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Increased Myogenic Reactivity of Uterine Arteries from Pregnant Rats with Reduced Uterine Perfusion Pressure

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Abstract

The etiology of preeclampsia remains unknown. However, a contributing factor to this hypertensive disease of pregnancy is a reduction in uterine perfusion pressure resulting in placental ischemia. Uterine arteries may be a major regulator of this process through changes in vascular reactivity and localized blood flow. The reduced uterine perfusion pressure (RUPP) pregnant rat is an established animal model of preeclampsia pathology. Pregnant Sprague Dawley rats were used for this investigation and subjected to RUPP or SHAM surgery on Day 14 of gestation. On Day 21 of gestation, animals were terminated and resistance-caliber uterine arteries were harvested and mounted on a pressurized arteriograph to examine myogenic reactivity, agonist induced vasodilation (methacholine and VEGF), and vasoconstriction (phenylephrine and U-46619). Resistance-caliber uterine arteries from RUPP animals exhibited increased myogenic reactivity and decreased vasodilation (methacholine and VEGF) compared to SHAM uterine arteries ($p < 0.05$). Phenylephrine and U-46619 induced constriction was similar in uterine arteries between RUPP and SHAM rats. These results suggest that resistance-caliber uterine arteries from RUPP pregnant rats are altered to reflect a more constrictive phenotype which may play a role in the development of maternal hypertension demonstrated in these animals and thereby potentially in preeclampsia.

Keywords

Preeclampsia; uterine artery; myogenic reactivity; RUPP; vasodilation

Introduction

Preeclampsia is a hypertensive disorder of pregnancy that is a leading cause of maternal and fetal mortality throughout the world. Reductions in placental perfusion have long been

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considered a central component in the etiology of preeclampsia. While the ultimate cause of preeclampsia remains unknown, inadequate remodeling of the maternal spiral arteries by invading trophoblasts is likely a contributing factor to the reduction in perfusion pressure leading to the placenta [1-2]. This reduction in perfusion pressure to the placenta may lead to the maternal high blood pressure and kidney and vascular dysfunction that occur during preeclampsia [3]. These characteristics of preeclampsia are possibly due to endothelial injury leading to increased peripheral vascular resistance and reduced tissue perfusion [1].

Animal modeling of preeclampsia is essential to elucidating vascular mechanisms associated with the pathology of the human disease, preeclampsia. The reduced uterine perfusion pressure (RUPP) pregnant rat is an animal model which exhibits preeclampsia-like pathophysiology [4]. This model has provided insights into vascular mechanisms associated with reduced uterine perfusion pressure and possibly what occurs during preeclampsia. In preeclampsia, maternal arteries exhibit increased vasoconstrictor responses and in RUPP rats large conduit arteries also exhibit a more constrictive phenotype [4]. Similarly, our lab has demonstrated that vascular myogenic reactivity is increased in RUPP mesenteric resistance arteries and that maternal vascular NO mediated responses are decreased favoring a contractile phenotype [5]. This finding does extend to other systemic vascular beds such as the renal circulation but is not well characterized in the uterine circulation. In one study a wire myograph system was used to examine uterine arcuate arteries. In this study, Anderson and colleagues have reported an increased constrictive phenotype in these arteries from RUPP animals [6]. However, resistance-sized uterine arteries further downstream in the uterine arcade may also provide regulation of placental perfusion and contribute to uterine resistance; however, to date these arteries have not been investigated in RUPP rats. The present study tested the hypothesis that resistance-caliber uterine arteries would result in a more robust increase in myogenic reactivity in pregnant rats with RUPP compared to SHAM. Additionally, resistance-caliber uterine arteries will exhibit decreased agonist induced vasodilation indicative of a defective endothelial NO response in RUPP compared to SHAM.

Materials and Methods

Animals

Female Sprague Dawley rats (8-12 weeks old; Hilltop Lab Animals, Scotsdale, PA) were used for this investigation. Rats were placed with a male overnight and the presence of sperm on a vaginal smear designated gestational Day 1 of pregnancy (22-23 day gestation). Rats were then singly housed for the duration of their pregnancy. All protocols were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Akron.

Surgical Manipulation

Pregnant female rats were subjected to reduced uterine perfusion pressure (RUPP) or SHAM surgery on Day 14 of gestation as previously described by our lab and others [4-5]. Briefly, animals were anesthetized with 2% isoflurane and the abdominal aorta was exposed via a midline incision. A silver clip (0.203 mm ID) was placed around the abdominal aorta below the renal arteries and above the iliac arteries. Similarly, two silver clips (0.106 mm ID) were placed around the uterine-ovarian arteries. SHAM animals underwent the same surgery but did not receive the silver clips. All animals where the surgical procedure resulted in total resorption of all the fetuses were excluded from the study.

