Ophthalmic Artery-Resistive Index and Evidence of Overperfusion-Related Encephalopathy in Severe Preeclampsia

Alexandre Simões Barbosa, Alamanda Kfoury Pereira, Zilma Silveira Nogueira Reis, Eura Martins Lage, Henrique Vitor Leite, Antonio Carlos Vieira Cabral

Abstract—Neurological findings in preeclampsia fulfill diagnostic criteria of posterior reversible encephalopathy syndrome (PRES), which is related to cerebral autoregulation impairment associated with high blood pressure. In preeclampsia, PRES may occur without a significant increase in blood pressure. Our aim was to investigate the association between ophthalmic artery resistive index (OARI) and clinical evidence of PRES, defined as the presence of headache and blurred vision, in patients with severe preeclampsia. OARI and main clinical and laboratory parameters were obtained in 112 patients with severe preeclampsia. Differences in these parameters were analyzed in the function of clinical evidence of PRES with a 2-sample t test. The area under receiver operating characteristic curve for each of these parameters in the function of clinical evidence of PRES was obtained. Logistic regression models were established with parameters categorized by cutoff points obtained in receiver operating characteristic curves. Among 112 patients with severe preeclampsia, 46 (41%) presented clinical evidence of PRES. These patients presented lower OARI ($P<0.0001$), higher mean blood pressure at admission ($P<0.0001$), higher mean blood pressure elevation after the first trimester ($P<0.0001$), and higher lactate dehydrogenase ($P<0.0001$) than those without clinical evidence of PRES. OARI presented an area under receiver operating characteristic curve of 0.810±0.039 (95% CI: 0.742 to 0.895; $P<0.0001$). OARI <0.56 was associated with clinical evidence of PRES, with an odds ratio of 12.67 (95% CI: 4.08 to 39.39; $P<0.0001$). Data suggest that OARI is a relevant biomarker of PRES in severe preeclampsia. (Hypertension. 2010;55:189-193.)

Key Words: preeclampsia ■ eclampsia ■ posterior reversible encephalopathy syndrome ■ ophthalmic artery ■ cerebral autoregulation

According to the literature, neurological involvement in preeclampsia-eclampsia syndrome (PEES) fulfills the criteria of posterior reversible encephalopathy syndrome (PRES).1-7 This condition refers to the acute or subacute onset of headache and visual symptoms, often associated with seizures and coma, produced by vasogenic edema primarily located in the subcortical white matter of parietooccipital lobes.1-7

Studies support that high blood pressure, impairment of autoregulation, vascular overdistension, and transudation into cerebral interstitium compose the pathophysiological substrate underlying PRES.1,3,5,8-10 In addition, endothelial damage, a major feature in PEES pathophysiology, is recognized as a relevant risk factor of PRES.4,5 Studies suggest that PRES associated with significant endothelial damage may develop without a relevant increase in blood pressure.4,5

Most clinical and laboratory parameters of PEES are inaccurate predictors of PRES.11-16 In addition, PRES often develops despite adequate medical monitoring.13-14 In a large epidemiological study, significant hypertension and proteinuria were absent in 38% of patients who developed seizures.14 Further, a significant number of patients present seizures as the first manifestation of PEES15 or during adequate monitoring in the hospital.14 On the other hand, studies have reported lower ophthalmic artery resistance in patients with severe preeclampsia, especially those with headache and visual symptoms.17-19 The aim of this study was to investigate the association between ophthalmic artery resistive index (OARI) and clinical evidence of PRES in severe preeclampsia.

Patients and Methods

The series was composed of patients with severe preeclampsia who were admitted to the maternity ward of the Hospital das Clínicas of the Universidade Federal de Minas Gerais, a leading national tertiary high-risk pregnancy center in Brazil. The series was composed of 112 consecutive patients, prospectively included in the study between January 2000 and July 2006. Inclusion criteria were as follows: (1) diagnosis of severe preeclampsia according to the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000)11,12; (2) no use of antihypertensive medication at admission, with the exception of...
metildopa in chronic hypertensive patients; (3) no use of magnesium sulfate at admission; and (4) a normal retinal pattern on ophthalmoscopic examination. Patients were excluded from this study for the following reasons: (1) unavailable 24-hour proteinuria; (2) smoking; (3) antiphospholipid antibody syndrome; (4) diabetes mellitus; (5) gestational diabetes; and (6) vascular ophthalmologic diseases, hypertensive retinopathy, or glaucoma. The study was approved by the ethics committee of the Hospital das Clínicas of the Universidade Federal de Minas Gerais. A written informed consent was obtained from every patient before participating in the study, in accordance with the ethical standards of the last revision of the Helsinki Declaration.

