

# Dopplerfluxometry of ophthalmic arteries and assessment of endothelial function in early and late preeclampsia\*

*Dopplerfluxometria de artérias oftálmicas e avaliação da função endotelial nas formas precoce e tardia da pré-eclâmpsia*

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**Abstract Objective:** To identify possible differences between endothelial dysfunction evaluated by brachial artery flow-mediated dilation and central hyperperfusion evaluated by dopplerfluxometry of ophthalmic artery in women with early- and late-onset preeclampsia. **Materials and Methods:** Flow-mediated dilation testing and dopplerfluxometry of ophthalmic artery were performed in 81 patients (26 with early preeclampsia, 30 with late preeclampsia, and 25 normotensive pregnant women – control group). **Results:** As compared with the control group, patients with preeclampsia presented lower values of flow-mediated dilation, both in cases of early preeclampsia ( $7.62 \pm 5.42\% \times 14.12 \pm 6.14\%$ ;  $p = 0.02$ ) and in cases of late preeclampsia ( $5.83 \pm 4.12\% \times 14.12 \pm 6.14\%$ ;  $p = 0.00$ ). No statistically significant difference was observed between early- and late-onset preeclampsia ( $7.62 \pm 5.42\% \times 5.83 \pm 4.12\%$ ;  $p = 0.09$ ). Values for dopplerfluxometry of ophthalmic artery were significant lower in patients with preeclampsia as compared with the control group, both in cases of early preeclampsia ( $0.631 \pm 0.024 \times 0.737 \pm 0.032$ ;  $p = 0.01$ ) and in cases of late preeclampsia ( $0.653 \pm 0.019 \times 0.737 \pm 0.032$ ;  $p = 0.03$ ). Again, no statistically significant difference was observed between early- and late-onset preeclampsia ( $0.631 \pm 0.024 \times 0.653 \pm 0.019$ ;  $p = 0.12$ ). Basically, the results demonstrate a decrease in values for dopplerfluxometry of ophthalmic artery in patients with early and late presentations of preeclampsia as compared with the control group, although with no statistically significant difference between the two presentations of the disease. **Conclusion:** The present results indicate the presence of endothelial dysfunction and central hyperperfusion in patients with early- and late-onset preeclampsia.

**Keywords:** Preeclampsia; Flow-mediated dilation; Ophthalmic arteries.

**Resumo Objetivo:** Avaliar possíveis diferenças entre a disfunção endotelial, avaliada pela dilatação fluxo-mediada, e hiperperusão central, avaliada por dopplerfluxometria da artéria oftálmica, entre pacientes portadoras da forma precoce e tardia da pré-eclâmpsia. **Materiais e Métodos:** O teste de dilatação fluxo-mediada e a dopplerfluxometria da artéria oftálmica foram obtidos de 81 gestantes, sendo 56 portadoras de pré-eclâmpsia (26 na forma precoce e 30 na forma tardia) e 25 gestantes saudáveis (grupo controle). **Resultados:** Portadoras de pré-eclâmpsia apresentaram valores menores de dilatação fluxo-mediada quando comparadas ao grupo controle, tanto na forma precoce ( $7,62 \pm 5,42\% \times 14,12 \pm 6,14\%$ ;  $p = 0,02$ ) como na forma tardia ( $5,83 \pm 4,12\% \times 14,12 \pm 6,14\%$ ;  $p = 0,00$ ). Não houve diferença quando foram comparadas as duas formas ( $7,62 \pm 5,42\% \times 5,83 \pm 4,12\%$ ;  $p = 0,09$ ). A dopplerfluxometria da artéria oftálmica apresentou-se significativamente menor nas pacientes portadoras de pré-eclâmpsia quando comparadas ao grupo controle, tanto na forma precoce ( $0,631 \pm 0,024 \times 0,737 \pm 0,032$ ;  $p = 0,01$ ) como na forma tardia ( $0,653 \pm 0,019 \times 0,737 \pm 0,032$ ;  $p = 0,03$ ). Não houve diferença entre as duas formas de apresentação ( $0,631 \pm 0,024 \times 0,653 \pm 0,019$ ;  $p = 0,12$ ). Os resultados basicamente demonstram redução nos valores de dilatação fluxo-mediada e dopplerfluxometria da artéria oftálmica nas formas tardia e precoce da pré-eclâmpsia quando comparadas ao grupo controle, sem, contudo, diferenças significativas entre as duas formas de apresentação da doença. **Conclusão:** Os resultados indicam a presença de disfunção endotelial e hiperperusão central em gestantes com pré-eclâmpsia, tanto na forma precoce como na tardia.