All animals were euthanized on Day 21 of gestation by an overdose of 2.5% Sodium Pentothal (50 mg/kg IP; EJ Lilly, Indianapolis, IN). The uterus was quickly excised and

placed in ice cold HEPES buffered solution at the following concentrations (mmol/L): sodium chloride 142, potassium chloride 4.7, magnesium sulfate 1.17, calcium chloride 2.5, potassium phosphate 1.18, HEPES 10, dextrose 5.5, and the pH was adjusted to 7.4. Litter size, fetal resorptions, and fetal weights were taken.

Uterine Arteries/Pressure Arteriograph

Resistance-caliber uterine arteries (200-300 μ m) were isolated and cleaned of excess tissue. Arteries were mounted on a pressure arteriograph (Living Systems, Burlington, VT) and pressurized to 60 mmHg. Fresh, heated (37°C) HEPES buffer at a pH of 7.4 was added to the bath for a 30 minute equilibration period. The arteries were given a conditioning stretch by increasing the intraluminal pressure to 100 mmHg and then returning the pressure to 60 mmHg for another 15 minute equilibration with fresh HEPES buffer.

Myogenic Reactivity

Resistance-caliber uterine arteries were precontracted to 70-85% of their initial diameter (i.e. ~25% constriction) with phenylephrine. This small amount of constriction eliminates tone differences in the arterial preparations and has been shown to optimize the myogenic response [7]. Once stable tone was achieved, the intraluminal pressure was decreased from 60 mmHg to 20 mmHg for 10 minutes. The pressure was then increased in a stepwise manner every 5 minutes by 20 mmHg to a maximum of 120 mmHg. Intraluminal diameters were measured at each pressure step with an electronic filar (Lasico, Los Angeles, CA).

Myogenic reactivity was calculated as a percent change from the initial arterial diameter at 20 mmHg using the following equation: $((D_x - D_{20})/D_{20}) * 100$. Constriction, as indicated by this equation, is a net zero or negative percent change and dilation is a positive percent change [5,8]. Myogenic reactivity was repeated in the presence of 100 μ M N^G-methyl-L-arginine (L-NMA) to block nitric oxide synthase production.

Vasodilation and Vasoconstriction

A separate set of arteries were constricted to 50% of their initial diameter with phenylephrine. The arteries were then exposed to cumulative concentrations of the endothelium dependent vasodilator methacholine (1nmol - 3 μ mol) or to vascular endothelial growth factor (VEGF) (0.05nmol – 9nmol). A subset of arteries was exposed to the endothelium independent vasodilator sodium nitroprusside (1nmol - 3 μ mol). Arterial responses are expressed as percent dilation in response to phenylephrine constriction for comparison. All vasodilation chemicals were purchased from Sigma (St Louis, MO).

A separate set of arteries were subjected to constriction with either the α -adrenergic agonist phenylephrine (Sigma, St Louis, MO) or the thromboxane receptor agonist U-46619 (Cayman Chemical, Ann Arbor, MI). Arteries were then exposed to increasing concentrations of the respective agonist (phenylephrine: 0.01 μ mol-3 μ mol; U-46619: 1nmol-3 μ mol). The responses were expressed as percent constriction and then normalized as percent maximum constriction for comparison.

Passive Mechanics

Passive mechanics of uterine arteries were evaluated in calcium free HEPES buffer with 0.1 mM EGTA and 0.1 mM papaverine to inactivate the smooth muscle of the vessel. A constant pressure of 60 mmHg was held and the vessel was equilibrated in this buffer for 15 minutes. The intraluminal pressure was then changed in a stepwise manner from 0-150 mmHg with luminal and wall diameters measured at each pressure. Wall:lumen ratios were calculated as follows: $\omega/\phi_{\text{inner}}$ where ω is the vessel wall thickness diameter and ϕ_{inner} is the luminal diameter. Wall stress was calculated with the following equation (assuming the

arterial wall is uniform), and is expressed in dynes/cm² (1 mmHg = 1333.2 dynes/cm²): T/ω , where T is equal to the intraluminal pressure (expressed in dynes/cm²) multiplied by the luminal radius and ω is the vessel wall thickness diameter. Arterial distensibility was calculated with the following equation: $[(\varnothing_x - \varnothing_{0\text{mmHg}}) - 1] \times 100$. In this equation, $\varnothing_x$ is the luminal diameter at a specific intraluminal pressure and $\varnothing_{0\text{mmHg}}$ is the luminal diameter at 0 mmHg and expressed as percent distensibility [9].