Blood pressure recordings were obtained by senior residents, using a calibrated mercury column sphygmomanometer (Becton, Dickinson and Company) and an acoustic stethoscope (3M Littman), after 5 minutes of rest in sitting position, with back and arm supported. Proper cuff size and bladder cuff length and width were calculated using systolic and diastolic blood pressures obtained, respectively by I and V Korotkoff sounds.11,12 The mean blood pressure from the first 2 records obtained at admission and after 6 hours (MBPA) and the mean blood pressure elevation over the mean blood pressure of the first trimester (MBPE) were used in statistical analysis. Soon after admission, blood tests for hemolysis, platelets count, liver enzymes measurement and coagulation profile were performed, and urine collection for 24-hour proteinuria measurement was initiated. These tests were repeated according to clinical status. Blood tests were performed with present hypertension and normal blood pressure at admission. Mean blood pressure was calculated using systolic and diastolic blood pressures obtained, respectively by I and V Korotkoff sounds.11,12 Classification criteria of severe preeclampsia were ≥1 of the following: (1) blood pressure ≥160/110 mm Hg; (2) proteinuria ≥2.0 g per 24 hours; (3) platelet count <100 000 mm^-3; (4) alanine or aspartate aminotransferases >50 IU/L; (5) urinary volume <500 mL per 24 hours; (6) pulmonary edema; (7) intense continuous headache; and (8) blurred vision.11,12

Data regarding mental status and headache were obtained with standardized questionnaires. Attention, temporal and spatial orientation, and verbal comprehension were evaluated. Headache was characterized according to its intensity, duration pattern, and localization. Photophobia (light oversensitivity) and photopsias (light flashes) were assessed. Visual acuity and visual field testing in each eye were, respectively, obtained with Snellen charts and a tangent screen perimeter, using the best refractive correction. Visual examination time for visual acuity and visual field testing was 5 minutes per eye on average. A comprehensive ophthalmoscopic examination was obtained in patients with visual symptoms, using an indirect ophthalmoscope (Keeler Instruments) and a Volk 20 diopter aspheric lens (Volk Optical Inc). Blurred vision was defined as visual acuity <0.6 from Snellen charts or visual field loss on a tangent screen perimeter. Questionnaires and visual testing were obtained by qualified staff members without information regarding clinical data. Intense, persistent headaches (>4 hours), associated with blurred vision, were labeled as clinical evidence of PRES.

Orbital color Doppler ultrasonography was performed by a qualified examiner (A.S.B.), within the first 12 hours after admission, without information regarding clinical data. Exams were performed using a color Doppler Medison 8800 device with a 7.5-MHz linear transducer (Medison) applied to closed eyes covered with methylcellulose gel.21 Patients were positioned in the dorsal decubitus with a slight left lateral tilt.2 Images were obtained using a sample volume of 0.2×0.2 mm and the lowest filter. A complete evaluation of orbital vessels was performed, initiating with identification of the ophthalmic artery and its branches. The ophthalmic artery was studied at its anterior segment, ~10 mm from the posterior scleral wall, nasally to the optic nerve, and outside branching sites.21 OARI measurements were obtained on the right eye, from a cycle of sequential regular spectral curves. The usual examination time was 5 minutes on average.

Differences in OARI, MBPA, MBPE, 24-hour proteinuria, lactate dehydrogenase (LDH), and platelets according to clinical evidence of PRES were obtained with a 2-sample t test. The association between each of these parameters with clinical evidence of PRES was evaluated using areas under the receiver operating characteristic (ROC) curves. In multivariate logistic models, each parameter was categorized according to cutoff values obtained in ROC curves. Differences of parameters according to evidence of PRES were considered significant when P < 0.05 in the 2-sample t test. The association between parameters with clinical evidence of PRES was considered significant when the inferior limit of the CI of the areas under ROC curves was >0.50. The deflection points in ROC curves were established as the intersection points of sensitivity and specificity curves in the identification of PRES according to each variable. Multivariate logistic models were established with variables categorized according to cutoff values obtained in ROC curves. Two categories were considered for each variable, “lower than” or “higher than” each cutoff value. The predictive value of each parameter was considered significant when the inferior limit of the odds ratio was >1. Statistical analyses were performed using Minitab 15 and SPSS 15 software.

