weight. On GD 21, rats were euthanized by exsanguination under isoflurane anesthesia.

Fig. 1. Representative images of the uterine and umbilical artery waveforms as measured by ultrasound biomicroscopy in normoxia and hypoxia groups at GD 20. Uterine artery waveforms (A: normoxia, B: hypoxia). Umbilical artery waveforms (C: normoxia, D: hypoxia). Peak systolic velocity (PSV) and end diastolic velocity (EDV) (dotted lines).
The uterus containing pups was removed, and its weight was measured and subtracted from the maternal weight taken before euthanasia. Fetal parameters, including body weight, crown-to-rump length, and abdominal circumference, were measured and averaged per litter. Heart and kidney weights of three, randomly chosen, pups per dam were obtained. The gross anatomy of the pups was also examined. All placentas were blotted dry, their diameter and weight were recorded and then dried at 40°C overnight, and their dry weight was measured. The ponderal index was calculated as 1000 (body weight) fetal heart weights were altered by hypoxia. The placental parameters, including wet weight, dry weight, and diameter between the groups [normoxia: 15 (14–17) pups vs. hypoxia: 15 (5–16) pups, P = 0.02], but the variance of litter size was statistically greater in the hypoxic group. In the hypoxia group, the average pup weight was significantly reduced (Fig. 2B). Crown-rump length and abdominal girth were significantly decreased by hypoxia, while ponderal index was not altered; demonstrating symmetrical growth restriction in the hypoxic group (Table 3). Neither absolute nor relative (normalized to body weight) fetal heart weights were altered by hypoxia. The absolute fetal kidney weight was decreased in the hypoxia group; however, the relative kidney weight (normalized to body weight) did not change (Table 3).

While total maternal body weight was decreased at GD 21 in dams exposed to hypoxia compared with their normoxic coun-

### RESULTS

#### Maternal blood pressure. Systolic, diastolic, mean arterial blood pressures, and maternal heart rate were increased following exposure to hypoxia (Table 1).

#### Uterine and umbilical artery resistance indices. In the uterine artery, RI, the ratio of PSV to EDV (S/D) and PI were decreases in the hypoxia group compared with the normoxic control. In contrast, in the umbilical artery, there were no significant changes in RI, S/D, or PI, but an increase in the umbilical vein RI was observed (Table 2). Fetal heart rate, assessed using the umbilical wave form, was higher following hypoxia (normoxia 245 ± 4 bpm vs. hypoxia: 263 ± 7 bpm, P < 0.05).

#### Reproductive phenotype and maternal weight gain. Placental parameters, including wet weight, dry weight, and diameter did not differ between the Normoxic and Hypoxic Groups (Fig. 2A and Table 3). Litter size was not significantly different between the groups [normoxia: 15 (14–17) pups vs. hypoxia: 15 (5–16) pups, P = 0.02], but the variance of litter size was statistically greater in the hypoxic group. In the hypoxia group, the average pup weight was significantly reduced (Fig. 2B). Crown-rump length and abdominal girth were significantly decreased by hypoxia, while ponderal index was not altered; demonstrating symmetrical growth restriction in the hypoxic group (Table 3). Neither absolute nor relative (normalized to body weight) fetal heart weights were altered by hypoxia. The absolute fetal kidney weight was decreased in the hypoxia group; however, the relative kidney weight (normalized to body weight) did not change (Table 3).

### Table 1. Blood pressure and heart rate at GD 5 and GD 20

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>GD 5</strong></td>
<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>139.60 ± 3.27</td>
<td>145.75 ± 4.84</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>104.25 ± 3.03</td>
<td>108.95 ± 4.72</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>115.70 ± 3.05</td>
<td>120.84 ± 4.72</td>
<td>0.34</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>410.98 ± 7.65</td>
<td>404.83 ± 13.05</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>GD 20</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124.51 ± 3.11</td>
<td>133.08 ± 2.91</td>
<td>0.05*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>90.10 ± 2.63</td>
<td>93.72 ± 2.71</td>
<td>0.05*</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>101.21 ± 2.77</td>
<td>109.39 ± 2.74</td>
<td>0.04*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>402.91 ± 6.22</td>
<td>431.43 ± 9.36</td>
<td>0.01**</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE; n = 10–16/group, GD, gestational day. *P ≤ 0.05, **P ≤ 0.01.