**Unitermos:** Pré-eclâmpsia; Dilatação fluxo-mediada; Artérias oftálmicas.

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## INTRODUCTION

Preeclampsia (PE) is a syndrome of multifactorial etiology globally responsible for the highest rate of maternal and fetal mortality<sup>(1)</sup>. Endothelial dysfunction is pointed out as the pathophysiological event behind the clinical manifestations and complications of such syndrome, from increased arterial pressure to hyperperfusion of the central nervous system<sup>(2,3)</sup>.

The vascular endothelium is a paracrine structure capable of, among other functions, to control the arterial tone by the release of vasoactive factors, particularly nitric oxide, that acts by promoting vasodilatation of the muscular coat<sup>(4)</sup>. Such mechanism assumes a greater importance during gestation, since the potential for arterial dilatation is critical to accommodate the increase in maternal blood volume and to allow appropriate placental perfusion. Brachial artery flow-mediated dilation (FMD) is a sonographic test that allows the indirect evaluation of the endothelial function. The study is based on the arterial dilation capacity as a response to an induced transient hypoxic stimulus<sup>(5,6)</sup>.

Central hyperperfusion is a result from the loss of capacity of self-regulation of the arterial flow in the central nervous system. This condition progresses with development of cerebral edema that is a direct cause of the typical tonic-clonic seizures of eclampsia<sup>(7)</sup>. The decrease in the ophthalmic artery resistive index (OARI) identified at dopplerfluxometry of ophthalmic arteries indicates the involvement of central arteries that culminates in hyperperfusion<sup>(8)</sup>.

A classification of PE based on the period of symptoms onset has been proposed, creating two categories as follows: early PE – with onset before the 34th gestational week –, and late PE – occurring after the 34th gestational week<sup>(9)</sup>. Such a classification is compatible with the pathophysiological basis of PE as placental deficiency<sup>(10)</sup> and the maternal hemodynamic condition<sup>(11)</sup> are taken into consideration in the differentiation between forms of PE.

Endothelial involvement and cerebral hyperperfusion may present distinct behaviors in relation to early- and late onset PE. The present study was aimed at evaluating

the behavior of endothelial function and cerebral blood flow by means of FMD test and Doppler spectral analysis of ophthalmic artery in women with early- and late-onset PE.

## MATERIALS AND METHODS

### Patients

The present cross-sectional study included 81 pregnant women divided into two groups as follows: 56 patients with PE and no other comorbidity, and 25 healthy pregnant women paired according to their ages and number of pregnancies. Among the 56 patients with PE, 30 presented late PE, and 26, early PE.

The diagnosis of PE was made in compliance with the criteria defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000. According to such classification, PE is defined as increase in arterial pressure after 20 weeks of gestation (pressure levels  $\geq 140 \times 90$  mmHg (in two measurements at a six-hour interval) associated with the presence of proteinuria ( $\geq 1+$  measured either with a reagent strip test or 24 hour proteinuria  $> 0.3$  g)<sup>(12)</sup>.

Patients with comorbidities such as chronic arterial hypertension, renal disease, coronary disease and infectious diseases were excluded from the study. Twin pregnancies, pregnancies with fetal malformation or altered fetal growth were also excluded as well as smoker patients, drug users, and patients taking nitrite-based drugs. Such situations are known to be associated with endothelial injury.

The present study was approved by the Committee for Ethics in Research of Hospital das Clínicas – Universidade Federal de Minas Gerais (HC-UFGM). The selected patients received explanations and signed a term of free and informed consents. Subsequently, the patients underwent brachial artery FMD.

### Brachial artery FMD

The technique to evaluate brachial artery FMD was performed with a Medison Sonoace 8800 color Doppler ultrasonography apparatus with a 4–8 MHz linear transducer. The patients were placed at rest in dorsal decubitus for 15 minutes. All the

patients had their arterial pressure measured and their brachial artery was identified medially in the antecubital fossa of the dominant upper limb. One image of the vessel was acquired at approximately 5 cm from the elbow of the upper limb, with a longitudinal section (B mode) at the moment of lesser distention of the vessel corresponding to cardiac diastole, and was obtained by means of image recovery on the cine loop display of the equipment. The image was frozen to get a mean of the three measurements of the vessel caliber (D1). After this first measurement, the sphygmomanometer cuff positioned proximally to the site of the brachial artery measurement was inflated for five minutes up to a pressure  $> 250$  mmHg, and later was slowly deflated. The mean of three further measurements of the vessel caliber was obtained with the already mentioned technique one minute after the cuff deflation (D2). The FMD value was obtained by the following equation:

$$\text{FMD (\%)} = [(D2 - D1)/D1] \times 100$$

where: D1 = basal diameter; D2 = post-occlusion diameter.

