

Pregnancy Prevents Hypertensive Remodeling of Cerebral Arteries

A Potential Role in the Development of Eclampsia

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Abstract—We investigated how hypertension during pregnancy affected passive structural (wall:lumen, wall stress) and active (myogenic activity) responses of the cerebral circulation. Female nonpregnant (NP; n=8) Sprague Dawley rats were compared with late-pregnant (LP; day 19 to 20, n=6) rats. Some animals were treated with the NO synthase inhibitor nitro-L-arginine in their drinking water to raise blood pressure. LP rats (n=6) were treated for the last 7 days of pregnancy (last trimester) to mimic preeclampsia and compared with NP rats treated for the same duration (n=8). Active and passive responses were determined on isolated and pressurized third-order posterior cerebral arteries. Nitro-L-arginine treatment significantly raised blood pressure in both groups of animals that was associated with increased wall thickness and wall:lumen ratio in the NP hypertensive animals versus controls ($P<0.05$). In contrast, this response to pressure was absent in LP animals, which had similar wall measurements. In addition, arteries from NP hypertensive animals had increased myogenic tone and pressure of forced dilatation compared with NP control animals ($P<0.01$). Again, this response was lacking in the LP hypertensive animals that had similar tone and pressure of forced dilatation as normotensive controls. The increased tone and wall thickness decreased wall stress in the NP hypertensive animals, a response that did not occur in LP hypertensive animals. Because medial hypertrophy is considered a protective response to elevated blood pressure, these results suggest that hypertension in pregnancy may predispose the cerebral circulation to autoregulatory breakthrough and blood–brain–barrier disruption when blood pressure is elevated, as during eclampsia. (*Hypertension*. 2006;47[Part 2]:619-626.)

Key Words: hypertension, pregnancy ■ cerebral arteries ■ pregnancy ■ eclampsia ■ hypertrophy

The neurological complications of eclampsia are thought to be similar to hypertensive encephalopathy in which an acute, excessive elevation in pressure causes forced dilatation of cerebral artery myogenic tone, autoregulatory breakthrough, and edema formation.^{1–3} Our previous work demonstrated that normal pregnancy may predispose the brain to eclampsia by lowering the pressure at which forced dilatation of cerebral arteries occurs.⁴ Whereas this effect may not be consequential if mean arterial pressure remains within the normal autoregulatory pressure range, it may cause blood–brain barrier (BBB) disruption and edema formation if pressure is elevated, as during hypertension in pregnancy and preeclampsia/eclampsia.

It is now established that chronic hypertension is associated with medial hypertrophy of both large and small cerebral arteries that increases the wall:lumen ratio.^{5–9} This response of the cerebrovascular smooth muscle to chronically elevated blood pressure is considered to be an important protective function.⁶ Several studies have shown that spontaneously hypertensive rats^{10,11} and stroke-prone spontaneously hypertensive rats¹² were less susceptible to BBB disruption during

acute hypertension than normotensive Wistar Kyoto rats that did not undergo medial hypertrophy. In addition, attenuation of medial hypertrophy in spontaneously hypertensive and stroke-prone spontaneously hypertensive rats increased the susceptibility of the BBB to disruption during acute hypertension.^{13,14} Therefore, it appears that hypertension-induced cerebral artery hypertrophy can stiffen the vascular wall, making cerebral arteries more resistant to forced dilatation during acute hypertension, thereby protecting the BBB.^{5,6}

Cerebral arteries can also undergo eutrophic remodeling in response to chronic hypertension, defined as a decrease in external and internal diameter such that cross-sectional area does not change.^{15–17} Similar to medial hypertrophy, remodeling in response to chronic hypertension is considered to be protective, because it serves to normalize circumferential wall stress that is elevated because of increased blood pressure and extend the autoregulatory curve to the higher range of pressures.^{5,6} Both hypertrophy and remodeling of large and small cerebral arteries attenuate the increased pressure in downstream microvessels, thereby protecting the BBB from disruption.¹⁸

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Hypertension during pregnancy is a unique form of hypertension that is somewhere between acute and chronic. During preeclampsia, elevations in mean arterial pressure occur after week 20 of gestation and are ameliorated by the birth of the fetus.¹⁹ A number of maternal organs are affected by hypertension in pregnancy, including the brain in the form of eclampsia.^{1–3,19,20} Eclampsia is a leading cause of maternal death, with classic neurological features that include headaches, nausea, visual disturbances, loss of consciousness, and convulsions.^{21–24} Although considerable effort has been made to understand the cause of hypertension in pregnancy and preeclampsia, little is known about how elevated blood pressure during pregnancy affects the cerebral circulation in a way that may either protect or predispose to the neurological complications of eclampsia.

In the present study, we used an established model of hypertension in pregnancy, that of NO synthase (NOS) inhibition, to raise arterial blood pressure in pregnant rats during the last trimester (ie, last 7 days) of pregnancy.^{25–27} This model of hypertension has been shown in male rats to cause both medial hypertrophy and eutrophic remodeling of cerebral arteries.^{8,9,16} We investigated how the combination of hypertension and pregnancy affected the structure (wall thickness, wall stress, and distensibility) and function (myogenic activity and forced dilatation) of third-order posterior cerebral arteries (PCAs). These arteries were chosen because imaging studies have shown that the posterior cerebral circulation is particularly vulnerable to forced dilatation and BBB disruption during eclampsia.^{28,29}