Statistics

Sigma Stat and Sigma Plot software was used for this investigation (Systat, San Jose, CA). Isolated uterine artery response data were analyzed using a two-way repeated measures ANOVA with a *post-hoc* Bonferroni test. Litter size, fetal resorptions, and fetal weights were analyzed using a one-way ANOVA. Student's t-test was used where applicable. Statistical significance was accepted if $p < 0.05$.

Results

Myogenic reactivity of resistance-sized uterine arteries (Figure 1) was increased in RUPP pregnant rats compared to SHAM operated controls ($F=6.6$; $p<0.05$). Blockade of nitric oxide (NO) synthase production with L-NMA in uterine arteries resulted in a significant increase in myogenic reactivity for SHAM operated controls ($F=8.7$; $p<0.05$) (Figure 2A) with no change for uterine arteries from RUPP rats (Figure 2B).

Endothelium dependent vasodilation induced by methacholine (Figure 3) was reduced in uterine arteries from RUPP pregnant rats compared to SHAM rats ($F=9.8$; $p<0.05$). Similarly, vasodilation in response to VEGF (Figure 4) was reduced in RUPP uterine arteries compared to SHAM rats ($F=30.3$; $p<0.01$). However, there were no differences demonstrated with RUPP and SHAM uterine arteries for the endothelium independent vasodilator sodium nitroprusside (Figure 5).

Phenylephrine (Figure 6) and U-46619 (thromboxane mimetic; Figure 7) constriction was not altered in uterine arteries from RUPP pregnant rats compared to SHAM pregnant rats.

Passive arterial distensibility of uterine arteries (Figure 8) was decreased in RUPP rats compared to SHAM ($F=14.5$; $p<0.001$).

No significant differences were found for passive structural/mechanical parameters at any of the intraluminal pressures studied (Table 1).

Litter size ($F=12.4$; $p<0.01$) was significantly decreased in RUPP animals (5.3 ± 2.2) compared to SHAM (13.2 ± 0.3). Additionally, fetal resorptions ($F=6.9$; $p<0.05$) were increased in RUPP rats (7.2 ± 2.3) compared to SHAM (0.8 ± 0.6). Fetal weights (g) ($F=17.6$; $p<0.01$) were significantly lower from RUPP mothers (2.6 ± 0.4) compared to SHAM (4.2 ± 0.1).

Discussion

Adequate uterine perfusion to the feto-placental unit is essential to the maintenance of uterine circulatory homeostasis and ultimately fetal health. Previous studies in rat uterine arteries have demonstrated enhanced vasoconstriction during pregnancy [10]. This enhancement in vasoconstriction is counterbalanced by an increase in nitric oxide (NO) mediated vasodilation during pregnancy [11-12]. As a result, resistance within the uterine circulation decreases with increased gestational age in humans in order to meet the demands of the developing fetus [13]. Studies investigating this mechanism have demonstrated

enhanced vasodilation in concert with reduced vascular tone which ultimately leads to increased uterine blood flow [14]. However, preeclampsia, a hypertensive disorder of pregnancy, is associated with reductions and/or reversals in uterine blood flow as demonstrated by Doppler velocimetry studies [15-17]. To further investigate the impact of reduced uterine perfusion, the RUPP model of a preeclampsia-like pathophysiology has been utilized. In this animal model, uterine and placental blood flow is reduced [18] and recently Tam Tam and colleagues demonstrated increased uterine artery resistance in RUPP dams [19]. These data suggest that uterine artery reactivity may be altered. In addition, Anderson and colleagues report a more constrictive phenotype in uterine arteries isolated from RUPP rats using a wire myograph [6]. However, the effect of reduced uterine perfusion pressure on resistance-caliber uterine arteries is not well characterized. Therefore the purpose of our study was to elucidate whether myogenic reactivity of resistance-caliber uterine arteries in response to reduced uterine perfusion pressure was altered and the role that nitric oxide (NO) played in this response.

