Effect of Pregnancy on Autoregulation of Cerebral Blood Flow in Anterior Versus Posterior Cerebrum

Marilyn J. Cipolla, Nicole Bishop, Siu-Lung Chan

Abstract—Severe preeclampsia and eclampsia are associated with brain edema that forms preferentially in the posterior cerebral cortex possibly because of decreased sympathetic innervation of posterior cerebral arteries and less effective autoregulation during acute hypertension. In the present study, we examined the effect of pregnancy on the effectiveness of cerebral blood flow autoregulation using laser Doppler flowmetry and edema formation by wet:dry weight in acute hypertension induced by phenylephrine infusion in the anterior and posterior cerebrum from nonpregnant (n=8) and late-pregnant (n=6) Sprague-Dawley rats. In addition, we compared the effect of pregnancy on sympathetic innervation by tyrosine hydroxylase staining of posterior and middle cerebral arteries (n=5–6 per group) and endothelial and neuronal NO synthase expression using quantitative PCR (n=3 per group). In nonpregnant animals, there was no difference in autoregulation between the anterior and posterior cerebrum. However, in late-pregnant animals, the threshold of cerebral blood flow autoregulation was shifted to lower pressures in the posterior cerebrum, which was associated with increased neuronal NO synthase expression in the posterior cerebral cortex versus anterior. Compared with the nonpregnant state, pregnancy increased the threshold of autoregulation in both brain regions that was related to decreased expression of endothelial NO synthase. Lastly, acute hypertension during pregnancy caused greater edema formation in both brain cortices that was not attributed to changes in sympathetic innervation. These findings suggest that, although pregnancy shifted the cerebral blood flow autoregulatory curve to higher pressures in both the anterior and posterior cortices, it did not protect from edema during acute hypertension. (Hypertension. 2012;60:705-711.)

Key Words: pregnancy ▪ cerebral blood flow autoregulation ▪ sympathetic innervation ▪ brain edema

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Eclampsia is thought to be similar to hypertensive encephalopathy in which an acute and excessive elevation in blood pressure, secondary to the preeclamptic state, causes decreased cerebrovascular resistance (CVR), autoregulatory breakthrough, and a large increase in cerebral blood flow (CBF) in excess of metabolic demands.1,2 Breakthrough of autoregulation during acute hypertension can be damaging to the blood-brain barrier (BBB) and can cause hydrostatic brain edema.3 Cerebral edema formation has been described in patients with severe preeclampsia and eclampsia and is thought to underlie the neurological symptoms associated with these conditions.1,2,4

The posterior cerebral cortex appears to be more susceptible to edema formation during acute hypertension associated with hypertensive encephalopathy and preeclampsia/eclampsia.1–4 The propensity for the edema to form in the posterior cerebrum has led to more recent terminology of “posterior reversible encephalopathy syndrome” to better incorporate the posterior nature of the neurological symptoms that include uncontrolled vomiting, cortical blindness, and severe and persistent headache.5 Although the underlying mechanism by which posterior reversible encephalopathy syndrome arises is largely unknown, several researchers have cited morphological studies showing a decrease in sympathetic innervation of the vertebrobasilar arteries versus those of the internal carotid artery system as the cause.6 Cerebral arteries and arterioles on the brain surface (pial vessels) are innervated extrinsically by sympathetic neurons for which the fibers originate in the superior cervical ganglia.7 This sympathetic innervation limits the pressure at which autoregulatory breakthrough occurs during acute hypertension.8 Thus, it has been speculated that decreased sympathetic innervation of posterior cerebral arteries (PCAs) leads to a lower pressure of autoregulatory breakthrough and a propensity for hydrostatic edema to form in the posterior cerebrum during acute hypertension.6

NO appears to be involved in CBF autoregulation and may have an effect during pregnancy. Pharmacological inhibition of NO synthase (NOS) shifts the pressure of CBF autoregulatory breakthrough to significantly higher pressures.9 Furthermore, a previous study by Talman10 showed that selective inhibition of neuronal NOS (nNOS) attenuated autoregulatory breakthrough, suggesting that NO production may be affecting CBF autoregulation through nNOS, in addition to