Methods

Animal Model

A rat model of pregnancy was used for all of the experiments. All of the procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Female virgin nonpregnant control (NP-CTL; n=8) Sprague Dawley rats were compared with late-pregnant control (LP-CTL; day 19 to 20; n=6) rats. Some animals were treated with the NOS inhibitor nitro-L-arginine (L-NAME) in their drinking water to raise arterial blood pressure. LP rats were treated with 0.7 g/L L-NAME (LP-HTN; n=6) for the last 7 days of pregnancy (last trimester) to mimic preeclampsia in humans, defined as hypertension (>140/90 mm Hg) after week 20 of gestation.¹⁹ NP animals were treated with 0.5 g/L L-NAME for 7 days (NP-HTN; n=8) to match the duration and extent of hypertension in the LP animals. A few NP animals were treated with L-NAME plus 25 mg/kg hydralazine (NP-Hydral; n=3; also in drinking water) to lower arterial pressure via a nonendothelial mechanism³⁰ in the presence of NOS inhibition. This group was used to compare passive structural changes in NP animals, because only those animals showed hypertension-induced changes.

Blood Pressure Measurements

Blood pressures were recorded daily by a tail-cuff technique using the Coda 6 System (Kent Scientific). Animals were placed in individual holders, and both an occlusion cuff and a volume pressure-recording cuff were placed close to the base of the tail. Volume pressure recording allowed the noninvasive measurement of 6 blood pressure parameters simultaneously: systolic blood pressure, diastolic blood pressure, mean blood pressure, heart pulse rate, tail blood volume, and tail blood flow.

Vessel Preparation and Pressurized Arteriograph System

On the day of an experiment, animals were anesthetized with isoflurane in oxygen and decapitated. The brain was quickly removed and placed in cold HEPES-physiological saline solution. A third-order branch of the PCA was carefully dissected, cleared of connective tissue, and placed in an arteriograph chamber (Living Systems). Arteries were mounted on 2 glass cannulas within the chamber, secured with nylon ties, and pressurized, as described previously.⁴ The entire chamber was placed on an inverted microscope with an attached video camera and monitor that allowed measurement of lumen diameter and wall thickness via video microscopy and video dimensional analysis (VDA). Temperature and pH were continually measured and maintained at $37 \pm 0.5^\circ\text{C}$ and 7.4 ± 0.05 , respectively.

Experimental Protocol

After equilibration for 1 hour at 25 mm Hg, the active response to pressure was determined by increasing pressure to 200 mm Hg in 25-mm Hg increments and measuring lumen diameter and wall thickness at each pressure once stable, ≈ 10 minutes. Papaverine (0.1 mmol/L) was then added to the bath to fully relax the vessels and obtain passive pressure-diameter measurements. In the presence of papaverine, pressure was lowered from 200 mm Hg to 0 mm Hg in 25-mm Hg increments until 50 mm Hg, after which pressure was lowered in 10-mm Hg increments. Diameter and wall thickness were measured at each pressure. Vessels were fixed while pressurized at 75 mm Hg with glutaraldehyde (2.5%) for measurement of passive media thickness by transmission electron microscopy, as described previously.³¹

Data Calculations

Wall:lumen ratio was calculated from the inner diameter and wall thickness measurements from the VDA by the equation $\phi_{\text{inner}}/\omega$, where ω is wall thickness and ϕ_{inner} is the internal diameter of the artery.

Wall stress was calculated by first calculating circumferential wall tension (T) by the equation $T = \text{pressure} \times r$, where r is the radius. Before T was calculated, pressure in mm Hg was converted to dynes per square centimeter (1 mm Hg = 1333.2 dynes/cm²), and radius in microns was converted to cm. For the purposes of this study, the PCA was considered to be a thin-walled cylindrical tube with orthotropic elasticity. The wall was assumed to be incompressible and homogeneous. Circumferential wall stress was then calculated by the equation T/ω , where ω is wall thickness.

Distensibility was calculated at each pressure, fully relaxed in papaverine, by determining diameter changes as a function of pressure and calculated by the following equation: $[(\phi_{\text{pressure}}/\phi_{10 \text{ mm Hg}}) - 1] \times 100$, where ϕ_{pressure} is the diameter at that particular pressure and $\phi_{10 \text{ mm Hg}}$ is the diameter at 10 mm Hg. Distensibility for each artery was normalized to the diameter at 10 mm Hg, because arteries often collapse at lower pressures.

Pressure-induced tone was calculated as a percentage decrease in diameter from the fully relaxed diameter in papaverine at each intravascular pressure by the equation $[1 - (\phi_{\text{tone}}/\phi_{\text{papav}})] \times 100\%$, where ϕ_{tone} is the diameter of vessels with tone and ϕ_{papav} is the diameter in papaverine.

Statistical Analysis

All of the results are presented as mean \pm SEM. Differences in blood pressure, passive structural measurements, passive and active wall stress, and distensibility were determined by 1-way ANOVA with a post hoc Student-Newman-Kuels test for multiple comparisons. Differences in active diameters and tone were determined by *t* test (between groups) and repeated-measures ANOVA (within groups to determine pressure of forced dilatation). Differences were considered significant at $P < 0.05$.

Drugs and Solutions

All of the experiments were conducted in a HEPES-physiological salt solution, the composition of which was (mM): NaCl (142), KCl (4.7), MgSO₄ (1.71), EDTA (0.50), CaCl₂ (2.8), HEPES (1.0), KH₂PO₄ (1.2), and glucose (5.0). HEPES, L-NAME, papaverine, and hydralazine were purchased from Sigma. L-NAME (0.5 or 0.7 g/L) and hydralazine (25 mg/kg) were added to the drinking water of the rats in the appropriate concentration, made fresh every other day. Papaverine was mixed each week as a stock solution (10⁻² M) and stored at 4°C.

