Magnetic resonance imaging and cerebrovascular hemodynamics in (pre)-eclampsia
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Chapter 4.

Increased cerebral blood flow in preeclampsia using magnetic resonance imaging

ABSTRACT

OBJECTIVE

To compare third trimester and non-pregnant cerebral blood flow of women with severe preeclampsia to normotensive controls using magnetic resonance imaging techniques.

STUDY DESIGN

Nine normotensive pregnant women and twelve untreated women with severe preeclampsia underwent velocity-encoded phase contrast magnetic resonance imaging of the bilateral middle and posterior cerebral arteries in the third trimester and at 6 to 8 weeks postpartum. Student t test was used for comparison with p < 0.05 considered significant.

RESULTS

Third trimester large cerebral artery blood flow was significantly higher in severe preeclampsia. Mean vessel diameter was unchanged except for the left posterior cerebral artery. There was no difference in mean vessel diameter or cerebral blood flow between the two groups while non-pregnant.

CONCLUSION

Cerebral blood flow is significantly increased in severe preeclampsia. We hypothesize that increased cerebral blood flow could ultimately lead to eclampsia through hyperperfusion and the development of vasogenic edema.
INTRODUCTION

Preeclampsia and eclampsia present with a specific constellation of neurological disturbances and neuroimaging lesions.¹ Cerebral lesions associated with preeclampsia-eclampsia were described anatomically by Sheehan and Lynch.² During the last decades these lesions have been characterized using both computed tomography and magnetic resonance imaging. Most often seen with eclampsia, the lesions usually represent areas of edema, but infarctions and thrombosis can also be seen.³⁻⁹

Over the years two major hypotheses have evolved to explain the development of cerebral lesions and grand mal seizures in eclampsia. The first theory emphasizes cerebrovascular overregulation with resulting extreme vasospasm and ischemia.¹⁰,¹¹ The second hypothesis centers around a failure of cerebrovascular autoregulatory mechanisms resulting in forced vasodilation, hyperperfusion, and vascular leakage with the subsequent development of reversible vasogenic edema some authors call hypertensive encephalopathy.⁸

Cerebral blood flow during pregnancy has been estimated using transcranial Doppler flow studies and normal pregnant women have been compared with preeclamptic women.¹²,¹³ Transcranial Doppler data can not necessarily be extrapolated to represent cerebral blood flow nor the adequacy of cerebral perfusion because the caliber or cross-sectional area of the artery in question can not be measured. However, when flow velocity measurements are compared, there is increased velocity in preeclamptic women compared with normal pregnancies. Magnetic resonance imaging was shown to accurately measure cerebral blood flow in each vessel studied and we employed this technology to ascertain measurements in normal pregnant women and pregnant women.⁹,¹⁴ In the present study we measured cerebral blood flow in women with preeclampsia to determine if hyperperfusion may play a role in the development of edema and infarctions in preeclampsia-eclampsia.
METHODS

Twelve patients who met the criteria for third trimester severe preeclampsia were recruited from the labor and delivery suite at Parkland Hospital before the onset of labor. Preeclampsia was defined according to the latest criteria of the National High Blood Pressure Education Program Working Group (new onset hypertension with persistent blood pressures ≥ 140/90 mmHg with ≥ 3+ protein on dipstick). Women with sustained blood pressures ≥ 160/110 mmHg were excluded from participation secondary to the need for intravenous antihypertensive medication. Those with cerebral symptoms such as headache or scotomata were excluded in order not to delay initiation of magnesium sulfate therapy. None of the women received any drugs or fluid therapy prior to the imaging studies.

Nine healthy pregnant women were recruited amongst employees or relatives of employees from the University of Texas Southwestern Medical School or Parkland Memorial Hospital to serve as normotensive controls. None of the normotensive controls or women with preeclampsia had a history of chronic hypertension, or cerebrovascular abnormalities. Their medication only included prenatal vitamins and iron and none were smokers. Standard contraindications for magnetic resonance imaging were employed.

The cohort of preeclamptic women as well as the cohort of normotensive women were part of prior studies evaluating cerebral blood flow using magnetic resonance imaging techniques. Study approval was obtained from the University of Texas Southwestern Medical School Investigational Review Board and all participants signed informed consent prior to enrolling in the study.