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endothelial NOS (eNOS). Inhibition of eNOS and nNOS may reduce NO-dependent vasodilation in cerebral vasculature, thus providing protection against forced dilatation in acute hypertension.10

Eclampsia and posterior reversible encephalopathy syndrome can occur at normal blood pressures, suggesting that autoregulation of CBF is shifted to a lower range of pressures during pregnancy.11–13 We previously measured CBF autoregulation in nonpregnant (NP) and late-pregnant (LP) rats and found that there was no difference in autoregulation or the pressure at which autoregulatory breakthrough occurred with pregnancy.9 However, our previous study measured CBF only in the anterior cerebral cortex during an acute infusion of phenylephrine to produce hypertension. Thus, the main goal of this study was to compare CBF autoregulation between the anterior and posterior cerebral cortex in NP and LP rats to determine whether autoregulation is less effective in the posterior cerebrum. In addition, brain water content was measured after acute hypertension to determine the influence of autoregulation and pregnancy on edema formation during increases in arterial pressure. In the current study, we used chloral hydrate as an anesthetic instead of pentobarbital that was used in our previous study because it may have relatively smaller effects on hemodynamic responses and less of an influence on CBF autoregulation.14,15 Sympathetic innervation of PCAs and middle cerebral arteries (MCAs) from NP and LP rats was measured to determine whether there is a relationship between autoregulation of CBF and sympathetic nerve density of the posterior versus anterior cerebrum during pregnancy, because these are the major vessels that supply the posterior and anterior cerebral cortices, respectively.16 Finally, mRNA expression of eNOS and nNOS were compared between anterior and posterior brain cortices from NP and LP animals to investigate the role of NO changes in CBF autoregulation in pregnancy.

**Methods**

**Animal Model of Pregnancy**
Female virgin NP and timed pregnant Sprague-Dawley rats were used for all of the experiments. Pregnant animals were bought from Harlan (Dublin, VA) on day 15 to 16 of pregnancy and used on day 19 to 20. Changes in CBF autoregulation were measured in LP rats, because this time during gestation is when eclampsia occurs most often.9 All of the procedures were approved by the institutional animal care and use committee at the University of Vermont, an Association for Assessment and Accreditation of Laboratory Animal Care–accredited institution. All protocols were in compliance with the National Institutes of Health Guide for the Care and Use of Animals.

**Measurement of CBF Autoregulation**
Animals were anesthetized initially with isoflurane (3% in oxygen) and maintained at 1.5% to 2.0% for placement of arterial and venous catheters, laser Doppler probes, and tracheostomy. Chloral hydrate was administered IV as bolus doses (a total of 200 mg/kg), whereas isoflurane was decreased stepwise until stopped. Two laser Doppler probes were placed above the MCA and PCA cerebral cortices after a burr hole was drilled. The laser Doppler probe for the MCA territory was placed 1 mm posterior from the coronal suture and 2 mm lateral from the sagittal suture, whereas the probe for PCA territory was placed 1 mm anterior from the lambda suture and 2 mm lateral from the sagittal suture. Animals were ventilated to maintain pH and blood gases within normal physiological ranges (see Table). CBF autoregulation was measured in NP (n=8) and LP (n=6) animals by continuously monitoring CBF in both the anterior and posterior cerebral cortex during an acute infusion of phenylephrine (Sigma, St Louis, MO) at an increasing rate of 4 to 48 μg/min in lactated Ringer’s solution to raise arterial blood pressure, as described previously.5 In addition to assessing CBF versus pressure curves, the upper limit of CBF autoregulation was determined as the pressure at which CBF increased by 20% from baseline, as has been done previously.17,18

**Brain Water Content**
After measurement of CBF or sham operation for control (n=4), the animals were decapitated under anesthesia and the brain removed for measurement of water content, as described previously.4 Briefly, the cerebellum and brain stem were removed, and the remaining cerebrum was sectioned in anterior and posterior regions that corresponded with the region for which CBF measurements were taken. The brain sections were weighed wet, dried overnight at 90°C, and then weighed again dry. Percentage of water content was calculated from the wet: dry weights from the following equation: (wet weight−dry weight)/wet weight×100%.