Results

Blood Pressures

Figure 1 shows systolic, diastolic, and mean arterial blood pressures for all of the groups of animals. Under normotensive conditions, LP-CTL animals had significantly lower blood pressures compared with NP-CTL ($P<0.05$). L-NAME treatment significantly elevated blood pressures in both groups of animals compared with controls ($P<0.01$); pressures were elevated on the first day after treatment and remained elevated for 7 days. It is worth noting that LP-HTN animals required a higher concentration on L-NAME compared with the NP-HTN animals (0.7 versus 0.5 g/L) to obtain a similar elevation in blood pressure. This may be because of the fact that pregnancy is a state of elevated NO,³² and, therefore, greater NOS inhibition was required. NP animals treated with L-NAME plus hydralazine had significantly lower blood pressures than those receiving L-NAME alone and were similar to controls.

Passive Measurements

All of the passive measurements are reported at 75 mm Hg, a pressure that these PCAs have been shown to operate at under normotensive conditions.³³ Although it is possible that intravascular pressure is elevated in the hypertensive animals, we do not know how remodeling of upstream vessels may contribute to pressure in these vessels, and, therefore, values are reported at a constant pressure for comparison purposes (see Discussion).

Table shows the passive structural measurements of PCAs from all of the groups of animals. There was no difference in inner diameter (ID) or outer diameter (OD) between any of the groups, except for the NP-Hydral group, which had significantly larger diameters compared with NP-HTN ($P<0.05$). Although both NP-HTN and LP-HTN groups tended to have smaller diameters than their controls, this was not statistically significant.

Wall thickness (measured off the VDA), media thickness (measured by transmission electron microscopy), and wall:lumen ratio were significantly greater in PCAs from NP-HTN compared with NP-CTL animals, demonstrating that just 7 days of L-NAME hypertension caused medial hypertrophy. However, pregnancy completely prevented this hypertension-induced response. There was no difference in wall thickness, media thickness, or wall:lumen ratio between LP-CTL and LP-HTN. In fact, LP-HTN animals had a significantly smaller wall thickness and media thickness compared with NP-HTN animals. Hydralazine treatment in the NP animals prevented hypertrophy, suggesting that elevated arterial pressure and not NOS inhibition caused medial hypertrophy in the NP-HTN animals.

Figure 2 shows the passive wall stress in PCAs from all groups of animals. Passive wall stress was significantly decreased in NP-HTN animals compared with NP-CTL ($P<0.05$), demonstrating that the effect of medial hypertrophy was to decrease wall stress. However, both groups of LP animals had similar wall stress because of a lack of medial hypertrophy in those animals. In fact, passive wall stress of LP-HTN animals was significantly elevated compared with NP-HTN ($P<0.05$). Hydralazine treatment that prevented medial hypertrophy also prevented the decrease in wall stress, which was similar to NP-CTL animals.

Figure 3 shows the passive distensibility for PCAs from all groups of animals. Both NP-CTL and NP-HTN animals had the least distensible arteries, suggesting that these vessels were the most stiff, although there was no statistical difference between HTN and CTL groups. Interestingly, hydral-

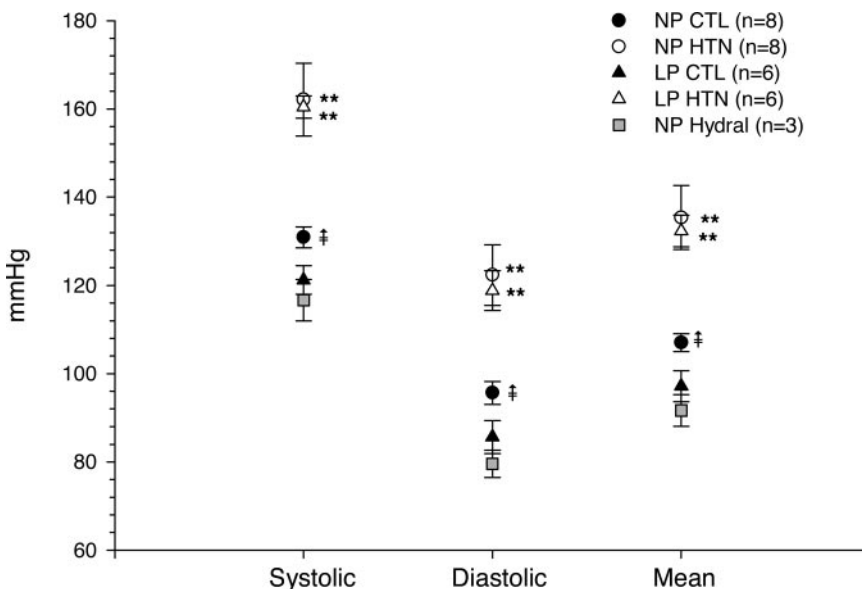


Figure 1. Blood pressure measurements (systolic, diastolic, and mean pressures) for all groups of animals. Closed symbols are normotensive animals (NP and LP), whereas open symbols were treated with the NOS inhibitor L-NAME to raise blood pressure. The shaded symbol represents NP animals that were treated with both L-NAME and hydralazine to lower blood pressure in the presence of L-NAME. * $P<0.05$ LP-CTL vs NP-CTL; ** $P<0.01$ NP-HTN and LP-HTN vs NP-CTL and LP-CTL, respectively.