### Table 2. Hemodynamic parameters of the uterine and umbilical vasculature, as assessed by ultrasound biomicroscopy at GD 20

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uterine artery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.63 ± 0.02</td>
<td>0.53 ± 0.01</td>
<td>0.0006***</td>
</tr>
<tr>
<td>PI</td>
<td>1.08 ± 0.08</td>
<td>0.74 ± 0.03</td>
<td>0.003**</td>
</tr>
<tr>
<td>S/D</td>
<td>2.93 ± 0.21</td>
<td>2.18 ± 0.05</td>
<td>0.007***</td>
</tr>
<tr>
<td>TAV, mm/s</td>
<td>541.43 ± 33.48</td>
<td>385.51 ± 28.83</td>
<td>0.001***</td>
</tr>
<tr>
<td><strong>Umbilical artery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.92 ± 0.01</td>
<td>0.90 ± 0.12</td>
<td>0.35</td>
</tr>
<tr>
<td>PI</td>
<td>1.68 ± 0.03</td>
<td>1.73 ± 0.11</td>
<td>0.67</td>
</tr>
<tr>
<td>S/D</td>
<td>14.57 ± 1.17</td>
<td>12.69 ± 1.76</td>
<td>0.36</td>
</tr>
<tr>
<td>TAV, mm/s</td>
<td>113.09 ± 6.68</td>
<td>123.83 ± 6.88</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Umbilical vein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.35 ± 0.02</td>
<td>0.45 ± 0.04</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE; n = 13–17/group, RI, resistance index; PI, pulsatility index; S/D, peak systolic velocity to end diastolic velocity ratio; TAV, time averaged velocity. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001.
terparts (normoxia: 461.0 ± 13.3 g vs. hypoxia: 424.1 ± 10.7 g, \( P < 0.0001 \)), maternal body weight without the uteroplacental unit was unaltered between groups (normoxia: 346.9 ± 10.9 g vs. hypoxia: 344.2 ± 9.7 g, \( P = 0.63 \)), suggesting that the difference lay only in the reduced fetal weights.

**Uterine artery ex vivo vascular function.** Uterine artery dilation to MCh demonstrated decreased sensitivity in the hypoxia group (Table 4). \( \text{l-NAME} \) significantly decreased responses to MCh in uterine arteries from normoxic dams (Fig. 3A, \( P < 0.01 \)) but not from the hypoxic dams (Fig. 3B). Assessment of the delta AUC of vasodilation to MCh in the presence or absence of \( \text{l-NAME} \) demonstrated that exposure to hypoxia caused a reduction in the contribution of NO to vasodilation (Fig. 3C). Sensitivity to the endothelium-independent agonist SNP was not altered following exposure to hypoxia (Table 4).

Uterine artery vasoconstriction in response to high K\( ^+ \) or PE was not altered by exposure to hypoxia (Table 4). \( \text{l-NAME} \) did not alter vasoconstriction to PE in either the normoxia or hypoxia groups (Fig. 4). Delta AUC of vasoconstriction to PE in the presence or absence of \( \text{l-NAME} \) was not altered between the groups (normoxia: 6.02 ± 1.58 vs. hypoxia: 5.25 ± 0.99, \( P = 0.68 \)).

**Mesenteric artery ex vivo vascular function.** Mesenteric artery dilation to MCh demonstrated no difference in sensitivity following exposure to hypoxia (Table 4). \( \text{l-NAME} \) significantly decreased sensitivity to MCh in both the Normoxia and Hypoxia Groups (Fig. 5, A and B, \( P < 0.05 \) and \( P < 0.001 \), respectively). However, hypoxia led to a significant increase in the contribution of NO to the dilation of mesenteric arteries, as assessed by the delta AUC (Fig. 5C). Sensitivity to SNP was not altered between the groups (Table 4).

