Reduced Endothelial Vascular Relaxation in Growth-Restricted Offspring of Pregnant Rats With Reduced Uterine Perfusion

Jason A. Payne, Barbara T. Alexander, Raouf A. Khalil

Abstract—Low birth weight as the result of placental insufficiency increases the risk of hypertension in young adults; however, the vascular mechanisms involved are unclear. We tested the hypothesis that intrauterine fetal growth restriction caused by placental insufficiency results in low-birth-weight offspring with impaired endothelium-dependent vascular relaxation, enhanced vasoconstriction, and hypertension. The body weight and arterial pressure were measured in young (4 weeks), adolescent (8 weeks), and adult (12 weeks) male offspring of normal pregnant rats and pregnant rats with reduced uteroplacental perfusion (intrauterine growth-restricted, IUGR), and aortic strips were isolated for measurement of isometric contraction. The body weight was lower whereas the arterial pressure was higher in IUGR than normal rats at 4 weeks (113±3 versus 98±2), 8 weeks (133±3 versus 121±6), and 12 weeks (144±4 versus 131±3 mm Hg). Phe (10⁻⁵ mol/L) caused an increase in active stress that was greater in IUGR than in normal rats at 4 weeks (12.4 versus 7.8), 8 weeks (13.3 versus 8.4), and 12 weeks (14.6 versus 9.0×10⁴ N/m²). Removal of the endothelium enhanced Phe-induced stress in normal but not IUGR rats. In endothelium-intact strips, acetylcholine (ACh) caused relaxation of Phe contraction and induced nitrite/nitrate production that were smaller in IUGR than normal rats. L-NAME (10⁻⁴ mol/L), which inhibits NO synthase, or ODQ (10⁻⁵ mol/L), which inhibits cGMP production in smooth muscle, inhibited ACh-induced relaxation and enhanced Phe contraction in normal but not IUGR rats. Thus endothelium-dependent NO-mediated vascular relaxation is inhibited in IUGR offspring of pregnant rats with reduced uteroplacental perfusion, and this may explain the increased vascular constriction and arterial pressure in young adults with low birth weight. (Hypertension. 2003;42[part 2]:768-774.)

Key Words: arteries • endothelium • nitric oxide • muscle, smooth, vascular • vasculature

Low birth weight has been suggested as a predisposing factor for increased arterial pressure in young adults.¹,² Epidemiological studies have also supported a relation between low birth weight and the risk of cardiovascular diseases such as hypertension.³–⁷ However, the mechanisms linking low birth weight and hypertension have not been clearly identified. The “fetal-origin” hypothesis proposes that in utero programming of cardiovascular diseases such as hypertension may occur as a result of decreased maternal food and protein intake or reduction in uteroplacental perfusion.¹,²,⁷ Animal models of adverse fetal environment induced by maternal malnutrition support a role for in utero programming of hypertension.⁸–¹⁰ It has been reported that protein restriction during the last third of gestation in the rat results in offspring with reduced renal function and hypertension.¹¹ It has also been shown that low birth weight caused by decreased maternal protein intake is associated with alterations in the kidney structure, the renin-angiotensin system, and the renal control mechanisms of the arterial pressure.¹⁰,¹¹ Additionally, undernutrition in early pregnancy has been shown to be associated with decreased endothelium-dependent vascular relaxation in blood vessels of late-gestation fetal sheep.¹² Other studies have shown an association between low birth weight caused by decreased maternal protein intake and changes in the vascular endothelium–derived contracting factors such as endothelin.¹¹

Although the majority of low-birth-weight infants in the Western world are the result of reduction in uteroplacental perfusion rather than maternal malnutrition,¹³ little is known regarding the renal and vascular mechanisms linking intrauterine growth restriction (IUGR) as the result of reduced uteroplacental perfusion and hypertension. We have recently worked on a rat model of hypertension of pregnancy produced by reduction in uteroplacental perfusion pressure (RUPP) during late pregnancy.¹⁴–¹⁹ A recent study has suggested possible alterations in the renal control mecha-

Received May 5, 2003; first decision May 23, 2003; revision accepted June 25, 2003.