Passive Structural Measurements of Posterior Cerebral Arteries From NP and LP Rats at 75 mm Hg

Group	ID (μm)	OD (μm)	Wall Thickness (μm)	Media Thickness (μm)	Wall:Lumen
NP-CTL (n=8)	207 \pm 9	224 \pm 9	9 \pm 0.8	4.7 \pm 0.5	0.042 \pm 0.004
NP-HTN (n=8)	190 \pm 6	213 \pm 6	12 \pm 1.2*	6.2 \pm 0.2†	0.062 \pm 0.008*
NP-Hydral (n=3)	223 \pm 9‡	240 \pm 6‡	9 \pm 1.3	4.9 \pm 0.4‡	0.040 \pm 0.007
LP-CTL (n=6)	222 \pm 7	240 \pm 7	8 \pm 0.3	5.1 \pm 0.4	0.038 \pm 0.002
LP-HTN (n=6)	205 \pm 6	221 \pm 7	8 \pm 0.8‡	5.4 \pm 0.2‡	0.040 \pm 0.004

* $P < 0.05$ vs NP CTL.

† $P < 0.01$ vs NP CTL.

‡ $P < 0.05$ vs NP HTN.

azine-treated animals had significantly increased distensibility at most pressures compared with NP-HTN animals.

Active Measurements

Figure 4 shows the active pressure versus diameter curves for PCAs from both groups of NP animals. NP-HTN animals had PCAs with significantly smaller active diameters compared with the NP-CTL animals over the entire pressure range, demonstrating that the NP-HTN animals had arteries with significantly greater myogenic tone. The percentage of tone in NP-CTL versus NP-HTN at 75 mm Hg was 22.8 \pm 5.8% versus 45.3 \pm 7.5% ($P < 0.05$). Increasing pressure within the myogenic pressure range from 75 to 150 mm Hg did not significantly alter diameter in either group of NP animals, demonstrating myogenic reactivity. However, when pressure was increased from 150 to 175 mm Hg in PCAs from NP-CTL animals, arterial diameter significantly increased, demonstrating forced dilatation of myogenic tone. Importantly, forced dilatation did not occur in the NP-HTN animals until pressure was increased from 175 to 200 mm Hg. Therefore, the pressure at which forced dilatation occurred was significantly greater in the NP-HTN group.

Figure 5 shows the active pressure versus diameter curves for PCAs from both groups of LP animals. Unlike the NP animals,

diameters were similar between the LP groups, suggesting that there was no difference in the level of myogenic tone. In fact, unlike the NP animals, the level of myogenic tone was similar between LP-CTL and LP-HTN: 30.8 \pm 5.1% versus 30.1 \pm 11% ($P > 0.05$). Increasing pressure within the myogenic pressure range did not significantly alter diameter, demonstrating myogenic reactivity in these arteries similar to NP animals. However, increasing pressure from 150 to 175 mm Hg caused forced dilatation in both groups of LP animals. Therefore, unlike the NP animals, L-NAME-induced hypertension had no effect on the pressure at which forced dilatation occurred in LP animals, which was considerably lower compared with NP-HTN animals.

Figure 6 shows the active wall stress in PCAs from both groups of NP and LP animals at 75 mm Hg. Wall stress was significantly lower in PCAs from NP-HTN animals compared with NP-CTL ($P < 0.05$) because of both the increase in myogenic tone and media thickness. However, there was no difference in wall stress in PCAs between LP-CTL and LP-HTN animals. In fact, PCAs from LP-HTN animals had significantly greater wall stress compared with NP-HTN animals ($P < 0.05$). Therefore, the response of NP animals to L-NAME hypertension (eg, medial hypertrophy and increased myogenic tone) decreased active wall stress, whereas the lack of a response in LP animals caused wall stress to remain elevated.

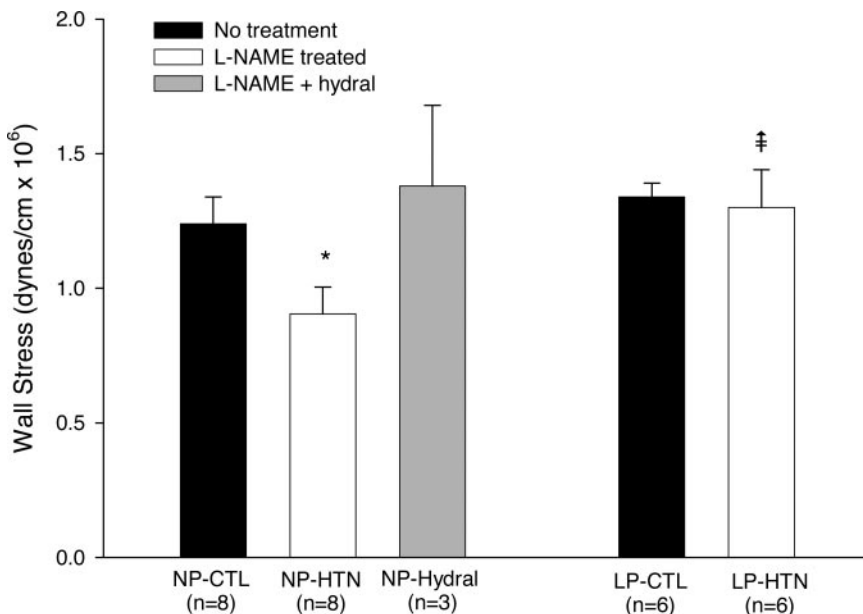


Figure 2. Passive wall stress at 75 mm Hg for all groups of animals. L-NAME hypertension (□) caused medial hypertrophy that decreased wall stress in the NP animals compared with normotensive controls (■). LP animals lacked any response to hypertension and had similar wall stress as their normotensive controls (▒). Hydralazine treatment (▒) in NP animals prevented the hypertension-induced medial hypertrophy and had similar wall stress as the controls. * $P < 0.05$ vs NP-CTL; † $P < 0.05$ vs NP-HTN.