Mesenteric artery constriction in response to high K\( ^+ \) or PE was not altered between the Hypoxia and Normoxia Groups (Table 4). \( \text{l-NAME} \) did not increase PE-induced vasoconstriction in either group (Fig. 6); therefore, the delta AUC of vasoconstriction to PE in the presence or absence of \( \text{l-NAME} \) was also not altered between the groups (normoxia: 1.94 ± 0.64 vs. hypoxia: 0.84 ± 0.09, \( P = 0.21 \)).

**Internal diameter of uterine and mesenteric arteries.** The internal diameter of both uterine and mesenteric arteries was not altered between the groups. Internal diameters were as follows: uterine arteries: (normoxia: 176 ± 9 \( \mu \)m vs. hypoxia: 200 ± 16 \( \mu \)m, \( P = 0.22 \)) and mesenteric arteries: (normoxia: 120 ± 3 \( \mu \)m vs. hypoxia: 128 ± 4 \( \mu \)m, \( P = 0.21 \)).

**DISCUSSION**

The current study demonstrates that hypoxia during rat pregnancy is a valid model of IUGR, which is associated with increased maternal blood pressure and altered vascular reactivity, using both in vivo and ex vivo assessments. Our data show that gestational hypoxia decreased uterine artery RI, as well as reduced the uterine artery sensitivity to the vasodilator MCh. No effect on vasoconstriction in response to PE or high K\( ^+ \) was noted. Hypoxia did not lead to a difference in the vascular dilation and constriction of the mesenteric artery but increased the contribution of NO to vasodilation. Fetal consequences of gestational hypoxia included symmetric growth restriction, an increase in the umbilical vein RI, but no change in the umbilical artery RI. Thus, although our data demonstrated a compensatory reduction in uterine artery RI in a rat model of hypoxia, this was not sufficient to prevent IUGR.

Our results in vivo demonstrated a reduction in the uterine artery RI in late gestation in animals exposed to hypoxia compared with those in normoxic conditions. Interestingly, and

![Fig. 2](http://ajpregu.physiology.org/)
in contrast to these results, a previous study in our laboratory showed unchanged uterine artery RI in mice after exposure to gestational hypoxia, demonstrating different maternal vascular responses to hypoxia between our rat and mouse models (25). However, our current results in rats parallel human observations, which show a reduction in uterine artery RI associated with IUGR in women living at high altitude (4300 m altitude) compared with women living at low altitude (sea level) (12).

In the fetal umbilical vessels, our study showed no changes in the umbilical artery RI, but an increase in the umbilical vein RI, following exposure to hypoxia, suggesting that different mechanisms may regulate the maternal and fetal vascular responses to hypoxia. Studies conducted in human pregnancies and animal models complicated with IUGR show variable data regarding the umbilical artery RI. For example, in pregnancies complicated with IUGR in women, umbilical artery RI was either increased (1, 3, 4, 14) or did not show a difference (27), compared with those with a normal pregnancy. In mice, umbilical artery RI was higher in hypoxia compared with normoxia in wild-type mice, but was not altered in catechol-O-methyl transferase (COMT\(^{-/-}\)) mice (25). Studies that assessed umbilical vein responses to hypoxia have shown variable data as well. In one study of both wild-type and COMT\(^{-/-}\) mice, umbilical vein RI was not different after exposure to hypoxia (25), while in human pregnancies complicated by IUGR, umbilical vein blood flow was decreased compared with normal pregnancy (19). Thus, on the basis of our data, which suggests a hypoxia-induced increase in umbilical vein RI, the relationship and mechanisms behind umbilical artery and vein blood flow parameters in animal models of IUGR warrant further investigation.

Our study also investigated mechanisms that could have an influence on maternal vascular responses following exposure to hypoxia. Our data demonstrated that the uterine artery sensitivity to MCh was decreased due to reduced NO-dependent modulation in the hypoxic group. This is in agreement with a previous study that showed a reduction in the effect of NOS inhibition in the uterine artery of pregnant guinea pig at high
vs. low altitude (32). However, in the current study, uterine artery RI decreased in vivo in the hypoxia group. This suggests the presence of early pathophysiological changes ex vivo, which did not translate into increased uterine vascular resistance when measured in vivo with ultrasonography. However, these subclinical changes may manifest further in the presence of comorbidities, such as obesity, diabetes, or maternal aging, thus affecting blood flow through the uterine vasculature. In addition, other factors regulate uterine vascular function in vivo, such as neuronal pathways, vascular remodeling, and shear stress (reviewed in Ref. 15), which were not directly assessed in the wire myograph system.