**Perivascular Sympathetic Nerve Density of MCA and PCA**
Separate sets of NP (n=5−8) and LP (n=5−7) animals were used to determine sympathetic nerve density of the MCA and PCA, as described previously.19 Briefly, segments of MCA and PCA were carefully dissected and immunohistochemically stained for tyrosine hydroxylase (TH) or the pan neuronal marker protein gene product 9.5 (PGP 9.5) to determine sympathetic nerve density and total nerve density, respectively. Micrographs of 3 areas of each vessel were taken using an Olympus fluorescent microscope at ×10 magnification. Nerve density was determined from each image using morphometric analysis that consisted of a grid overlay and counting intersect points per vessel area. Averages of the 3 photomicrographs per vessel were used for comparison.

**mRNA Expression of eNOS and nNOS in Anterior and Posterior Brain Cortices**
In a separate set of animals, anterior and posterior brain cortices from NP (n=3) and LP (n=3) rats were collected to determine expression levels of eNOS and nNOS using real-time quantitative PCR methods, as described previously.20 All of the collected samples were stored in RNase inhibitor (1 U/μL, RiboLock, Fermentas, Glen Burnie, MD) at −80°C. Standard techniques for quantitative PCR were performed by the Vermont Cancer Center DNA Analysis Facility at the University of Vermont, as described previously.20 Samples were DNase treated. Primers of eNOS, nNOS, and mitogen-activated protein kinase 6 (housekeeping control) were purchased from Applied Biosystems (Foster City, CA). All of the Assay-on-Demand primers were validated by the manufacturer for efficiency and did not detect homologs. All of the samples were run in duplicates. Data were analyzed using the \(-2^{\Delta\Delta CT}\) method.21

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NP indicates nonpregnant; LP, late pregnant; CBF, cerebral blood flow.
Data Analysis and Statistics
CBF autoregulatory curves and brain water content were analyzed by 1-way ANOVA to determine differences between NP versus LP and anterior versus posterior. Two-way ANOVA was used to determine the influence of pregnancy and brain region and their interaction on the upper limit of CBF autoregulation, perivascular nerve density, and brain water content. A t test was used to compare mRNA expression levels between groups. Differences were considered significant when \( P<0.05 \).

Results

Effect of Brain Region on CBF Autoregulation in NP and LP Rats
Figure 1 shows the change in CBF versus arterial blood pressure in the anterior and posterior cerebral cortices in NP (Figure 1A) and LP (Figure 1B) rats. In NP rats, CBF rose relatively linearly in both brain regions, and there was no difference in autoregulation between the anterior and posterior cortex. The pressure at which CBF increased 20% from baseline in NP rats was 133±4 mmHg in the posterior cortex and 141±4 mmHg in the anterior cortex (not significant). In LP rats, there was a difference in autoregulation between the 2 brain regions. The pressure at which CBF increased 20% from baseline was 149±2 mmHg in the posterior cortex but was increased to 165±3 mmHg in the anterior cortex \((P<0.05)\), demonstrating less effective autoregulation of CBF in the posterior brain region during pregnancy with elevated arterial pressure.

Effect of Pregnancy on CBF Autoregulation in the Anterior Versus Posterior Cerebral Cortex
Because preeclampsia and eclampsia are pregnancy-specific disorders, it is possible that pregnancy affects autoregulation differently in the posterior versus the anterior cerebrum. Thus, we also compared the effect of pregnancy on autoregulation of CBF in each brain region. Figure 2 shows the change in CBF versus arterial blood pressure in the anterior (Figure 2A) and posterior (Figure 2B) cerebral cortex for NP and LP rats. In both brain regions, autoregulation of CBF was shifted to higher pressures during pregnancy. Thus, although there was less effective autoregulation of CBF in the posterior cerebral cortex with acute hypertension during pregnancy, when compared with the NP state, pregnancy had more effective autoregulation in both brain regions.

