Ultrasound in Med. & Biol., Vol. 35, No. 1, pp. 1–7, 2009

0301-5629/09/$–see front matter

ELSEVIER

doi:10.1016/j.ultrasmedbio.2008.08.004

● *Original Contribution*

THE VISUALLY-EVOKED CEREBRAL BLOOD FLOW RESPONSE IN WOMEN WITH A RECENT HISTORY OF PREECLAMPSIA AND/OR ECLAMPSIA

E. G. H. J. MARTENS,*† L. L. H. PEETERS,‡ E. D. GOMMER,*§ W. H. MESS,* F. N. VAN DE VOSSE,† V. LIMA PASSOS,¶ and J. P. H. REULEN*

*Department of Clinical Neurophysiology, University Hospital Maastricht, Maastricht; †Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven; ‡Department of Gynecology and Obstetrics, University Hospital Maastricht, Maastricht; §Department of Biomedical Engineering, University Hospital Maastricht, Maastricht; and ¶Department of Methodology and Statistics, Maastricht University, The Netherlands

(*Received* 17 *January* 2008; *revised* 11 *July* 2008; *in final form* 5 *August* 2008)

Abstract—Several studies provide evidence for altered cerebral hemodynamics during (pre)eclampsia. Whether (pre)eclampsia has a persistent negative impact on cerebral hemodynamics, possibly contributing to an elevated risk of premature stroke, is unknown. The aims of this study were (i) to refine and apply a control system-based method previously introduced by Rosengarten to quantify the visually-evoked blood flow response of the posterior cerebral artery (PCA); and (ii) to test the hypothesis with this method that cerebral hemodynamics in women with a recent history of (pre)eclampsia is abnormal relative to that in parous controls. Hereto, we recorded cerebral blood flow velocity (CBFV) in the PCA by transcranial Doppler (TCD) sonography during cyclic visual stimulation in 15 former preeclamptics, 13 former eclamptics and 13 controls. The typical CBFV response was fitted with the step response of a second-order-linear model enabling quantification by parameters K (gain), ζ (damping), ω (natural frequency), T_v (rate time) and T_d (time delay). The method refinement introduced here consisted of response filtering before quantification and of considering the individual instead of group-averaged response patterns. Application of this refinement reduced the fitting errors (1.4 ± 1.2 *vs.* 3.2 ± 1.8, $p < 0.01$). Intergroup differences in model parameters were not found. Although statistically not significant, a trend was observed that critical damping ($\zeta>1$) occurred more frequently in the combined group of former patients than in the controls (7 of 28 *vs.* 1 of 13, $p = 0.16$). Critical damping ($\zeta>1$) reflects an abnormal response, which is either compensated for by a rise in rate time ("intermediate"; $\zeta>1$; $T_v > 20$) or remains uncompensated ("sluggish"; $\zeta>1$; $T_v < 20$). Critical damping increased significantly ($p = 0.039$) with (pre-)eclampsia-to-test-interval in the PE+E patients with abnormal responses ($\zeta>1$), suggesting that (pre)eclampsia might induce diminishing cerebral hemodynamic function over time. Based on a system-analytical classification approach, the data of this study provide evidence for individual CBFV responses to be abnormal in former (pre)eclamptics compared with controls. Further study is needed to reveal how the abnormal CBFV response classification reflects cerebrovascular dysfunction. (E-mail: esther.martens@mumc.nl) **© 2008 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Transcranial Doppler sonography, Cerebral blood flow, (Pre)eclampsia, Control system analysis.**

INTRODUCTION

Formerly (pre)eclamptic women have a five times higher chance to die from cerebral hemorrhage (Irgens et al. 2001) and a three to nine-year shorter life expectancy (Arnadottir et al. 2005) than women who had uneventful pregnancies. Whether this predisposition of former patients is related to a common denominator such as abnormal cerebral hemodynamics is unclear.

Preeclampsia is a hypertensive pregnancy complication triggered by endothelial dysfunction. The syndrome is defined by the concomitant presence of pregnancy-induced hypertension and *de novo* pathologic proteinuria (Sibai et al. 2005). Abnormal renal, hepatic and clotting function often accompany the disorder, sometimes with the presence of neurological symptoms such as visual disturbances and headache (Noris et al. 2005). The development of seizures or coma unrelated to other

Address correspondence to: Esther G. H. J. Martens, MSc, Department of Clinical Neurophysiology, University Hospital Maastricht, P.O. Box 5800, NL-6202 AZ Maastricht, The Netherlands. E-mail: esther.martens@mumc.nl

cerebral conditions indicates progression of preeclampsia to "eclampsia," the most severe complication of preeclampsia. (Pre)eclampsia has been shown to affect the cerebral perfusion (Riskin-Mashiah et al. 2005; Zunker et al. 2000). The cerebral circulation during (pre)eclampsia is often evaluated using transcranial Doppler ultrasonography (TCD). This technique is widely used to estimate the cerebral perfusion because it is noninvasive, cost-effective and has a better time-resolution than other methods *e.g.* fMRI or PET (Lohmann et al. 2006). Several TCD studies provide evidence for altered cerebral hemodynamics (Belfort et al. 2002; Riskin-Mashiah et al. 2001, 2005; Zunker et al. 2000) and impaired cerebral autoregulation (Oehm et al. 2003) during (pre)eclampsia.