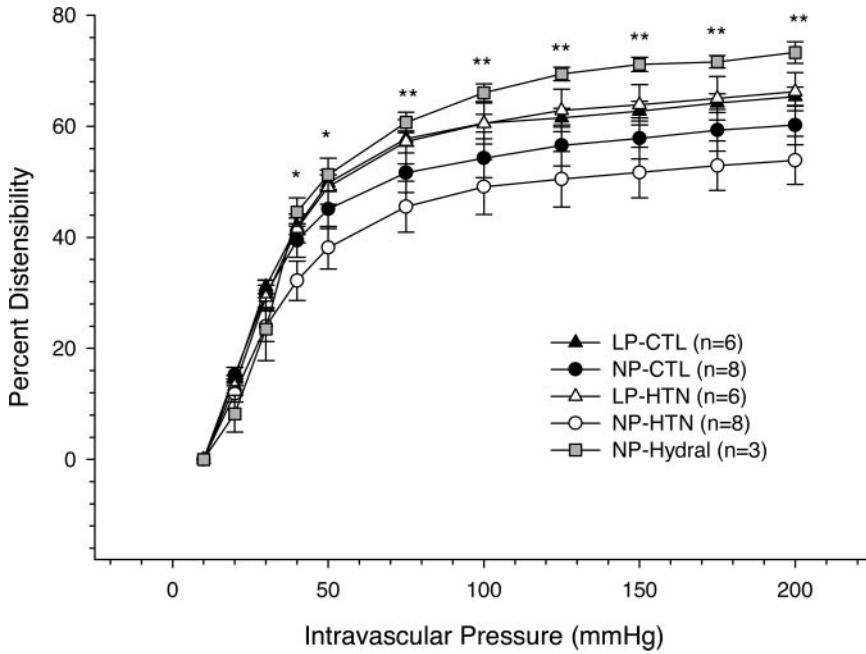


Figure 3. Percent distensibility of arteries from all groups of animals. NP-hypertensive animals (○) had arteries that were the least distensible whereas NP animals treated with L-NAME and hydralazine had significantly greater distensibility compared with NP animals treated with L-NAME alone. * $P < 0.05$ vs NP-HTN; ** $P < 0.01$ vs NP-HTN.

Discussion

There are several major findings of this study. First, just 7 days of L-NAME-induced hypertension caused medial hypertrophy of PCAs from NP animals that significantly reduced wall stress. In addition, L-NAME hypertension increased pressure-induced tone and affected the active pressure-diameter curve of NP-HTN animals such that forced dilatation occurred at higher pressures compared with normotensive controls. Second, pregnancy completely prevented any response to hypertension, including a lack of medial hypertrophy, changes in tone, and a similar pressure of forced dilatation as normotensive controls. Both groups of hypertensive animals had diameters that were considerably smaller than their normotensive controls. It is worth noting

that diameters and wall stress were all reported at 75 mm Hg, mostly because we could not assume that vessels upstream were not undergoing medial hypertrophy and/or remodeling that increased resistance and lowered pressure in the third-order PCA. However, if intravascular pressure was higher because of increased blood pressure, this would have altered the outcome in several ways. First, passive diameters would be more similar between normotensive and hypertensive animals, suggesting that medial hypertrophy, but not remodeling, occurred in the NP animals in response to hypertension. Second, passive wall stress in PCAs from the NP-hypertensive animals would be similar to the normotensive controls, as opposed to being decreased. Similarly, wall stress would be significantly increased in PCAs from LP-

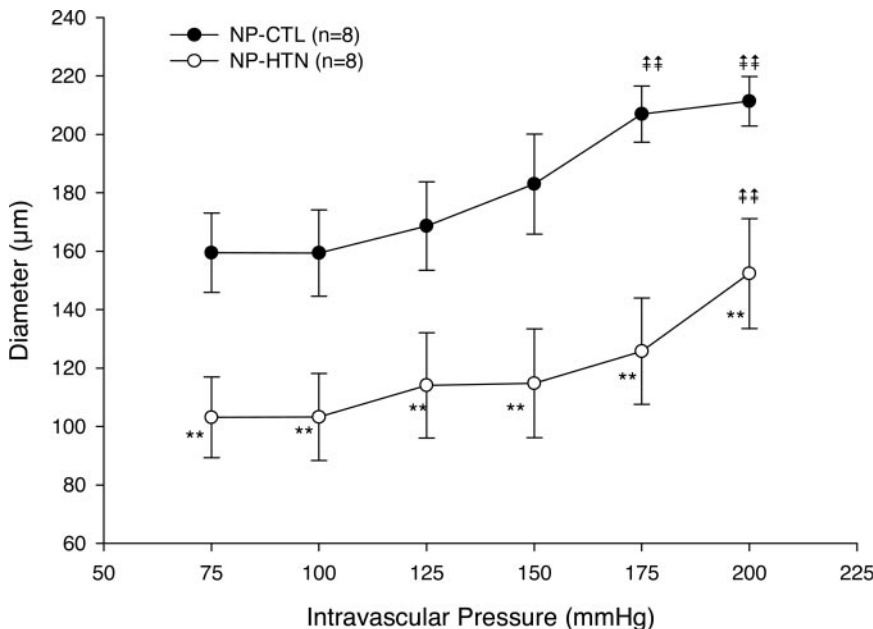


Figure 4. Active pressure vs diameter curves for NP rats. Hypertensive animals (○) had significantly smaller diameters compared with their normotensive controls (●) because of significant myogenic tone. Also, forced dilatation of myogenic tone occurred at significantly greater pressure (between 175 and 200 mm Hg) in the hypertensive animals compared with controls (between 150 and 175 mm Hg). ** $P < 0.01$ vs NP-CTL; †† $P < 0.01$ vs 75 mm Hg.