Effect of Pregnancy and Brain Region on Water Content After Acute Hypertension
Brain water content was compared as a measure of edema formation in the anterior versus posterior cerebral in the same NP and LP animals for which autoregulation of CBF was determined. Figure 3 shows that the anterior cerebrum had significantly greater water content versus the posterior cerebrum in both NP and LP rats. However, LP animals had significantly greater edema in both brain regions versus NP despite having more effective autoregulation of CBF during acute hypertension. To determine whether the increase in water content in the anterior cerebrum was because of an effect of acute hypertension or an overall increase in that region at baseline, water content was compared in sham-operated NP animals (NP basal). We found that water content was significantly increased in the anterior cortex versus the posterior at baseline without hypertension, as shown in Figure 3.

Sympathetic Innervation of MCA Versus PCA From NP and LP Rats
To assess the relationship between sympathetic innervation and autoregulation of CBF in the anterior versus posterior cerebral cortex, we measured nerve density of TH- and PGP 9.5-stained PCAs and MCAs from NP and LP rats. Figure 4 shows that PCAs had significantly increased sympathetic innervation versus MCAs in both NP (Figure 4B) and LP (Figure 4C) animals. In addition, there was no effect of pregnancy on sympathetic innervation of PCAs or MCAs. Comparison of TH and PGP 9.5 innervation showed no difference between the two, suggesting that sympathetic
nerve fibers compose a major proportion of perivascular innervation of cerebral arteries.

Effect of Pregnancy on Expression of eNOS and nNOS in Brain Cortices
To investigate the potential role of NOS as an underlying mechanism by which pregnancy affected CBF autoregulation, mRNA expression levels of eNOS and nNOS were compared in NP and LP animals in anterior and posterior cerebral cortices (Figure 5A, 5B, 5D, and 5E). Expression of eNOS was decreased in anterior ($P<0.093$) and posterior ($P<0.01$) cortices from LP versus NP animals. However, nNOS was unaffected by pregnancy in either brain region. Because the posterior cerebral cortex was significantly less effective than the anterior at autoregulation of CBF during pregnancy, eNOS and nNOS expressions were compared between brain regions in LP animals (Figure 5C and 5F). Expression of nNOS was significantly decreased in the anterior cortex versus posterior, whereas eNOS expression was decreased but not significantly.

Discussion
In the present study, we compared autoregulation of CBF in the anterior and posterior cerebral cortex from NP and LP rats and the relationship between effectiveness of autoregulation and edema formation during acute hypertension. We also investigated how pregnancy affected sympathetic innervation of cerebral arteries and eNOS and nNOS expressions, because these factors may underlie changes in CBF autoregulation. We found that, in NP animals, there was no difference in CBF autoregulation between brain regions; however, in LP animals, autoregulation was shifted to lower pressures in the posterior versus the anterior cortex. Interestingly, pregnancy shifted the autoregulatory curves in both brain regions to higher pressures compared with the NP state. The increased effectiveness of CBF autoregulation during pregnancy was not associated with an increase in perivascular sympathetic innervation but was related to decreased eNOS expression in both brain regions compared with NP animals. In addition, there was a regional difference in nNOS expression in LP animals such that the posterior cerebral cortex, which had less effective CBF autoregulation, had increased nNOS expression. Lastly, despite more effective autoregulation of CBF during pregnancy, LP animals had greater edema formation during acute hypertension in both brain regions compared with NP, a result that is similar to what we have shown previously.