From the Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Miss (J.A.P., B.T.A.); and from Research and Development, Department of Veterans Affairs Medical Center, West Roxbury, and the Department of Medicine, Harvard Medical School, Boston, Mass (R.A.K.).

Correspondence to Raouf A. Khalil, MD, Harvard Medical School, VA Boston Healthcare–Research, 1400 VFW Parkway, 3/2B123, Boston, MA 02132. E-mail raouf_khalil@hms.harvard.edu

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Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000084990.88147.0C
isms of the arterial pressure in growth-restricted offspring of pregnant rats with reduced uteroplacental perfusion. However, the vascular mechanisms linking IUGR in response to decreased uteroplacental perfusion and hypertension are unclear.

The vascular endothelium is known to release endothelium-derived relaxing factors such as nitric oxide (NO). NO diffuses into the smooth muscle, where it stimulates the enzyme guanylate cyclase leading to increased cGMP production and smooth muscle relaxation.

The purpose of this study was to test the hypothesis that low birth weight caused by IUGR is associated with impaired endothelium-dependent vascular relaxation and enhanced vascular constriction. To test this hypothesis, we used offspring of normal pregnant rats and offspring of a pregnant rat model of RUPP produced by clipping the uterine and ovarian arteries during late pregnancy. Experiments were designed to investigate (1) whether the vascular constriction to the α-adrenergic agonist phenylephrine (Phe) is enhanced in growth-restricted compared with normal rats; (2) whether the vascular relaxation to acetylcholine (ACh) is reduced in growth-restricted compared with normal rats; and (3) whether the changes in vascular constriction/relaxation in blood vessels of growth-restricted rats involve alterations in the endothelium-dependent NO-cGMP pathway.

**Methods**

### Pregnant Rats

Female timed-pregnant Sprague-Dawley rats were purchased from Harlan Sprague-Dawley Inc and housed individually 1 to 1 cage in a temperature-controlled room (23°C) and maintained on ad libitum standard rat chow and tap water in a 12 hour/12 hour light/dark cycle. All procedures were performed in accordance with the guidelines of the Animal Care and Use Committee at the University of Mississippi Medical Center.

### Protocol for Reduction of Uteroplacental Perfusion Pressure

On day 14 of pregnancy, pregnant rats destined to be in the RUPP group were anesthetized with isoflurane; the abdominal cavity was opened by a midline incision, the abdominal aorta was exposed, and a silver clip (0.23-mm ID) was placed around the aorta above the iliac bifurcation as described. This procedure has been shown to reduce uterine perfusion pressure in the gravid rat by approximately 40%. Because compensation of blood flow to the placenta occurs in pregnant rats through an adaptive increase in ovarian blood flow, a silver clip (0.1-mm ID) was also placed on the main uterine branches of both the right and left ovarian arteries. Normal pregnant rats were sham-operated.

### Offspring Rats

All pregnant rats were allowed to deliver at term. The offspring of normal sham-operated pregnant rats were referred to as the normal group. The offspring of pregnant rats that underwent the surgical procedure to reduce the uteroplacental perfusion were referred to as the IUGR group. The litter size and the birth weight of the normal and IUGR pups were recorded within 12 hours after delivery. Because the litter size was smaller in RUPP rats compared with normal pregnant rats, litter sizes of the normal and IUGR rats were matched. All pups were marked for identification by tattooing (Spaulding Special electronic Tattoo Marker, Spaulding and Rogers). Pups were weighed twice per week after birth and were weaned at 3 weeks of age. Rats were studied at 4 weeks, 8 weeks, and 12 weeks of age.