All the studies were performed by a single investigator of the HC-UFGM, trained and certified in ultrasonography.

### Dopplerfluxometry of ophthalmic arteries

Color Doppler imaging of the orbit was obtained by a trained investigator who did not know the clinical data of the patients. The studies were performed with a Medison 8800 high-resolution color Doppler equipment with a 7.5 MHz linear transducer applied on closed eyes covered with methylcellulose gel. The patients were positioned in dorsal decubitus and on average the studies took five minutes to be completed. A comprehensive evaluation of the orbit was performed, identifying the ophthalmic artery and respective branches. The anterior branch of the ophthalmic artery was evaluated at approximately 10 mm from the posterior scleral wall, nasally to the optic nerve. The OARI was obtained on the right eye of the patients after a cycle of at least three consecutive regular waveforms. Figure 1 shows studies obtained in a normotensive patient and in a patient with PE.

**Statistical analysis**

The normality for continuous variables was evaluated by means of the Shapiro-Wilk test. The Kruskal-Wallis test was utilized for comparison between groups of non-parametric variables, with the post-hoc Dunn procedure for comparison of pairs of groups. Analysis of variance (ANOVA) was utilized to compare parametric variables. The results were expressed as median ± interquartile range or mean ± standard deviation for non-parametric and parametric variables, respectively. All the analyses were performed with the aid of the software Statistical Package for Social Sciences version 18 (SPSS; Chicago, IL, USA).

**RESULTS**

Table 1 shows the demographic characteristics of the three groups. The patients with late PE presented higher body mass index than the patients with early PE or those in the control group.

As regards FMD results, as compared with the control group, the patients with both early and late PE presented lower values ( $7.62 \pm 5.42\% \times 14.12 \pm 6.14\%$ ;  $p = 0.02$ ) and ( $5.83 \pm 4.12\% \times 14.12 \pm 6.14\%$ ;  $p = 0.00$ ), respectively. However, no statistically significant difference was observed in the comparison between early- and late-onset PE ( $7.62 \pm 5.42\% \times 5.83 \pm 4.12\%$ ;  $p = 0.09$ ).

The OARI was significantly lower in the patients with early and late PE as compared with the control group ( $0.631 \pm 0.024$

$\times 0.737 \pm 0.032$ ;  $p = 0.01$ ) and ( $0.653 \pm 0.019 \times 0.737 \pm 0.032$ ;  $p = 0.03$ ), respectively. Again, no statistically significant difference was observed between early- and late-onset PE ( $0.631 \pm 0.024 \times 0.653 \pm 0.019$ ;  $p = 0.12$ ).

The results for FMD and OARI are shown on Table 2.

**DISCUSSION**

Vascular endothelial injury, clinically characterized as endothelial dysfunction, was extensively demonstrated in patients with PE, by means of FMD<sup>(13,14)</sup>. Lower values of such test have already been demonstrated in patients who subsequently developed PE, indicating that such test can be utilized to predict clinical manifestations of

PE<sup>(15,16)</sup>. Apparently, endothelial dysfunction precedes clinical PE manifestations and persists up to one year after delivery, which would also explain the higher incidence of cardiovascular complications in women with previous history of PE<sup>(17)</sup>.

Hyperperfusion of the central nervous system demonstrated by lower OARI values has also been observed in patients with PE<sup>(18)</sup>. The utilization of such index plays a relevant role in the differential diagnosis between PE and chronic arterial hypertension. Patients with chronic arterial hypertension tend to present OARI results similar to those of normotense pregnant women<sup>(19)</sup>. Considering that the differentiation between chronic arterial hypertension and PE, either by clinical or by laboratory means, is not always simple, dopplerfluxo-