In contrast to our previous study that measured CBF autoregulation in the anterior cerebral cortex only and found no difference with pregnancy, the current study found that both anterior and posterior cerebral cortices had CBF autoregulatory curves that were shifted to higher pressures compared with NP animals (Figure 2). The major difference in the present study was the use of chloral hydrate as an anesthetic.
versus pentobarbital. Although all of the anesthetics affect CBF autoregulation, chloral hydrate has been shown to have less effect on the cardiovascular system and, thus, is used often for in vivo studies.\textsuperscript{14,15} Indeed, compared with pentobarbital, chloral hydrate anesthesia limited the percentage change in CBF during acute hypertension to only $\approx 50\%$ compared with $\approx 250\%$ in the previous study at similar arterial pressures. However, chloral hydrate has been shown to uncouple CBF from metabolism to a greater extent than pentobarbital.\textsuperscript{22} Thus, the difference in the shape of the CBF autoregulation curves from our previous study that used pentobarbital and the current study that used chloral hydrate

![Figure 4. Perivascular sympathetic innervation of posterior (PCA) and middle (MCA) cerebral arteries from nonpregnant and late-pregnant rats. Nerve density of tyrosine hydroxylase-stained arteries (A) was significantly greater in PCAs vs MCAs from both nonpregnant and late-pregnant rats. B and C show nerve density of tyrosine hydroxylase-stained arteries vs the pan neuronal stain protein gene product 9.5 (PGP 9.5) from nonpregnant and late-pregnant animals, respectively. There was no difference in innervation with pregnancy. *$P<0.05$ and **$P<0.01$ vs PCA.]

![Figure 5. mRNA expression of endothelial NO synthase (eNOS) and neuronal NO synthase (nNOS) in anterior and posterior brain cortices from nonpregnant (NP) and late-pregnant (LP) rats. eNOS (A through C) and nNOS (D through F) expression in NP versus LP animals in anterior (A and D) and posterior (B and E) cortex. eNOS expression was decreased in both the anterior and posterior cerebral cortices with pregnancy. Regional differences in expressions in LP rats are presented in C and F for eNOS and nNOS, respectively. nNOS expression was increased in posterior brain cortex from LP rats vs that of anterior. *$P<0.05$; **$P<0.01$ vs corresponding controls.]

could reflect differences in CVR and/or metabolism induced by the different anesthetics.

Interestingly, the use of chloral hydrate unmasked a difference in CBF autoregulation with pregnancy. This rightward shift in the CBF autoregulatory curve during pregnancy was not attributed to increased perivascular sympathetic innervation but was related to decreased eNOS expression. Inhibition of NOS has been shown to shift the CBF autoregulatory curve to higher pressures, and although we did not measure eNOS activity or NO production itself, it is possible that decreased eNOS in the brain during pregnancy was at least partially responsible for the shift in CBF autoregulation to higher pressures during pregnancy.

The shift in the CBF autoregulatory curve to higher pressures during pregnancy was greater in the anterior compared with the posterior cerebral cortex. Again, this regional difference in CBF autoregulation in the pregnant brain was related to increased nNOS in the posterior versus the anterior cerebral cortex (Figure 5C and 5F). Selective inhibition of nNOS was also shown to shift the CBF autoregulatory curve to higher pressures. Thus, it is possible that decreased eNOS expression increases CVR overall during pregnancy and is responsible for the shift in the CBF autoregulatory curve, whereas decreased nNOS in the anterior cortex during pregnancy results in more effective autoregulation of CBF in that brain region. Although studies have shown increased eNOS expression in pregnancy in other vascular beds, it has not been measured previously in the brain. Similar to the present study, a previous study found that nNOS expression and activity were decreased in the periventricular nuclei of the brain during late pregnancy.