### Tissue Preparation

On the day of the experiment, the rats were anesthetized by inhalation of isoflurane. The thoracic aorta was rapidly excised, placed in oxygenated Krebs solution, and cleaned of connective tissue. The aorta was cut transversely into 3-mm-wide rings. Aortic rings were cut open into strips. For endothelium-intact aortic strips, extreme care was taken throughout the procedure to avoid injury of the endothelium. For endothelium-denuded aortic strips, the endothelium was removed by gently rubbing the vessel interior with wet filter paper. Removal of the endothelium was verified by the absence of ACh relaxation in tissues precontracted by submaximal concentrations of Phe.

### Isometric Contraction

One end of the aortic strip was attached to a glass hook by using a thread loop and the other end was connected to a Grass force transducer (FT03). Aortic strips were stretched to Lmax (1.5 the unloaded initial length, L). The strips were allowed to equilibrate for 1 hour in a water-jacketed, temperature-controlled tissue bath filled with 50 mL Krebs solution continuously bubbled with 95% O2, 5% CO2 at 37°C. The changes in isometric contraction were recorded on a Grass polygraph (model 7D).

A control contraction was elicited by applying phenylephrine (Phe, 10^{-5} mol/L) to the tissue bath solution. Once the Phe contraction reached a plateau, the tissue was rinsed with Krebs solution 3 times, 10 minutes each. The whole procedure of contraction and washing was repeated 2 times. Increasing concentrations of Phe were applied, the contractile responses were recorded, and concentration-response curves were constructed. In other tissues, a contraction to submaximal concentration of Phe (3×10^{-5} mol/L) was elicited (50% to 70% of maximum). Increasing concentrations of ACh or sodium nitroprusside were added, and the extent of vascular relaxation was measured. In other experiments, the tissues were pretreated for 30 minutes with Nω-nitro-L-arginine methyl ester (L-NAME, 10^{-4} mol/L) to inhibit NO synthase or with 1H-NOS-1,2-oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, 10^{-3} mol/L) to inhibit cGMP production in smooth muscle, and the effects on the Phe-induced constriction and on the ACh-induced relaxation of Phe constriction were observed.

### Nitrite/Nitrate Production

Endothelium-intact aortic strips were placed in test tubes containing 2 mL Krebs solution aerated with 95% O2/5% CO2 at 37°C, and the solution was changed every 30 minutes for 1 hour. Samples for basal accumulation of nitrite or nitrate, formed from released NO were first taken. The Krebs solution was replaced, and the strips were stimulated with different concentrations of ACh for 5 minutes. The strips were rapidly removed, dabbed dry with filter paper, and weighed. The incubation solutions were assayed for the stable end product of NO, NO2. Briefly, samples of incubation solution (50 μL, in triplicate) were mixed in a 96-well microtiter plate with 100 μL of the Griess reagent. The chromophore generated by the reaction with nitrate was detected spectrophotometrically (550 nm) with the use of a microplate reader (THERMOMax, Molecular Devices). The concentration of nitrate in the solutions was determined by standard curve method.
of nitrate was calculated by using a calibration curve with known concentrations of NaNO2.30

Solutions, Drugs, and Chemicals
Normal Krebs solution contained (in mmol/L): NaCl, 120; KCl, 5.9; NaHCO3, 25; NaH2PO4, 1.2; dextrose, 11.5; MgCl2, 1.2; CaCl2, 2.5, at pH 7.4. Stock solutions of L-phenylephrine HCl, acetylcholine, sodium nitroprusside, and L-NNAME (Sigma) were prepared in distilled water. 1H-1,2,4-oxadiazolo4,3-quinoxalin-1-one (ODQ) (Calbiochem) was dissolved in dimethyl sulfoxide (DMSO). The final concentration of DMSO in solution was <0.01%. All other chemicals were of reagent grade or better.