Myogenic reactivity is the active response of a blood vessel to changes in intraluminal pressure and is an integrated response of the entire blood vessel (i.e. endothelium, smooth muscle, and adventitia)[20]. During gestation, the uterine arteries undergo hypertrophy and increases in myogenic reactivity in order to ensure proper placental perfusion. Placental underperfusion and fetal growth restriction can occur if the increases in myogenic reactivity are not balanced by increases in vasodilatory capacity. In a rodent model of growth restriction, maternal undernutrition results in increased uterine artery vasoreactivity due to a defective NO mediated response [21]. Similarly in the RUPP model, the increased myogenic reactivity observed in resistance-caliber mesenteric arteries is mediated in part by NO [5,22]. In the RUPP model, uterine artery myogenic reactivity is also significantly increased compared to the SHAM controls ($p<0.05$). The increase in myogenic reactivity in the uterine arteries isolated from RUPP rats is also due to decreased NO production since blocking NO production with N^G-methyl-L-arginine (L-NMA) had no effect on the uterine arteries isolated from RUPP rats. However, SHAM uterine arteries incubated with L-NMA responded to intraluminal pressure increases with vasoconstriction similar to what was observed in the RUPP uterine arteries ($p<0.05$).

The role of NO in the mediation of decreased arterial reactivity and vasodilation in pregnancy has been well established [14,23-24]. Studies in protein restricted gravid rats have demonstrated that vasodilation is blunted due to a decreased NO response [25]. Studies of human myometrial resistance arteries from preeclamptic women have demonstrated increased uterine artery reactivity due to decreased NO production [26-27]. These deficiencies are likely caused by a defective endothelium in preeclampsia [1]. Our laboratory [5,22] and others [28] have demonstrated that endothelial NO deficiency may be involved in the pathology associated with RUPP. Vasodilatory responses of uterine arteries to the endothelium dependent vasodilator methacholine from RUPP rats were decreased compared to SHAM controls ($p<0.05$). Similarly, vasodilation in response to vascular endothelial growth factor (VEGF) was attenuated in uterine arteries from RUPP pregnant rats compared to SHAM ($p<0.01$). Ni and colleagues have demonstrated a role for VEGF in uterine vasodilation through a NO mechanism in normal pregnancy [29]; therefore, disruptions of this pathway may play role in the pathophysiology of preeclampsia [30]. In fact, Gilbert and colleagues demonstrated a role for VEGF in the hypertension associated with RUPP [31] possibly working through the NO mechanism. In addition, Itoh and colleagues have reported a decrease in VEGF induced dilation in uterine arteries after maternal protein restriction during pregnancy in the rat [25]. A role for VEGF and the VEGF 2 receptor in the regulation of hypertension in mice has been demonstrated by Facemire and associates [32]. All of these studies further support the hypothesis that a defective NO response may be playing a role in the pathology associated with RUPP.

Additionally, blockade of NO with L-NMA blunted the dilation responses in SHAM uterine arteries but not RUPP uterine arteries (data not shown). Sodium nitroprusside is an endothelium independent vasodilator and can be used as an assessment of autocoid function. No differences were found between RUPP and SHAM uterine arteries in vasodilation to sodium nitroprusside. This data suggests that the cellular machinery for NO dilation is intact and that likely differences in vasodilation between RUPP and SHAM uterine arteries are due to a defective endothelium. We speculate that defects in NO production or subsequent NO signaling play a role however, the exact mechanism for the decreases in endothelial mediated NO responses is not known but is currently under investigation in our lab.

We also investigated the responses of the uterine arteries to phenylephrine (α -adrenergic agonist) and U-46619 (thromboxane receptor agonist). The vasoconstrictor responses were similar between RUPP and SHAM rats. This is in agreement with our previous report that phenylephrine constriction in mesenteric resistance arteries from RUPP and SHAM rats was unaltered [5,22]. Taken together our data indicate that the vasodilatory responses of uterine arteries are inhibited as part of the pathophysiology of RUPP and possibly contribute to the fetal growth restriction noted in this model.

In addition to active, functional responses of RUPP uterine arteries, passive structural and mechanical parameters were also investigated. We found no differences in wall thickness and wall:lumen ratios between RUPP and SHAM uterine arteries. Similarly, circumferential wall stress of uterine arteries demonstrated no differences between RUPP and SHAM. However, uterine artery distensibility, a measurement indicative of arterial compliance and extracellular matrix components such as collagen and elastin, was significantly decreased in RUPP uterine arteries compared to SHAM. This suggests altered remodeling in the uterine arteries isolated from RUPP rats. The decreases in distensibility may prevent the increases in uterine perfusion necessary to accommodate the developing fetuses. Indeed, RUPP has been recently demonstrated to result in enlarged cardiomyocytes, increased heart weight, and increased left ventricular collagen deposition [33].