Despite more effective autoregulation of CBF during pregnancy, only pregnant animals developed edema formation during acute hypertension. This result is similar to our previous study. Unlike CBF autoregulation, no regional difference in edema was observed. Although all of the animals had more water content in the anterior cortex, the magnitude of the increase in water with acute hypertension in pregnant animals was similar in the anterior and posterior cerebrum. It is likely that changes in BBB permeability and vascular volume are responsible for edema formation during pregnancy. For example, we showed previously that LP animals had significantly greater BBB permeability in response to acute hypertension compared with NP animals. The increased BBB permeability in vivo during pregnancy was shown to be because of outward remodeling of brain arterioles that increased vascular volume and decreased CVR during acute hypertension. Pregnancy also increased BBB permeability of isolated arterioles in response to an acute elevation in intravascular pressure but only at pressures >180 mm Hg. Another study showed that pregnancy did not increase hydraulic conductivity of the BBB, further suggesting that hemodynamic changes during pregnancy, including decreased CVR in response to acute hypertension that increases BBB permeability, are responsible for the increase in edema formation.

There are several limitations of our study that are important to note. First, we did not find that the posterior brain region was more susceptible to edema formation, as has been shown in humans. This may be because of limitations of the model of acute hypertension used that includes the use of anesthesia. In addition, this model of acute hypertension does not allow for sustained blood pressure elevation beyond ~30 minutes because of systemic effects that precipitously drop arterial pressure. This short duration of hypertension may limit edema formation, especially in the NP animals. Second, previous studies in humans found less perivascular sympathetic innervation of PCAs versus MCAs, a result that we did not find. In fact, we found that the PCA was more innervated with TH-stained nerves than the MCA. The discrepancy may be because of species differences (rat versus human) or staining methods. Both TH and dopamine β-hydroxylase are markers for sympathetic innervation. Depending on the activation state of the sympathetic nerves, the concentration of these 2 enzymes varies, which may be causing the difference between the 2 studies. Lastly, vasoconstriction elicited by release of norepinephrine from sympathetic nerves is thought to be protective against breakthrough of CBF autoregulation in acute hypertension. However, we did not find any association of perivascular sympathetic innervation and CBF autoregulation.

It is worth noting that we used a model of normal pregnancy to measure CBF autoregulation and edema formation in response to acute hypertension. An understanding of CBF autoregulation changes during normal pregnancy is important because women who develop preeclampsia exhibit a wide spectrum of signs and symptoms ranging from severe hypertension and proteinuria to mild or absent hypertension with no proteinuria. However, changes in CBF autoregulation may be different during preeclampsia in which there is endothelial dysfunction. One study that used transcranial Doppler to measure changes in CBF velocity in response to increases in blood pressure induced by a postural change found that preeclamptic women had a more pronounced decrease in mean flow velocity, suggesting a stronger autoregulatory response. However, intact autoregulation may not be the only factor important for neurological complications associated with preeclampsia/eclampsia. Circulating cytokines and growth factors that increase BBB permeability during preeclampsia have been shown to cause neuronal hyperexcitability and seizure activity.

**Perspectives**

Despite improved autoregulation of CBF during pregnancy, brain edema was pronounced in pregnant animals after acute hypertension. This is likely because of enhanced BBB permeability and increased vascular volume that occurs during pregnancy. Thus, a focus on changes in BBB and edema formation during normal pregnancy and preeclampsia/eclampsia may be more important than hemodynamics for the development of neurological complications during these conditions.

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Disclosures

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Summary

CBF autoregulation in both the anterior and posterior cerebrum were improved during pregnancy, possibly mediated by a NO-dependent pathway. However, more effective CBF autoregulation did not protect against pregnancy-specific edema formation during acute hypertension.

Novelty and Significance

What Is New?

- During pregnancy, the posterior cerebrum was less effective at autoregulation of CBF during acute hypertension compared with the anterior cerebrum that was related to increased nNOS expression.
- Compared with the NP state, pregnancy improved autoregulation in both the anterior and posterior cerebrum that was not related to perivascular sympathetic innervation but was related to decreased eNOS expression.

What Is Relevant?

- Despite improved autoregulation of CBF during pregnancy, acute hypertension caused a significant increase in brain edema compared with NP animals in both the anterior and posterior cerebrum, suggesting that factors such as increased BBB permeability during pregnancy are responsible for edema formation and not changes in hemodynamics.
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