Statistical Analysis
The developed force was corrected for the cross-sectional area of each individual strip and expressed as active stress (N/m2), using the equation Stress=force/cross-sectional area, where cross-sectional area=wet weight/(tissue density×length of the strip), and tissue density=1.055 g/cm³. Data were analyzed and expressed as mean±SEM. Data were compared by means of ANOVA with multiple classification criteria—rat type (normal versus IUGR), condition of endothelium (intact versus denuded), and vascular pretreatment (nontreated versus pretreated with L-NNAME or ODQ)—followed by the Bonferroni posttest to compare selected groups or the Dunnet posttest to compare all groups with the normal nontreated group. Differences were considered statistically significant at a level of P<0.05.

Results
The birth weight in offspring of normal rats was 6.6±0.2 g. The birth weight was significantly reduced (P<0.01) in IUGR rats (5.8±0.1 g) compared with normal rats. Both normal and IUGR rats showed significant increases in body weight with age. However, the body weight was consistently smaller in IUGR compared with normal rats at 4, 8, and 12 weeks of age (Table). In normal 4-week rats, the MAP was 98±2 mm Hg. MAP was significantly greater in 8-week (P<0.006) and 12-week (P<0.001) compared with 4-week normal rats (Table). The MAP in IUGR rats at 4 weeks, 8 weeks, and 12 weeks of age was consistently greater than that in the corresponding age group of normal rats (Table). At 12 weeks of age, MAP in IUGR rats was significantly greater (P=0.016) than that in age-matched normal rats (Table).

In endothelium-intact aortic strips from all groups of rats, Phe caused concentration-dependent increases in active stress (Figure 1). The Phe-induced vascular constriction increased with age and was enhanced in the 8-week and 12-week rats compared with 4-week normal and IUGR rats (Table). The maximal Phe (10⁻⁵ mol/L) constriction was significantly greater (P<0.001) in IUGR compared with normal rats at 4 weeks, 8 weeks, and 12 weeks of age (Table and Figure 1A). When the Phe response was presented as a percentage of maximum Phe constriction and the ED₅₀ was calculated, Phe was significantly more potent (P=0.009) in 12-week IUGR compared with normal rats (Figure 1B and Table). Removal of the endothelium significantly enhanced (P<0.05) the Phe-induced active stress in normal rats but not in IUGR rats (Figure 1A and Table). Phe was significantly more potent (P<0.05) in causing constriction in endothelium-denuded than endothelium-intact strips from normal rats (Figure 1B and Table). On the other hand, the potency of Phe was not significantly different between endothelium-denuded and endothelium-intact strips from IUGR rats (Figure 1B and Table).
In endothelium-intact vascular strips from normal rats, pretreatment with L-NAME (10^{-4} mol/L) for 30 minutes to inhibit NO synthase significantly enhanced (P<0.05) the maximal Phe-induced active stress (Figure 2A and Table). Also, plotting of Phe response as a percentage of maximum and calculation of Phe ED50 showed that in normal 12-week rats, Phe was more potent (P<0.002) in causing constriction in the presence than in the absence of L-NAME (Figure 2C and Table). In contrast, in vascular strips from IUGR rats, the maximal Phe-induced stress and the Phe ED50 in the presence of L-NAME were not significantly different from that in the absence of L-NAME (Figures 2B and 2D and Table).

Similarly, in endothelium-intact vascular strips from normal rats, pretreatment with ODQ (10^{-5} mol/L) for 30 minutes to inhibit cGMP production in smooth muscle significantly enhanced (P<0.05) the maximal Phe-induced stress (Figure 2A and Table). Also, plotting of Phe response as a percentage of maximum and analysis of the Phe ED50 in normal rats showed that Phe was significantly more potent (P<0.002) in causing constriction in the presence than in the absence of ODQ (Figure 2C and Table). In contrast, in vascular strips from IUGR rats, maximal Phe-induced stress and the Phe ED50 in the presence of ODQ were not significantly different from that in the absence of ODQ (Figures 2B and 2D, and Table).