All women were studied on a 1.5T magnet (Signa Horizon LX NVI, GE, Milwaukee, WI) A single shot fast spin echo T2 weighted sequence in the axial plane was obtained first to document edema or other findings as later interpreted by a radiologist. A rapid three dimensional time of flight magnetic resonance angiogram sequence of the circle of Willis (TR=22, TE=4, flip angle = 20°, NSA=1) using magnetization transfer contrast enhancement was performed with the resulting magnetic resonance angiogram maximum intensity projection reconstructed from a data matrix of 64 slices (1.6 mm thickness, 18 cm FOV, 256 x 224 matrix). Velocity images were then obtained of the proximal right and left middle cerebral arteries and right and left posterior cerebral arteries. In order to ensure that the velocity images
were obtained in a straight section of the artery under investigation, a scout image (TR=34, TE=17, flip angle = 20°, 20 cm FOV, 512 x 256 matrix), perpendicular to the vessel in the circle of Willis visualized in the maximum intensity projection was recorded for each artery. A peripherally gated phase contrast sequence (TR=34, TE=7, flip angle = 40°, 3 mm slice thickness, 20 cm FOV, 256 x 256 matrix) was applied lateral to the bifurcation of the internal carotid artery and perpendicular to the course of the artery as seen on the scout image to obtain velocity information. Velocity encoding was in the slice select direction with a set value of 120 cm/s. This range of encoded velocities has been found to be effective for measuring normal cerebral arterial flow velocities and should allow for the unambiguous measurement of higher velocities which are predicted in the event that significant vasospasm was found.9,17

A single shot fast spin echo T2 weighted sequence in the axial plane was used to document the presence or absence of cerebral edema. All study participants returned 6-8 weeks postpartum for a non-pregnant cerebral blood flow determination. Of the women with preeclampsia, one elected not to return due to claustrophobia and one was lost to follow-up.

Cerebral blood flow measurements [Flow (mL/min) = vessel area (cm²) x velocity (cm/min)] were determined at the bilateral proximal middle and posterior cerebral arteries. Cerebral blood flow was analyzed with Student t tests to compare differences between the 2 groups at both time intervals in each artery for each patient. Statistical significance was defined as p < 0.05.
RESULTS

Cerebral blood flow was measured at a mean gestational age of 36.8 ± 2.6 weeks in the preeclampsia group, whereas this was 37.2 ± 1.0 weeks for the control group (p = 0.67). Mean birthweight was 2666 ± 673 grams in the preeclampsia group versus 3477 ± 527 grams in the control group (p < 0.01). Eight of the twelve women with preeclampsia were nulliparous, whereas this was the case for five of the nine controls. Systolic blood pressure in women with preeclampsia was 156 ± 9.7 and 100.5 ± 8.1 diastolic. All women in the control group remained normotensive. The T2 images of the preeclamptic women were without evidence of cerebral edema. In women with preeclampsia cerebral blood flow was significantly increased in all four vessels (Figure C), while, except for the left posterior cerebral artery, there was no change in mean blood vessel area (Figure D). Although there was a statistical significant difference in the left posterior artery mean diameter, the actual 0.14 mm difference between the two means is beyond the resolving capacity of the magnetic resonance imaging technique. There was no difference in cerebral blood flow nor mean vessel diameter between the two groups in the non-pregnant state (Figures E and F).
**Figure C.** Comparison of calculated blood flow in normotensive and women with preeclampsia in the third trimester. *Closed bars*, Preeclampsia group; *gray bars*, normotensive control subjects. *RMCA*, Right middle cerebral artery; *LMCA*, left middle cerebral artery; *RPCA*, right posterior cerebral artery; *LPCA*, left posterior cerebral artery.

**Figure D.** Comparison of vessel diameter in normotensive and women with preeclampsia in the third trimester. *Closed bars*, Preeclampsia group; *gray bars*, normotensive control subjects. *RMCA*, Right middle cerebral artery; *LMCA*, left middle cerebral artery; *RPCA*, right posterior cerebral artery; *LPCA*, left posterior cerebral artery.
Figure E. Comparison of nonpregnant cerebral blood flow in normotensive and women with preeclampsia. Closed bars, Preeclampsia group; gray bars, normotensive control subjects. RMCA, Right middle cerebral artery; LMCA, left middle cerebral artery; RPCA, right posterior cerebral artery; LPCA, left posterior cerebral artery.

Figure F. Comparison of nonpregnant vessel diameter in normotensive and women with preeclampsia. Closed bars, Preeclampsia group; gray bars, normotensive control subjects. RMCA, Right middle cerebral artery; LMCA, left middle cerebral artery; RPCA, right posterior cerebral artery; LPCA, left posterior cerebral artery.
DISCUSSION

Women with severe preeclampsia had a significantly increased cerebral blood flow at term when compared with normotensive controls in the third trimester. This increase in cerebral blood flow is not related to vasodilation of the major cerebral arteries because the diameter of the four main vessels was unchanged in preeclamptic women. These observations corroborate the findings of Belfort et al who used transcranial Doppler ultrasound studies to estimate cerebral blood flow using flow velocity.\textsuperscript{12}

The strength of this study is with the use of magnetic resonance imaging technology that allows accurate assessment of flow in arteries arising from the Circle of Willis. In our previous study we found that cerebral blood flow was decreased significantly in late pregnancy compared with values determined two months postpartum.\textsuperscript{14} Thus, the 20 percent increase in cerebral blood flow in severe preeclampsia is associated with levels similar to non-pregnant values. We can only speculate whether this increase is due to downstream vasodilation, increased cardiac output, increased mean arterial pressure, or local central nervous system factors of autoregulation.