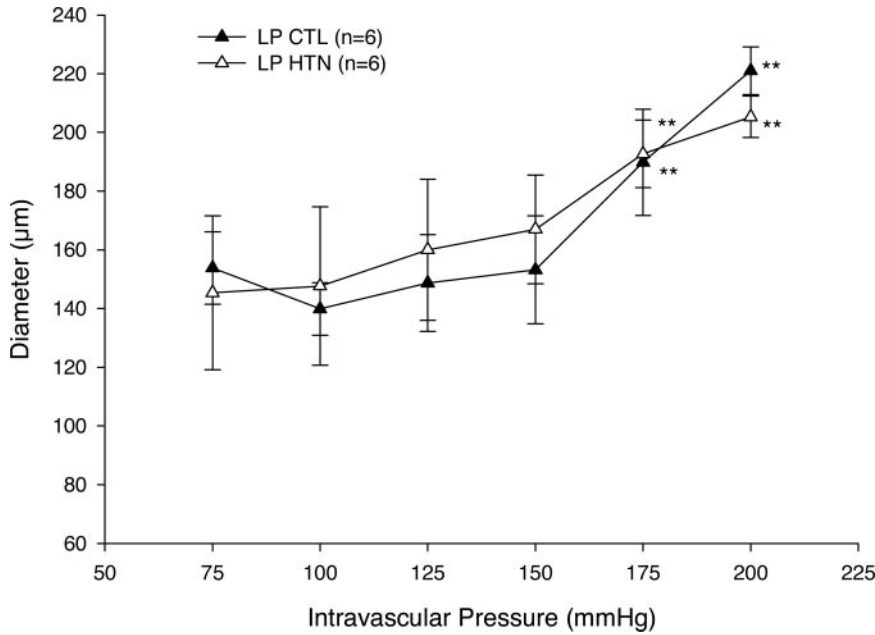


Figure 5. Active pressure vs diameter curves for LP animals. Normotensive (\blacktriangle) and hypertensive (\triangle) LP animals had similar diameters over the entire pressure range because of similar levels of myogenic tone. Both groups of LP animals forced dilatated at similar pressures (between 150 and 175 mm Hg). $**P < 0.01$ vs 75 mm Hg.

hypertensive animals compared with normotensive controls. This would suggest that medial hypertrophy in the NP-hypertensive animals is an adaptive process that serves to normalize wall stress, whereas this mechanism is maladapted in the LP animals.

Both medial hypertrophy and eutrophic remodeling in response to chronic hypertension are considered to have important protective effects in the cerebral circulation.^{5,6,10-14} The increased blood pressure during hypertension produces an elevation in wall tension and wall stress that is reduced to normotensive levels by both increased wall thickness and decreased diameter. In addition, hypertrophy and remodeling also serve to attenuate increases in pressure in the downstream microvessels that would transmit the elevated arterial pressure to the microcirculation and potentially cause endo-

thelial cell damage and BBB disruption.¹⁸ Therefore, the lack of a response to hypertension in LP animals seemingly makes the cerebral circulation vulnerable to forced dilatation, autoregulatory breakthrough, and BBB disruption under conditions in which arterial blood pressure is raised, such as eclampsia. It is worth noting that a previous study demonstrated that the cerebral endothelium during pregnancy was more permeable in response to an acute elevation in pressure compared with the NP state.³¹ Therefore, the lack of protective hypertrophy and remodeling of cerebral arteries during hypertension in pregnancy, together with increased vascular permeability, would likely contribute to brain edema that leads to eclampsia.

Another factor that has been shown to decrease wall stress is the vasoconstrictor influence of myogenic tone.³⁴ In the

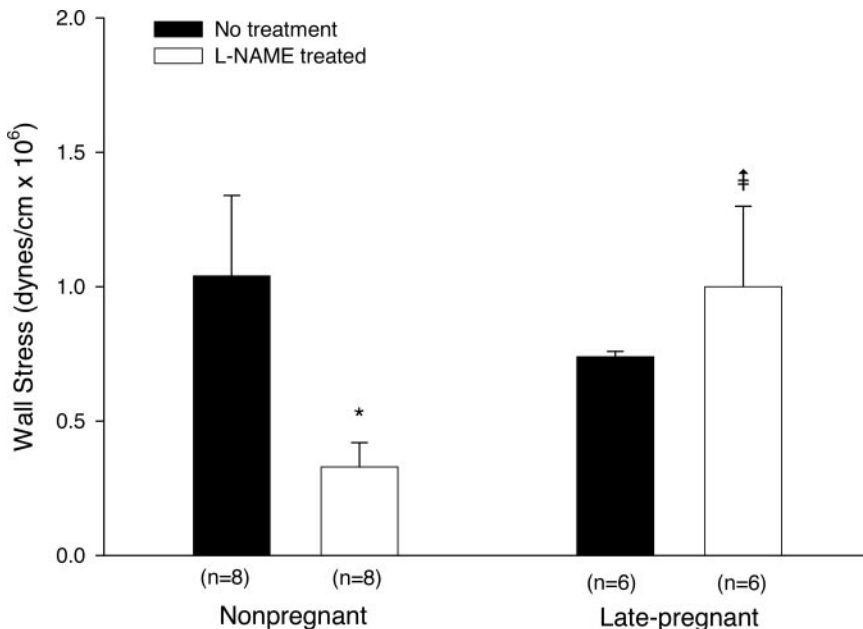


Figure 6. Active wall stress at 75 mm Hg in NP and LP control (\blacksquare) and hypertensive (\square) animals. Hypertension significantly decreased active wall stress in the NP animals because of increased myogenic tone and medial hypertrophy. However, active wall stress was significantly elevated in LP-hypertensive animals because of a complete lack of response to hypertension. $*P < 0.05$ vs NP-CTL; $\dagger P < 0.05$ vs NP-HTN.