In endothelium-intact aortic strips from normal rats at 4, 8, and 12 weeks of age, ACh caused concentration-dependent relaxation of Phe (3×10^{-3} mol/L) contraction (Table and Figure 3A). The ACh-induced relaxation was significantly reduced (P<0.001) in IUGR compared with normal rats in all age groups (Table and Figure 3B). Since the Phe constriction was greater in vascular strips from IUGR rats compared with normal rats, experiments were performed on strips from IUGR rats at 12 weeks of age in which the Phe concentration was lowered to 1×10^{-3} mol/L to produce a submaximal contraction that is roughly equal in magnitude to the contraction observed in strips from 12-week-old normal rats precon-
tracted with $3 \times 10^{-7}$ mol/L Phe. These experiments showed that the ED$_{50}$ of ACh in vascular strips from 12-week-old IUGR rats precontracted with $1 \times 10^{-7}$ mol/L Phe (2.4$ \pm $0.1$ \times 10^{-8}$ mol/L) was not significantly different from that in strips precontracted with $3 \times 10^{-7}$ mol/L Phe (2.3$ \pm $0.1$ \times 10^{-8}$ mol/L).

Pretreatment of endothelium-intact vascular strips from normal rats for 30 minutes with L-NAME ($10^{-4}$ mol/L) to inhibit NO synthase or ODQ ($10^{-5}$ mol/L) to inhibit cGMP production in smooth muscle significantly inhibited ($P<0.01$) ACh-induced relaxation (Figure 3A). In contrast, pretreatment of endothelium-intact vascular strips from IUGR rats with L-NAME ($10^{-4}$ mol/L) or ODQ ($10^{-5}$ mol/L) did not significantly affect ACh-induced relaxation (Figure 3B).

In endothelium-intact vascular strips from normal rats at 4 weeks of age, the basal nitrite/nitrate (NOx) production was 36.2$ \pm $7.6 pmol/mg tissue weight. ACh significantly increased NOx production in vascular strips from normal rats in all age groups (Figure 4 and Table). The basal and ACh-induced NOx production were significantly reduced ($P<0.001$) in IUGR compared with normal rats (Figure 4 and Table).

In endothelium-denuded vascular strips, sodium nitroprusside (SNP), an exogenous NO donor and a standard guanylate cyclase activator, caused concentration-dependent relaxation of Phe contraction. The SNP-induced relaxation was not significantly different in vascular strips from normal compared with IUGR rats (Figure 5).

**Discussion**

The main findings of the present study are (1) low birth weight is associated with increased MAP in IUGR compared with normal rats, (2) Phe-induced vascular constriction is enhanced in arteries from IUGR compared with normal rats, (3) endothelium-dependent vascular relaxation is reduced in arteries from IUGR compared with normal rats, and (4) changes in vascular relaxation and constriction in IUGR rats appear to involve alterations in the endothelium-dependent NO-cGMP pathway.

Previous studies have suggested a strong relation between low birth weight and the risk of hypertension.1–6,31,32 Experimental studies have also shown that maternal undernutrition induced by protein restriction during gestation in the rat results in offspring that are hypertensive.5–10 However, because of the good perinatal care, malnutrition represents a small portion of low birth weight in the Western world. Thus, a strong correlation between low birth weight and hypertension in well-nourished populations suggests that fetal undernutrition as a result of placental insufficiency rather than maternal malnutrition may be the major cause of IUGR in the Western world.13,31–33 Therefore, it would probably be more relevant to study the low birth weight–related hemodynamics and vascular changes in IUGR offspring of an animal model of pregnancy with reduced uteroplacental perfusion.

**Figure 3.** ACh-induced relaxation of Phe contraction in endothelium-intact aortic strips of normal (A) and IUGR adult (12-week) rats (B) in the absence or presence of L-NAME or ODQ. Aortic strips were incubated in the absence or presence of L-NAME ($10^{-4}$ mol/L) or ODQ ($10^{-5}$ mol/L) for 30 minutes. Submaximal Phe contraction was elicited, then ACh was added and the percentage of relaxation of Phe contraction was measured. Data points represent mean$\pm$SEM of measurements in 9 to 24 aortic strips from 9 to 12 rats of each group. *Measurements in the presence of L-NAME or ODQ are significantly different ($P<0.05$) from that in the absence of L-NAME or ODQ.