Although symptoms of preeclampsia, like visual disturbances such as seeing flashing lights, and other cerebral perfusion-related complaints *e.g.* headache usually disappear postpartum, it is conceivable that the preeclampsia-related endothelial damage persists subclinically for a prolonged period. Functional evaluation of visual neurovascular coupling (NVC), which represents the control mechanism that adjusts the local blood flow to the metabolic demand of the visual cortex, provides an estimate of the cerebral hemodynamics and, indirectly, of the cerebral endothelial function.

The objectives of this study were (i) to refine and apply a second-order linear model–based method to quantify the visually-evoked blood flow response of the posterior cerebral artery (PCA); and (ii) to use this method for testing the hypothesis that cerebral hemodynamics in women with a recent history of (pre)eclampsia is abnormal relative to that in parous controls. To this end, we estimated the NVC function at least 3 mo postpartum in two groups of either healthy formerly preeclamptic or eclamptic women who fully recovered from their complicated pregnancy, and we compared the results with those obtained in a reference group of healthy parous controls.

PATIENTS AND METHODS

Patients

We assessed the NVC in three groups, *i.e.* two patient groups of former preeclamptics (PE, $n = 15$) and formerly eclamptics (E, $n = 13$), respectively, and a reference group of healthy parous controls (C, $n = 13$). The controls were matched with the patient groups for age, body mass index (BMI) and time elapsed between delivery and measurement session. The study was approved by the Institutional Review Board, and all participating subjects gave written informed consent. Former preeclamptic and eclamptic women were selected from the database of the Department of Obstetrics and Gynecology of the University Hospital Maastricht.

Table 1. Demographics and outcome of preceding pregnancy of the participants in the two patient subgroups (PE and E) and control group (C)

	C ($n = 13$)	PE ($n = 15$)	E ($n = 13$)
Age (y)	33 ± 3	31 ± 4	33 ± 3
BMI during testing (kg/m^2)	24 ± 3	24 ± 3	26 ± 3
Interval birth to test (mo)	24 ± 14	19 ± 12	29 ± 19
Primipara during testing	23% (3/13)	60% (9/15)	46% (6/13)
Birth gestational age (wk)	39 ± 1	30* ± 2	32* ± 5
Neonatal weight (g)	3383 ± 368	1051* ± 315	1812* ± 1055

* $p < 0.05$.

The inclusion criteria for the preeclamptic group were a recent history (elapsed time 0.25 to 6 y) of a pregnancy complicated by preeclampsia, defined as *de novo* hypertension (>140/90 mm Hg) and pathological proteinuria after the 20th week of pregnancy (Sibai et al. 2005). Women enrolled in the eclampsia group had a recent history of a pregnancy (elapsed time 0.25 to 6 y) complicated by eclampsia, defined as the *de novo* development of seizures during pregnancy. We only included subjects older than 18 y at the time of pregnancy in any of the study groups. Controls had an uncomplicated pregnancy in their recent history and were matched with the patient groups with respect to age, BMI and the length of the period between delivery and measurement (birth-to-test interval). Women with a history of chronic hypertension; a renal, metabolic, neurological or cerebrovascular disorder; the use of statins; or the presence of a new pregnancy, were excluded from this study. In addition, women were only evaluated after resumption of the menstrual cycle and discontinuation of breast feeding. Table 1 lists the demographic and clinical features (mean and standard deviation) of the two patient subgroups and the controls.

Flow recording method

TCD measurements were performed using a Multidop® X 4 Doppler device (DWL, Sipplingen, Germany). A 2-MHz probe was mounted on a headband and cerebral blood flow velocity (CBFV) was measured in the P2 segment of the PCA. From the envelope of the CBFV signal, we used the beat-to-beat peak systolic CBFV values for analysis. The Doppler device was coupled to the measurement computer, the Task Force® Monitor (CNSystems, Graz, Austria), enabling concomitant recording of CBFV, electrocardiogram and arterial finger blood pressure.

Visual stimulus paradigm

Data were recorded during repetitive cycles of visual stimulation using a colored cartoon video on an