Results

Twenty-six patients (23%) presented clinical evidence of PRES. Mild deficits of attention, as well as temporal and spatial orientation, were, respectively, observed in 11 (46%) and 7 (23%) patients. No significant deficits or verbal comprehension were observed. Most patients described headache as intense (92%), steady (88%), or diffuse (78%), with a mean 5.5 ± 1.0 hours of duration. Mean visual acuity was 0.4 ± 0.1 and was bilateral and symmetrical. Intense and steady photopsias and photophobia were, respectively, reported by 19 (73%) and 18 (69%) patients. Most findings in visual fields were generalized loss in 20 (77%). Central field sparing was observed in 14 patients (36%). Patients without clinical evidence of PRES presented no headache or mild sporadic headache, associated with normal visual acuity and normal visual fields. No focal neurological deficits were observed on this series. A flowchart of patients in the study is presented in the Figure.

Patients with clinical evidence of PRES presented lower OARI (P < 0.0001), higher MBPA and MBPE (P = 0.002 and P < 0.0001), higher LHD (P < 0.0001), and lower platelets (P = 0.042) than asymptomatic patients. Similar 24-hour proteinuria, maternal, and gestational ages were obtained between these groups (respectively, P = 0.112, P = 0.882, and P = 0.223). Among the 26 patients with clinical evidence of PRES, 6 were asymptomatic at the time of orbital color Doppler. These patients developed clinical evidence of PRES 2 to 4 days after OARI was obtained. These patients presented similar OARI than those for whom orbital color Doppler was performed after the onset of symptoms (P = 0.568). Epidemiological, clinical, and laboratory parameters are presented in Table 1.

Patients with isolated and superimposed preeclampsia presented a similar frequency of clinical evidence of PRES (P = 0.562). Among patients with PRES, those with isolated and superimposed preeclampsia presented similar OARI (P = 0.256), MBPA (P = 0.356), LHD (P = 0.125), platelets (P = 0.812), 24-hour proteinuria (P = 0.523), maternal ages (0.458), and gestational ages (P = 0.523). Among patients with superimposed preeclampsia and clinical evidence of PRES, no difference in OARI was obtained between patients using no medication and those using metildopa (P = 0.859).
ROC curves showed a significant association between clinical evidence of PRES and OARI, MBPA, MBPE, LDH, and platelets. Among these, OARI was the main parameter associated with clinical evidence of PRES, as demonstrated by the largest estimated area under ROC curve (0.85±0.039 [95% CI: 0.780 to 0.920]; P<0.0001). Areas under ROC curves, CIs, and P values are presented in Table 2. The deflection points in ROC curves were 0.56 for OARI, 136 mm Hg for MBPA, 40 mm Hg for MBPE, 2.5 g per 24-hour for proteinuria, 600 U/L for LDH, and 100 000/mm³ for platelets. These cutoff values were used for categorization in logistic models.

A multivariate logistic model was established in the function of clinical evidence of PRES. The inclusion of parameters and interaction factors after OARI produced no further improvement over OARI alone. Therefore, the univariate logistic model for OARI was the final model, suggesting that OARI is the main predictor of clinical evidence of PRES. The

### Table 2. Areas Under ROC Curves for Clinical Evidence of PRES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A&lt;sub&gt;E&lt;/sub&gt;</th>
<th>A&lt;sub&gt;IC&lt;/sub&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OARI</td>
<td>0.850±0.040</td>
<td>0.780 to 0.920</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MBPA, mm Hg</td>
<td>0.741±0.050</td>
<td>0.633 to 0.850</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MBPE, mm Hg</td>
<td>0.800±0.050</td>
<td>0.702 to 0.900</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h proteinuria, g/24 h</td>
<td>0.605±0.060</td>
<td>0.492 to 0.720</td>
<td>0.106</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>0.775±0.050</td>
<td>0.669 to 0.880</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Platelets, ×10³</td>
<td>0.625±0.070</td>
<td>0.490 to 0.750</td>
<td>0.064</td>
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</table>

A<sub>E</sub> indicates estimate of area under ROC curve; A<sub>IC</sub>, CI of the area under ROC curve.