**Figure 4.** Basal and ACh-induced nitrite/nitrate production in endothelium-intact aortic strips of normal and IUGR adult (12-week) rats. Data points represent mean$\pm$SEM of measurements in 18 to 24 aortic strips from 9 to 12 rats of each group. *Measurements are significantly different ($P<0.05$) between IUGR and normal rats.

**Figure 5.** SNP-induced relaxation of Phe contraction in endothelium-denuded aortic strips of normal and IUGR adult (12-week) rats. Submaximal Phe contraction was elicited, then increasing concentrations of SNP were added and the percentage of relaxation of Phe contraction was measured. Data represent mean$\pm$SEM of measurements in 18 to 24 strips from 9 to 12 rats of each group.
A goal of the current study was to determine whether a model of placental insufficiency in late gestation induced by reduction of uteroplacental perfusion in pregnant rats resulted in IUGR offspring predisposed to development of hypertension. Placental insufficiency was induced by a chronic RUPP initiated at day 14 of gestation in the pregnant rat.14–18 IUGR offspring from the RUPP rats had significantly lower birth weights compared with offspring from normal pregnant rats. Also, the body weight was consistently lower in the IUGR rats compared with the normal rats at various age groups. The body weight was reduced in the IUGR rats compared with the normal rats by 25% at 4 weeks, 9% at 8 weeks, and 11% at 12 weeks of age. Also, MAP was significantly increased in IUGR offspring compared with normal rats as early as 4 weeks of age, and a significant increase in MAP was still evident at 12 weeks of age. Thus, the decreases in body weight observed in the IUGR rats compared with the normal rats were associated with significant elevations in MAP.

We have also found that the vascular constriction to Phe is enhanced in IUGR compared with normal rats. In search for the possible mechanisms involved in the enhanced vascular constriction in the IUGR rats, we found that removal of the endothelium enhanced the Phe-induced constriction in normal rats but had minimal effects in IUGR rats. Also, the ACh-induced relaxation was reduced in IUGR compared with normal rats. These results provide evidence that an endothelium-dependent relaxation pathway is active in normal rats and inhibited in IUGR rats.

The vascular endothelium is known to release relaxing factors such as NO.21–23 The reduced ACh-induced relaxation in IUGR rats could be due to a decrease in the synthesis/release of NO from endothelial cells or may reflect a change in the sensitivity of vascular smooth muscle to relaxation by NO. The sensitivity of vascular smooth muscle to relaxation by NO could be evaluated by its sensitivity to relaxation by exogenous NO donors such as SNP. The observation that the relaxation of endothelium-denuded vascular strips to SNP was not different between IUGR and normal rats suggests that the decreased relaxation in the IUGR rats is not due to decreased vascular smooth muscle sensitivity to NO and more likely is due to changes in the synthesis/release of NO.

We have observed that pretreatment of the vascular strips from normal rats with L-NAME, which blocks NO synthesis, inhibited ACh-induced vascular relaxation and enhanced Phe-induced constriction (Figures 2 and 3 and Table). However, in vascular strips from IUGR rats, L-NAME did not significantly affect ACh-induced vascular relaxation or Phe-induced constriction. These results suggest that NO synthesis by endothelial cells is impaired in the IUGR rats. This is supported by the observation that both the basal and the ACh-induced nitrite/nitrate production were reduced in vascular strips from the IUGR compared with normal rats.

The NO produced by endothelial cells is known to promote vascular relaxation by activating guanylate cyclase and increasing the production of cGMP in smooth muscle.24,25 ODQ, which inhibits guanylate cyclase and decreases cGMP production in smooth muscle,26,29 inhibited ACh-induced vascular relaxation and enhanced Phe-induced constriction in vascular strips from normal rats (Figures 2 and 3 and Table).