present study, PCAs from NP-HTN animals had considerably greater myogenic tone compared with their normotensive controls ($22.8 \pm 5.8\%$ versus $45.3 \pm 7.5\%$ at 75 mm Hg; $P < 0.05$). This may be because of NOS inhibition that diminishes the vasodilator influence of NO or because of endothelial cell damage that is associated with this model of hypertension.²⁶ In any case, the effect of the increased myogenic tone was two-fold. First, in combination with increased wall thickness, increased tone diminished diameter and additionally decreased wall stress in PCAs from those animals. Second, the increased tone caused arteries to force dilatate at significantly higher pressures, suggesting that the vascular wall was stiffer. Both of these consequences of chronic hypertension are thought to contribute to extending the autoregulatory curve to the higher range of pressures, thus preventing autoregulatory breakthrough.⁶ In addition, because tone is an active vasoconstrictor response, vasodilator reserve may be greater in these animals as well. However, the fact that the LP animals did not have a difference in myogenic tone between groups ($30.8 \pm 5.1\%$ versus $30.1 \pm 11\%$; $P > 0.05$) and underwent forced dilatation at similar pressures suggests that LP-hypertensive animals would have similar autoregulatory curves as normotensive controls. The significance of this finding is that pregnancy may predispose to forced dilatation, autoregulatory breakthrough, and edema formation under conditions of elevated arterial pressure, as occurs during eclampsia.

The mechanism by which medial hypertrophy occurs during NOS inhibition has been investigated previously in male rats and appears to be different for large arteries and small arterioles. Medial hypertrophy was shown in the basilar arteries to be because of elevated arterial pressure without involving the NO pathway.⁹ In contrast, NOS inhibition by either L-NAME treatment or endothelial NOS-deficient mice showed medial hypertrophy even in the absence of increased pulse pressure, suggesting that NO alone inhibits medial hypertrophy.^{8,35} In the present study, the mechanism by which L-NAME treatment caused medial hypertrophy in NP-HTN animals was investigated by examining a group of animals that were given L-NAME plus hydralazine to lower arterial blood pressure through a nonendothelial mechanism. Lowering blood pressure with hydralazine prevented the medial hypertrophy and the associated decrease in wall stress, suggesting that the cause of the hypertrophy was elevated arterial blood pressure and not L-NAME or NOS inhibition. It should be noted, however, that the presence of hydralazine significantly increased both passive distensibility and the size of the lumen, suggesting that, similar to other studies,³⁶ hydralazine treatment alone had an effect on cerebral artery structure.

Although it is not surprising that NP animals responded to L-NAME hypertension with changes in cerebral artery structure (medial hypertrophy) and function (increased tone and reactivity to pressure), it is the lack of response during pregnancy that is important, because it may predispose the brain to autoregulatory breakthrough and the neurological complications of eclampsia if arterial pressure is elevated. Although this study did not determine how pregnancy prevented the response of the cerebral circulation to L-NAME-

induced hypertension, it likely relates to the significant physiological changes that occur during pregnancy, including increased glomerular filtration rate, decreased systemic vascular resistance, and a refractoriness to both angiotensin II and adrenergic stimulation.³⁷ Although little is known how pregnancy alters the cerebral circulation, it is also possible that pregnancy alters the phenotype of the cerebrovascular smooth muscle such that it does not respond to the same cues for growth and remodeling as NP animals.

Perspectives

The major finding of this study is that pregnancy prevented protective hypertensive remodeling and hypertrophy of cerebral arteries and failed to increase the pressure at which forced dilatation occurred. Taken together, these results suggest that pregnancy may predispose the brain to autoregulatory breakthrough and edema formation when arterial pressure is elevated, as during eclampsia. Because hypertension is one of the most common medical complications of pregnancy that affects both maternal and fetal health, understanding how the cerebral circulation responds to elevated arterial blood pressure is an important step toward possibly preventing life-threatening consequences, including eclampsia.