Discussion

Preeclampsia is a multisystemic, heterogeneous condition characterized by endothelial damage, coagulation cascade activation, and vascular tonus imbalance. Neurological involvement compatible with PRES is a major feature in the clinical spectrum of preeclampsia. On the other hand, PEES is a well-established cause of PRES. Headache and visual symptoms, the main clinical manifestations of PRES, composed the best indicators of the risk of seizures in PEES. In our study, headache and visual symptoms were carefully characterized. The comprehensive ophthalmoscopic examination performed in our study excluded retinal findings related to PEES and avoided significant bias in the characterization of clinical evidence of PRES.

The ROC curve constitutes an authoritative method for the analysis of accuracy of biomarkers. In addition, the deflection point in the ROC curve provides the best cutoff point for categorization of variables in logistic models. ROC curves suggested that OARI <0.56; MBPA and MBPE, respectively, >136 and 40 mm Hg; and LDH >600 U/L present significant associations with clinical evidence of PRES. Multivariate logistic models suggest that, among these parameters, OARI is the most relevant predictor of clinical evidence of PRES. OARI ≤0.56 was associated with a 12.67 higher chance of clinical evidence of PRES. On the basis of ROC curves obtained in this study, a progressively higher probability of PRES occurs with progressively lower OARI values.

### Table 3. Full Multivariate Logistic Regression Model for Clinical Evidence of PRES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR&lt;sub&gt;E&lt;/sub&gt;</th>
<th>OR&lt;sub&gt;IC&lt;/sub&gt;</th>
<th>z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OARI</td>
<td>11.19</td>
<td>2.79 to 44.92</td>
<td>3.40</td>
<td>0.001</td>
</tr>
<tr>
<td>MBPA, mm Hg</td>
<td>0.96</td>
<td>0.19 to 4.89</td>
<td>0.05</td>
<td>0.958</td>
</tr>
<tr>
<td>MBPE, mm Hg</td>
<td>0.56</td>
<td>0.09 to 3.37</td>
<td>0.63</td>
<td>0.529</td>
</tr>
<tr>
<td>24-h proteinuria, g/24 h</td>
<td>1.37</td>
<td>0.42 to 4.42</td>
<td>0.53</td>
<td>0.599</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>1.40</td>
<td>0.37 to 5.34</td>
<td>0.50</td>
<td>0.621</td>
</tr>
<tr>
<td>Platelets, ×10³</td>
<td>1.59</td>
<td>0.64 to 3.97</td>
<td>1.00</td>
<td>0.319</td>
</tr>
</tbody>
</table>

OR<sub>E</sub> indicates the estimate odds ratio; OR<sub>IC</sub>, CI of the odds ratio.

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**Table 1. Epidemiological and Main Parameters in the Function of Clinical Evidence of PRES**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PRES (−) (N = 86)</th>
<th>PRES (+) (N = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>27.9±7.1</td>
<td>28.3±6.7</td>
<td>0.882</td>
</tr>
<tr>
<td>Gestational age</td>
<td>31.9±4.7</td>
<td>32.9±3.4</td>
<td>0.223</td>
</tr>
<tr>
<td>MBPA, mm Hg</td>
<td>138.0±12.5</td>
<td>145.5±18.6</td>
<td>0.002</td>
</tr>
<tr>
<td>MBPE, mm Hg</td>
<td>42.0±15.7</td>
<td>61.0±16.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h proteinuria</td>
<td>2.96±2.55</td>
<td>2.80±2.47</td>
<td>0.112</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>911±597</td>
<td>1204±650</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Platelets, ×10³</td>
<td>229±56</td>
<td>68±46</td>
<td>0.042</td>
</tr>
<tr>
<td>OARI</td>
<td>0.58±0.05</td>
<td>0.53±0.03</td>
<td>&lt;0.0001</td>
</tr>
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</table>

Values are expressed in mean±SD.
Among patients with clinical evidence of PRES, those with isolated and those with superimposed preeclampsia presented similar OARI, suggesting that this classification is irrelevant for OARI interpretation. Similarly, among patients with superimposed preeclampsia, OARI measurements were unrelated to the use of metildopa. These findings are supported by experimental data that demonstrate reversion of cerebral artery remodeling associated with chronic hypertension during pregnancy. This could reduce the upper limit of autoregulation, preventing the protective effect of remodeling and increasing the risk of PRES. Although patients with preexisting chronic hypertension are considered less susceptible to PRES, patients with and without previous chronic hypertension presented a similar prevalence of clinical evidence of PRES.