Interestingly, a previous study by Mateev et al. (16) showed that hypoxia in guinea pigs prevented the normal pregnancy-associated increase in uterine artery vasodilator responses to flow. However, the addition of the nitric oxide synthase inhibitor N\textsuperscript{G}-nitro-L-arginine (L-NNA) increased uterine artery flow-mediated vasodilation in hypoxic animals. Nitric oxide inhibition would be expected to impair vasodilation, and this unexpected result indicates that in guinea pigs, hypoxia disrupted the normal NO-dependent vascular responses. These data highlight the complex regulation of endothelium-dependent vasodilator pathways in pregnancy and the effect of hypoxia. Indeed, in our current study, maternal exposure to hypoxia differentially affected the contribution of NO to uterine and mesenteric artery vasodilation. We demonstrate that the NO contribution to vasodilation was decreased in uterine arteries but increased in mesenteric arteries. This may be due to differences in their primary vasodilatory mechanisms, whereby uterine arteries relied almost exclusively on NO, whereas mesenteric arteries demonstrated a greater contribution of non-NO mediated vasodilation. Therefore, it is important to

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**Mesenteric artery**

![Figure 5](http://ajpregu.physiology.org/)

**Fig. 5.** Mesenteric artery responses to the vasodilator MCh in the absence or presence of L-NAME in normoxia (A) and hypoxia (B) groups. C: summary delta AUC (the difference between MCh-induced vasodilation ± L-NAME) in normoxia and hypoxia groups. Data are presented as means ± SE (n = 5/group). *P ≤ 0.05.

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**Mesenteric artery**

![Figure 6](http://ajpregu.physiology.org/)

**Fig. 6.** Mesenteric artery responses to the vasoconstrictor PE in the absence or presence of L-NAME in normoxia (A) and hypoxia (B) groups. Data are presented as means ± SE (n = 4–6/group).
understand vascular bed differences when assessing the impact of maternal hypoxia.

Our data show that hypoxia exposure did not cause significant changes in placental size or weight compared with the control; however, there was a significant reduction in the fetal body weight. A similar study in which pregnant rats were exposed to a similar duration of hypoxia from day 6 to 20, but at 13%, O2 showed an increase in placental weight in the hypoxia group, but without inducing an IUGR phenotype (21). This suggests that the increase in placental size might “compensate” for the suboptimal environment caused by hypoxia and prevent IUGR and that the lower oxygen levels (11% O2) used in our study could attenuate this compensation.

In summary, this study illustrates how a hypoxic environment in pregnancy may affect both maternal and fetal vascular function. These data show that vascular responses to hypoxia are complex and vascular bed specific. Therefore, developing therapeutic interventions to benefit uteroplacental function must consider all of these (sometimes conflicting) vascular effects. Only through this holistic approach will there be hope to improve neonatal outcomes.

Perspectives and Significance

This study combined both in vivo and ex vivo evaluations of maternal vascular responses to hypoxia in a rat model of IUGR. The main findings were that vasodilator responses to NOS stimulation were reduced in uterine, but not mesenteric arteries, in pregnant rats housed in a hypoxic environment (11% O2, GD 6–20). Assessment of the uteroplacental circulation showed a reduction in uterine artery RI, which may be a compensatory response to reduced oxygen availability. However, we did observe vascular dysfunction in the uterine artery ex vivo, suggesting preclinical changes in vessel reactivity, which may be exacerbated in the presence of other comorbidities. These findings prompt further investigations into methods by which uterine vascular function and blood flow are affected by hypoxia in animal models, methods that could be translated to human application.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.M.A. and S.T.D. conceived and designed the research; M.M.A. performed experiments; M.M.A. analyzed data; M.M.A., J.S.M., C.-L.C., and S.T.D. interpreted results of experiments; M.M.A. prepared figures; M.M.A. drafted manuscript; M.M.A., J.S.M., C.-L.C., and S.T.D. edited and revised manuscript; M.M.A., J.S.M., C.-L.C., and S.T.D. approved final version of manuscript.

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