Acknowledgments

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References

1. Zunker P, Happe S, Georgiadis AL, Louwen F, Georgiadis D, Ringelstein EB, Holgreve W. Maternal cerebral hemodynamics in pregnancy-related hypertension. A prospective transcranial Doppler study. *Ultrasound Obstet Gynecol.* 2000;16:179-187.
2. Zeeman GG, Fleckenstein JL, Twickler DM, Cunningham FG. Cerebral infarction in eclampsia. *Am J Obstet Gynecol.* 2004;190:714-720.
3. Thomas SV. Neurologic aspects of eclampsia. *J Neurol Sci.* 1988;155:37-43.
4. Cipolla MJ, Vitullo L, McKinnon J. Cerebral artery reactivity changes during pregnancy and the postpartum period: A role in eclampsia? *Am J Physiol.* 2004;268:H2127-H2132.
5. Baumbach GL, Dobrin PB, Hart MN, Heistad DD. Mechanics of cerebral arterioles in hypertensive rats. *Circ Res.* 1988;62:56-64.
6. Heistad DD, Baumbach GL. Cerebral vascular changes during chronic hypertension: good guys and bad guys. *J Hypertens.* 1992;10(Suppl 7):S71-S75.
7. Baumbach GL, Heistad DD. Cerebral circulation in chronic arterial hypertension. *Hypertension.* 1988;12:89-95.
8. Chillon J-M, Ghoniem S, Baumbach GL. Effects of chronic nitric oxide synthase inhibition on cerebral arterioles in rats. *Hypertension.* 1997;30:1097-1104.
9. Morreau P, Takase H, Kung CF, van Rooijen M, Schaffner T, Luscher TF. Structure and function of the rat basilar artery during chronic nitric oxide synthase inhibition. *Stroke.* 1995;26:1922-1929.
10. Johansson BB. Cerebrovascular permeability to protein in spontaneously hypertensive rats (SHR) after acute blood pressure elevation. *Clin Exp Pharmacol Physiol.* 1976;(Suppl 3):97-100.
11. Mueller SM, Heistad DD. Effects of chronic hypertension on the blood-brain barrier. *Hypertension.* 1980;2:809-812.
12. Sadoshima S, Heistad DD. Sympathetic nerves protect the blood-brain barrier in stroke-prone spontaneously hypertensive rats. *Hypertension.* 1982;4:904-907.
13. Sadoshima S, Busija DW, Heistad DD. Mechanisms of protection against stroke in stroke-prone spontaneously hypertensive rats. *Am J Physiol.* 1983;244:H406-H412.

14. Mueller SM, Ertel PJ, Felten DL, Overhage JM. Sympathetic nerves protect against blood-brain barrier disruption in the spontaneously hypertensive rats. *Stroke*. 1982;13:83–88.
15. Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension*. 1989;13:968–972.
16. Chillon J-M, Baumbach GL. Effects of chronic nitric oxide synthase inhibition on cerebral arterioles in Wistar-Kyoto rats. *J Hypertens*. 22:529–534.
17. Hadju MA, Baumbach GL. Mechanics of large and small cerebral arteries in chronic hypertension. *Am J Physiol*. 1994;35:H1027–H1033.
18. Werber AH, Heistad DD. Effects of chronic hypertension and sympathetic nerves on the cerebral microvasculature of stroke-prone spontaneously hypertensive rats. *Circ Res*. 1984;55:268–294.
19. Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet*. 1993;341:1447–1454.
20. Barron WM. Hypertension. In: *Medical Disorders of Pregnancy*. Barron W, Lindheimer M, eds. St. Louis, MO: Mosby Year Book; 1991:1–41.
21. Wityk RJ, Pessin MS. Hypertensive encephalopathy. In: *Cerebrovascular Disease*. Batjer HH, ed. Philadelphia, PA: Lippincott Raven Publishers; 1997:97–102.
22. Donaldson JO. Eclamptic hypertensive encephalopathy. *Semin Neurol*. 1988;8:230–233.
23. Villar MA, Sibai BM. Eclampsia. In: Arias F, ed. *Obstetrics and Gynecology Clinics of North America. High Risk Pregnancy*. Philadelphia, PA: WB Saunders; 1988:356–377.
24. Donaldson JO. Eclampsia. In: Donaldson JO, eds. *Neurology of Pregnancy*. London: WB Saunders; 1989:269–310.
25. Molnar M, Suto T, Toth T, Hertelendy F. Prolonged blockade of nitric oxide synthesis in gravid rats produces sustained hypertension, proteinuria, thrombocytopenia, and intrauterine growth retardation. *Am J Obstet Gynecol*. 1994;170:1458–1466.
26. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction. *Hypertension*. 2001;38:718–722.
27. Granger JP, Alexander BT, Bennett WA, Khalil RA. Pathophysiology of pregnancy-induced hypertension. *Am J Hypertens*. 2001;14:178S–185S.
28. Engelter ST, Provenzale JM, Petrella JR. Assessment of vasogenic edema in eclampsia using diffusion imaging. *Neuroradiology*. 2000;42:818–820.
29. Dahmus MA, Barton JR, Sibai BM. Cerebral imaging in eclampsia: magnetic resonance imaging versus computed tomography. *Am J Obstet Gynecol*. 1992; 167:935–941.
30. Shultz PJ, Raij L. Effects of antihypertensive agents on endothelium-dependent and endothelium-independent relaxations. *Br J Clin Pharmacol*. 1989;28(Suppl 2):151S–157S.
31. Cipolla MJ, Vitullo L, DeLance N, Hammer E. The cerebral endothelium during pregnancy: A potential role in the development of eclampsia. *Endothelium*. 2005;12:5–9.
32. Salas SP. Role of nitric oxide in maternal hemodynamics and hormonal changes in pregnant rats. *Biol Res*. 1998;31:243–250.
33. Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res*. 1990;66:8–17.
34. Brekke JF, Gokina N, Osol G. Vascular smooth muscle cell stress as a determinant of cerebral artery myogenic tone. *Am J Physiol*. 2002;283: H2210–2216.
35. Baumbach GL, Sigmund CD, Faraci FM. Structure of cerebral arterioles in mice deficient in expression of the gene for endothelial nitric oxide synthase. *Circ Res*. 2004;95:822–829.
36. Hajdu MA, Heistad DD, Ghoneim S, Baumbach GL. Effects of antihypertensive treatment on composition of cerebral arterioles. *Hypertension*. 1991;18(Suppl II):II-15–II-21.
37. Monga M. Maternal cardiovascular and renal adaptation to pregnancy. In: Creasy RK, Resnik R, Iams J, eds. *Maternal Fetal Medicine: Principles and Practice*. Philadelphia, PA: Saunders; 2004:111–120.