However, ODQ did not significantly affect ACh-induced vascular relaxation or Phe-induced constriction in IUGR rats. These results further support the hypothesis that NO synthesis/release by endothelial cells and thereby the activity of the NO-cGMP pathway in smooth muscle is reduced in IUGR rats.

It is important to emphasize the following cautionary remarks regarding the above interpretations. First, although the decrease in endothelial cell function and the increase in vascular constriction in IUGR rats could contribute to the observed elevation in arterial pressure, the vascular changes may also be secondary to arterial pressure alterations. Further analysis of the time course of the changes in vascular reactivity and the increase in arterial pressure in rats <4 weeks of age should help determine whether the relation between these 2 parameters is causal or associative in nature. Second, although the reduction in vascular relaxation and increase in vascular constriction in pregnant rats could explain, in part, the increase in arterial pressure, other factors such as the renal, neural, and hormonal control mechanisms of the arterial pressure could also be involved. This is supported by a recent report that placental insufficiency in late pregnant rats results in low-birth-weight offspring with significant reduction in kidney function and the renal control mechanisms of the arterial pressure.30 Third, the vascular endothelium releases other vasodilator substances in addition to NO, such as prostacyclin and endothelium-derived hyperpolarizing factor.34,35 This may explain why in the vascular strips from the IUGR rats some relaxation to ACh was still observed and was not completely inhibited by L-NAME or ODQ. On the other hand, the complete absence of ACh-induced relaxation in endothelium-denuded strips from IUGR rats still supports the contention that the ACh-induced relaxation is endothelium-dependent. Fourth, although the present results provide evidence that the enhanced vascular constriction in IUGR rats may involve inhibition of the endothelium-dependent NO-cGMP pathway, we cannot rule out possible increase in endothelium-derived contracting factors and/or the sensitivity of vascular smooth muscle to contracting factors in IUGR rats. This is supported by the observation that incubation of endothelin-intact vascular strips from normal rats in the presence of L-NAME or ODQ caused an enhancement of Phe-induced constriction to levels that were still less than that observed in IUGR rats (Figure 2 and Table). This is also supported by reports that low birth weight caused by maternal malnutrition is associated with increased endothelin-1 production.11 The possible increase in endothelin-1 production in IUGR rats could then lead to additional alterations in the cellular mechanisms of vascular smooth muscle contraction and should represent important areas for future experiments.

Perspectives

Low birth weight predisposes children and young adults to hypertension. IUGR resulting from complications of pregnancy such as preeclampsia is a major cause of low birth weight, particularly in the Western world. Low-birth-weight offspring of pregnant rats with reduced uteroplacental perfusion are good animal models to study the vascular mecha-
nisms of the hypertension associated with IUGR. The current study has shown that an endothelium-dependent vascular relaxation pathway involving the release of NO from endothelial cells but not the smooth muscle response to NO is inhibited in systemic vessels of intrauterine growth-restricted offspring of pregnant rats with reduced uteroplacental perfusion. The decreased NO-mediated vascular relaxation pathway in growth-restricted rats may explain the increased vascular constriction and arterial pressure in the young and adults with low birth weight. However, whether the decreased NO-mediated vascular relaxation is due to increased amount or activity of NO synthase remains to be clarified. Also, whether a decrease in other endothelium-derived relaxing factors such as prostacyclin or hyperpolarizing factors may contribute to the decreased vascular relaxation associated with intrauterine growth restriction is unclear. Furthermore, the contribution of endothelium-derived contracting factors such as endothelin and/or thromboxane A2 to the increased vascular constriction associated with intrauterine growth restriction should be examined in future experiments.

Acknowledgments

This work was supported by grants from the National Heart, Lung, and Blood Institute (HL-52696, HL-65998). Dr Khalil is an Established Investigator of the American Heart Association.

References

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_Hypertension._ 2003;42:768-774; originally published online July 21, 2003;
doi: 10.1161/01.HYP.0000084990.88147.0C
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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