**Table 1** Demographic characteristics of 81 pregnant women participating in the study.

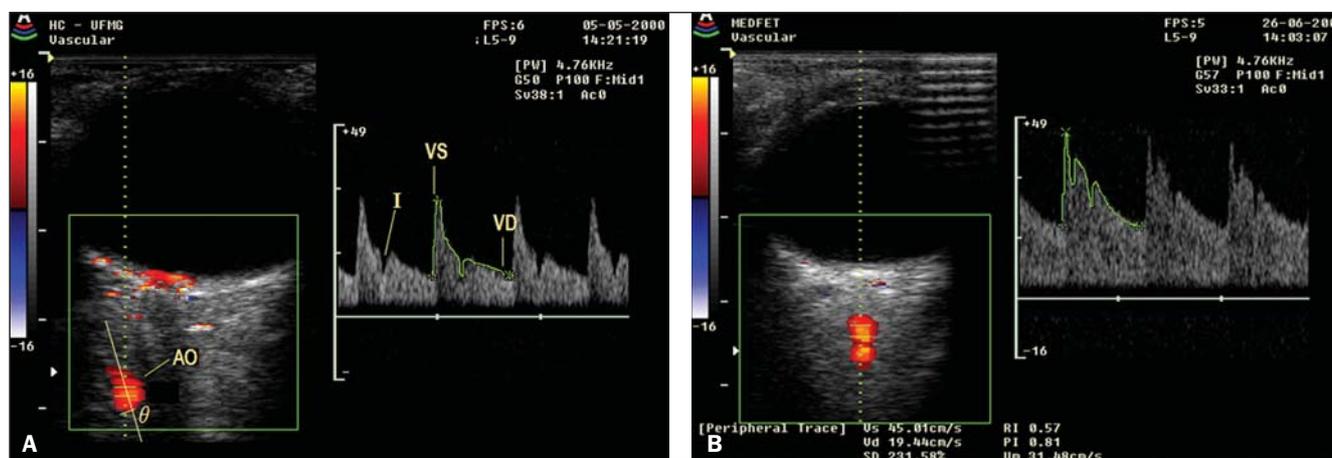
	Early PE (n = 26)	Late PE (n = 30)	Control group (n = 25)	p value
Maternal age (years)	29 ± 6.4	30 ± 4.2	28 ± 7.1	0.18
Gestational age (weeks)	29 ± 3.4	36 ± 2.1	30 ± 4.2	0.02
Number of pregnancies	1 ± 1.2	1 ± 1.8	1 ± 2.1	0.43
Body mass index (g/m <sup>2</sup> )	24.7 ± 8.5	29.2 ± 9.8	23.6 ± 12.1	0.04

Note: Body mass index calculated with basis on the pre-gestational weight of the patients.

**Table 2** Results regarding brachial artery FMD and OARI.

	Early PE	Late PE	Control group	p value
Basal diameter of brachial artery (mm)	3.25 ± 6.27	3.02 ± 7.22	3.12 ± 4.14	0.23
FMD (%)	7.62 ± 5.42	5.83 ± 4.12	14.12 ± 6.14	0.003
OARI	0.631 ± 0.024	0.653 ± 0.019	0.737 ± 0.032	0.017

FMD, flow-mediated dilation; OARI, ophthalmic artery resistive index.



**Figure 1.** Dopplerfluxometry of ophthalmic artery. **A:** Doppler of ophthalmic artery of a normotense patient. **B:** Doppler of ophthalmic artery of a patient with preeclampsia demonstrating increased diastolic flow and consequential decrease in the resistive index.

metry of ophthalmic artery could play a relevant role not only in the diagnosis but also in the definition of the approach to patients with high pressure levels during pregnancy.

The classification of PE into early- and late-onset PE has been extensively utilized<sup>(9)</sup>. A study developed in the authors' institution has demonstrated that early-onset PE is associated with a high rate of maternal and fetal complications<sup>(20)</sup>. Early PE is responsible for 10% of cases of PE, but, besides prematurity, it is known that in such cases there is a higher rate of fetuses with intrauterine growth restriction<sup>(21)</sup>. Probably, the worst degree of placentation demonstrated by higher indices of uterine artery pulsatility, and that is also more enhanced in cases of early PE, explains the placental insufficiency and the intrauterine growth restriction in these cases<sup>(22)</sup>.

Patients with early PE probably would present lower values for FMD and OARI as compared with patients with late PE, explaining the higher rate of maternal complications. However, such results were not found in the present study. Explanations might be based on maternal constitutional factors of patients with late PE. In spite of the exclusion of comorbidities, such pregnant women presented higher body mass indices and might have latent diseases that already run their course with endothelial dysfunction, among them plurimetabolic syndrome, which would lead to lower indices in the tests, particularly regarding FMD. Such lower values could explain the similarity in results as compared with the patients with early-onset PE who theoretically would present a greater involvement

of the endothelial function solely resulting from PE.

Concluding, the present results indicate the presence of endothelial dysfunction and hyperperfusion of central nervous system in pregnant women with both early and late PE, but with no significant difference between the clinical presentations of the syndrome.

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