Hypertensive encephalopathy is likely operative in some form in the genesis of cerebral lesions in eclampsia. The two theories of hypoperfusion secondary to vasospasm and hyperperfusion secondary to increased blood flow to explain the development of cerebral lesions in eclampsia may not be mutually exclusive. First, since in most cases cerebral edema is completely reversible, hyperperfusion that exceeds the retaining capacity of the brain capillary beds must be at play. Several investigators corroborated this by demonstrating increased cerebral perfusion pressures and/or increased blood flow velocities in women with preeclampsia compared with normotensive pregnant controls.\textsuperscript{12,13,18} Other imaging techniques employed in preeclampsia also reinforce the hyperperfusion theory. Naidu applied a single photon emission CT scan to 63 eclamptic women and observed perfusion deficits in watershed areas of all subjects.\textsuperscript{19} Second, that ischemia plays a role is now inarguable since infarcts develop in almost a fourth of eclamptic women.\textsuperscript{3} Hypertensive encephalopathy is the clinical correlate of blood-brain barrier damage resulting from an acute rise in blood pressure. This is believed to be associated with a failure of autoregulatory mechanisms which, in turn, leads to passive
overdistension of the cerebral resistance vessels and to subsequent hyperperfusion. Extravasation of fluids and proteins may occur resulting in vasogenic edema. Severe vasogenic edema may reduce cerebral perfusion to cause focal ischemia. This is likely because all areas of infarction seen in eclamptic women are encapsulated within areas of severe vasogenic edema. Tamaki et al reported studies in hypertensive rats that also support this hypothesis. They showed that minor degrees of cerebral edema were related to normal or increased cerebral perfusion whereas more marked areas of cerebral edema were accompanied by reduced perfusion with infarction. In addition to acute arterial hypertension systemic endothelial dysfunction and altered hemostasis might contribute to the pathogenesis of cerebral damage in hypertensive encephalopathy. It is now widely accepted that preeclampsia and eclampsia are characterized by generalized endothelial cell activation.

The findings now presented indicate that increased cerebral blood flow likely precedes the onset of convulsions. However, from our own clinical observations we know that women with chronic hypertension who present with significant hypertension but without proteinuria do generally not develop eclamptic convulsions. An intact endothelium appeared to be necessary in order to elicit the pressure dependent reduction of diameter in cat cerebral arteries to maintain cerebral autoregulation. We therefore speculate that certain endothelial factors may play a role in preeclampsia that may not be occurring in women with significant chronic hypertension. It is these endothelial factors combined with elevated blood pressure and not elevated blood pressure alone that may result in the central nervous system edema that characterizes eclampsia. Indeed, Riskin and colleagues demonstrated that in chronically hypertensive women without preeclampsia increased mean arterial pressure did not result in increased cerebral blood flow velocity using transcranial Doppler ultrasound. It may be a combination of the acuteness of the blood pressure rise “the delta change” and endothelial factors rather than the absolute blood pressure value that are the most important factors in the development of eclamptic convulsions.

We have become humbled by the complexity of the cerebrovascular circulation. Although we used the somewhat oversimplified equation of Flow = velocity X area, the physiology of this vascular bed is much more complex. On the one hand physiological factors affect cerebral blood flow that are not taken into
account. First is the dynamic pressure-flow relationship between the arterial blood pressure and intracranial pressure. Additional factors include the vascular smooth muscle and endothelial cells as well as the complex feedback system in the cerebral tissue. Changes in this system secondary to pregnancy are virtually unknown, although we do know that calculated flow in the large vessels of the brain decrease with increases in gestation.\textsuperscript{14} Other factors affecting the cerebral circulation include metabolic and neurogenic influences, which are also governed by more or less variable feedback loops.\textsuperscript{26} Oxygen extraction capability plays a major role as well.\textsuperscript{27} Physical properties also come into play; rather than dealing with steady flow in a rigid tube we are dealing with pulsatile flow in branching blood vessels that have a variable compliance.

Our study finds increased blood flow calculations by MRI in the middle and posterior cerebral arteries of women with severe preeclampsia that is significantly different from normotensive controls. The increased blood flow in severe preeclampsia suggests a hyperperfusion model for cerebral edema, which in the setting of endothelial factors may interrupt the delicate balance between capillary and cellular perfusion pressures. Based on this information, the use of therapeutic agents that result in vasodilatation in this setting may be questioned. Our finding also stresses the importance of understanding the underlying hyperperfusion mechanism of preeclampsia before consideration of new treatment options.
REFERENCES