One limitation of our study is that in the RUPP model the reduction in uterine perfusion pressure is surgical so we cannot differentiate the surgical intervention from changes in placental signaling. However, our study does provide insights into the vascular consequences of reduced uterine perfusion pressure which is central to the pathophysiology of preeclampsia. These studies demonstrate that the maternal endothelial dysfunction extends to the uterine circulation with increased myogenic responses and decreased responses to vasodilators. This is combined with altered remodeling favoring less distensible uterine arteries. Overall the consequences of these alterations could have a negative impact on uterine blood flow and fetal growth.

Conclusion

In conclusion, our results indicate that uterine artery reactivity was altered in response to reductions in uterine perfusion pressure. The responses of the uterine arteries demonstrate a more constrictive phenotype in RUPP pregnant rats. Specifically, myogenic reactivity of resistance-caliber uterine arteries in RUPP was increased compared to SHAM. Blockade of NO with L-NMA significantly increased myogenic reactivity of resistance-caliber uterine arteries in SHAM animals but not RUPP. Uterine arteries from RUPP dams also exhibited decreased vasodilation to two vasodilators (methacholine and VEGF). These data indicate a possible defective NO mediated response in uterine arteries after reductions in uterine perfusion pressure.

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Figure 1.

Myogenic reactivity of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). Myogenic reactivity of uterine arteries was increased in RUPP rats compared to SHAM controls (* $p < 0.05$).

A

B

Figure 2.

(A) Myogenic reactivity of resistance-caliber uterine arteries with and without L-NMA incubation from SHAM pregnant rats (means $\pm$ SEM). Preincubation of uterine arteries from SHAM pregnant rats with L-NMA significantly increased myogenic reactivity (* $p < 0.05$).

(B) Myogenic reactivity of resistance-caliber uterine arteries with and without L-NMA incubation from RUPP pregnant rats (means $\pm$ SEM). Preincubation of uterine arteries in RUPP pregnant rats with L-NMA did not alter myogenic reactivity.

Figure 3. Methacholine induced vasodilation of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). Methacholine vasodilation was significantly reduced in uterine arteries from RUPP rats compared to SHAM controls (* $p < 0.05$).

Figure 4. VEGF induced vasodilation of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). VEGF vasodilation was significantly reduced in uterine arteries from RUPP rats compared to SHAM controls (* $p < 0.05$).

Figure 5. Sodium nitroprusside vasodilation of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). Sodium nitroprusside vasodilation was similar in uterine arteries from RUPP and SHAM rats.

Figure 6. Phenylephrine constriction of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). Phenylephrine constriction was similar in uterine arteries from RUPP and SHAM rats.

Figure 7. U-46619 constriction of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). U-46619 constriction was similar in uterine arteries from RUPP and SHAM rats.

Figure 8. Passive distensibility (%) of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). Uterine arteries from RUPP rats were less distensible compared to SHAM uterine arteries (* $p < 0.001$).

Table 1

Structural and mechanical parameters of resistance-caliber uterine arteries from RUPP and SHAM pregnant rats (means $\pm$ SEM). No differences were found between treatment groups at any of the given pressures.

		Intraluminal Pressure (mmHg)						
		20	40	60	80	100	120	150
Passive Diameter (μm)	SHAM	231.4 ± 7.8	283.7 ± 10.6	303.8 ± 11.4	314.3 ± 12.1	323.4 ± 14.1	326.6 ± 13.8	332.1 ± 13.9
	RUPP	270.3 ± 21.9	298.5 ± 23.1	312.8 ± 23.2	318.7 ± 23.6	325.3 ± 24.1	329.1 ± 23.8	333.6 ± 23.6
Wall Thickness (μm)	SHAM	28.4 ± 1.7	24.2 ± 1.7	22.0 ± 1.6	20.2 ± 1.3	18.9 ± 1.5	17.5 ± 1.5	17.3 ± 1.4
	RUPP	27.5 ± 3.4	23.5 ± 2.8	22.2 ± 2.7	19.6 ± 1.9	17.8 ± 1.4	16.9 ± 1.3	16.4 ± 1.3
Wall:Lumen	SHAM	0.12 ± 0.01	0.09 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
	RUPP	0.10 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
Wall Stress (dynes/cm ²)	SHAM	1.1 ± 0.1	3.3 ± 0.3	5.8 ± 0.4	8.7 ± 0.6	12.1 ± 1.0	15.9 ± 1.2	20.2 ± 1.4
	RUPP	1.5 ± 0.3	3.7 ± 0.5	6.3 ± 0.9	9.7 ± 1.4	13.1 ± 1.7	16.6 ± 2.0	21.8 ± 2.6