In PEES, evidence suggests that central overperfusion is a major pathophysiological feature of PRES. This finding corroborates studies that demonstrate the association between ophthalmic artery overflow with headache and visual symptoms, as well as middle cerebral artery overflow with headache and seizures. Impaired cerebral vascular autoregulation is considered the basic pathophysiological event underlying PRES. Studies support that PRES associated with PEES occurs without a significant rise in blood pressure, suggesting that, at least in some patients, blood pressure plays a secondary role in cerebral autoregulation impairment. The relevance of endothelial damage on cerebral autoregulation was proposed by Schwartz and colleagues. Although increased vascular tonus is a well-described effect of endothelial damage, evidence suggests that, in PRES, the ultimate manifestation of endothelial damage in central territories is autoregulatory impairment, overdistension, and overperfusion. Low and high vascular tonus are not mutually exclusive in central territories and may coexist. Schwartz et al demonstrated that abnormal red blood cell morphology and high LDH levels, which are consistent with endothelial damage, are associated with PRES. Nevertheless, no evaluation of endothelial function was performed in studies of PRES associated with PEES.

Vasogenic edema is usually more intense in parietoccipital lobes, suggesting that posterior vascular territories are especially susceptible to damage. This predominance might be related to regional differences in sympathetic tonus regulation between vertebrobasilar and carotid systems. Although sympathetic tonus is increased in preeclampsia, posterior territories present a lower fiber density. The shifting of blood flow from the carotid to the vertebrobasilar system might further increase the risk of endothelial damage because of overperfusion in posterior territories. Nevertheless, the precise mechanism of the preferential involvement of posterior territories in PEES remains speculative.

Important contributions to a better understanding of vascular events related to PEES, especially those associated with PRES, have been provided by studies on the renin-angiotensin-aldosterone system. Angiotensin II is a major cause of oxidative stress and endothelial damage. Experimental studies demonstrate that angiotensin II infusion produces endothelial damage not related to high blood pressure. Most authors believe that angiotensin II is not increased in PEES. Nevertheless, a large range of its biological effects in PEES can be produced by angiotensin II type 1 (AT1) autoantibodies. AT1 autoantibodies contribute to increasing peripheral sympathetic tonus, superoxide formation, and endothelial damage. AT1 autoantibodies/AT1 induce soluble Fms-like tyrosine kinase, which is considered a major cause of endothelial damage in PEES. Evidence suggests that endothelial damage antedates clinical manifestations of preeclampsia, which might contribute to a earlier autoregulation impairment in the presence of high blood pressure. AT1 autoantibodies represent a potential link among high blood pressure, endothelial damage, and central overperfusion in PEES.

Our study presents significant limitations. First, neuroimaging was lacking to confirm the diagnosis of cerebral edema. Nevertheless, cerebral imaging is considered unnecessary for the diagnosis and management of most women with PEES and should be reserved for women with atypical manifestations, particularly those presenting focal neurological deficits. Similarly, Schwartz et al stated that imaging studies are unnecessary in PRES, when clinical evidence is sufficient to establish the diagnosis. In this series, clinical presentation compatible with PRES, absence of focal neurological deficits, and complete resolution of symptoms supported the diagnosis. Because neuroimaging is unusual in PEES, even in patients with neurological manifestations, the design of this study is consistent with current obstetric practice. Second, our findings reflect a population with severe preeclampsia admitted in a tertiary center. OARI can perform differently in settings characterized by patients with milder disease. Low OARI should be interpreted differently in these settings.

Perspectives
Preeclampsia is characterized by its high heterogeneity and unpredictable clinical course. Some authors stand that neurological manifestations in preeclampsia are unpredictable by current interventions. Therefore, the search for biomarkers in preeclampsia management is a major line of research in this condition. Blood pressure, proteinuria, and other major laboratory parameters are inadequate in evaluating the risk of adverse outcomes in preeclampsia. Although vasospasm is historically considered the major pathophysiological event underlying preeclampsia onset and progression, a relevant body of evidence suggests that neurological manifestations are overperfusion related. This study presents a contribution for the use of OARI as a biomarker of PRES in preeclampsia. Orbital color Doppler OARI is a safe, noninvasive test that provides relevant information regarding central circulation. Introducing OARI in clinical practice might improve the evaluation of PEES. However, additional studies are required to establish the role of OARI in preeclampsia management.

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None.
References


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