*Journal of the American Society of Hypertension* 8(11) (2014) 820–826

Research Article

# Impaired coronary microvascular function and increased intima–media thickness in preeclampsia

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Manuscript received May 27, 2014 and accepted August 18, 2014

## Abstract

There is an association between preeclampsia (PE) and excessive morbidity and mortality. Some recent studies have revealed the presence of endothelial dysfunction in PE patients with inflammatory activity. Moreover, it has been argued that the chronic inflammatory state involved in PE leads to an acceleration in atherosclerosis. Accordingly, our goal in this study is to determine whether there is any coronary microvascular dysfunction and increase in the intima–media thickness in patients who had mild PE 5 years before, without the presence of any traditional cardiovascular risk factors. The study included 33 mild PE patients (mild preeclampsia is classified as a blood pressure (BP) of 140/90 mm Hg or higher with proteinuria of 0.3 to 3 g/d) whose mean age was 33.7 years old, and 29 healthy women volunteers whose mean age was 36.1 years old. Each subject was examined using transthoracic echocardiography 5 years after their deliveries. During the echocardiographic examination, coronary flow reserve (CFR) and carotid intima–media thickness (IMT) were measured. There was a statistically lower CFR value in PE patients as compared with controls ($2.39 \pm 0.48$ vs. $2.90 \pm 0.49$; $P < .001$). On the other hand, there was a significant increase in their IMT and high–sensitivity C–reactive protein (hs–CRP) values (respectively, $0.59 \pm 0.15$ vs. $0.46 \pm 0.10$; $P < .001$ and $3.80 \pm 2.10$ vs. $2.33 \pm 1.79$; $P = .004$). There was a negative correlation between the CFR values of the PE patients and hs-CRP ($r = -0.568$; $P = .001$) and IMT ($r = -0.683$, $P < .001$) results.We determined in the study that there was impaired CFR and increased carotid IMT in patients with PE, and, moreover, that these adverse effects were significantly correlated with hs-CRP. J Am Soc Hypertens 2014;8(11):820–826. 

*Keywords:* Carotid atherosclerosis; CFR; endothelial function; toxemia.

## Introduction

Preeclampsia (PE) represents one of the most important causes of maternal morbidity and mortality, affecting between 3% and 5% of all the pregnancies in the world, and is characterized by the impairment of general vascular dilatation.[1,2] It is known that the insufficiency of trophoblast invasion in early pregnancy leads to the impairment of angiogenesis in the mother, as well as to the upsetting of the balance between nitric oxide and reactive oxygen products, which controls vascular tonus and the coagulation cascade, and that this situation leads to the emergence of the clinical manifestations of the disease.[3] The primary cause of the impaired circulatory homeostasis in PE is endothelial dysfunction. As a result, there occurs a maternal reaction that involves endothelial cell dysfunction caused by the stimulated inflammatory response, and hypertension develops.[3,4] It has been shown recently that patients with PE face a increased risk of developing cardiovascular diseases in later years.[5–7] Although coronary endothelium secretes many products, it has not yet been possible to develop a single blood test that could detect the early–stage changes in endothelium as well as in the endothelial function. Many invasive and non–invasive methods are in use today to assess the damages in coronary endothelium.

Conflict of interest: none.
Financial support: none.

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1933-1711/$ - see front matter 
http://dx.doi.org/10.1016/j.jash.2014.08.012

Among these methods, transthoracic coronary flow reserve (CFR) measurement is used to examine epicardial coronary arteries as well as to evaluate the integrity of coronary microvascular circulation, non–invasively. Several studies have validated the feasibility of this method in evaluating CFR in the middle to distal portion of the left anterior descending artery (LAD).[8] Britten et al have suggested that the presence of CFR in normal to mildly diseased arteries is an independent predictor for the development of atherosclerosis within the next decade.[9]

Transthoracic CFR correlated significantly with well–established noninvasive predictors of atherosclerosis, and Gulu et al suggest that it can be used as a surrogate for coronary atherosclerosis.[10] Our hypothesis in the study was that, given the role of PE in the development of several cardiovascular complications, it might also lead to coronary microvascular dysfunction as well as to thicker carotid intima–media thickness (IMT). Our goal in this study was to determine, excluding coronary risk factors, whether CFR and IMT are impaired in patients with PE.

## Methods

### *Study Population*

All subjects met the inclusion and exclusion criteria and were recruited from patients who delivered in Baskent University Obstetrics Clinic.

### *Inclusion Criteria*

The study included 46 patients between the ages of 18 and 40 years of age who had had PE at least 5 years before. The control group included otherwise having gestational hypertension 38 healthy parous women who came to Baskent University Obstetrics and Gynecology Department in the same age group, with similar body mass index (BMI) and with normal blood pressure (BP) both during their daily lives and in their past pregnancies. These women were recruited and studied between 2009 and 2013. Mild preeclampsia was diagnosed as having a BP of 140/90 mm Hg or higher and with proteinuria of 0.3 to 3 g/d. The study excluded patients and controls with renal or any systemic disease, smokers, those with thyroid dysfunction, chronic alcohol users (>50 g/d), pre–existing cardiovascular disease, those who were current and recent smokers, those that were still breastfeeding, and finally, those who had undergone a heavy case of PE (pronounced increase in BP [systolic BP $\geq$160 mm Hg and/or diastolic BP $\geq$110 mm Hg] and/or massive proteinuria [$\geq$5000 mg/24 h]), including the HELLP (Hemolyse Elevated Liver Enzymes Low Platelets) syndrome.[11] Our study originally included 66 patients with PE. Because of the consideration that smoking could impair the CFR and confound the results, current and recent smokers (12 subjects in all) were excluded from the study. An additional eight subjects were excluded on account of their pre–existing heart disease The necessary measurements were made in the 46 remaining patients with PE who met the criteria of the study. The study was carried out in accordance with the Declaration of Helsinki and fulfilled as a single center study in Baskent University Obstetrics and Gynocology Clinic. Informed consent of all the participants was received beforehand, and the institutional ethics committee approved the study protocol (KA09/372).

The age, gender, and BMI data were recorded. Similarly, serum transaminase enzyme, serum bilirubin, serum uric acid, fasting blood glucose, total cholesterol, high–density lipoprotein (HDL) cholesterol, low–density lipoprotein (LDL) cholesterol, and triglyceride levels were measured using original kits, by the help of Abbott-Aeroset autoanalyzer (Chicago, IL, USA). The plasma levels of high–sensitivity C–reactive protein (hs–CRP) were measured using a highly sensitive sandwich enzyme–linked immunosorbent assay (ELISA) technique, by the help of Abbott-Aeroset autoanalyzer (Chicago, IL, USA).

### *Echocardiographic Examination*

An Acuson Sequoia C256 Echocardiography System, which was equipped with a 3V2c broadband transducer with second harmonic capability (Acuson, Mountain View, CA, USA), was used to examine each subject. Each subject assumed the lateral decubitus position to undergo two-dimensional, M-mode, and Doppler echocardiographic examinations. The echocardiographic images thus obtained were recorded on VHS videotapes. The pulsed Doppler sample volume was positioned over the mitral leaflet tips. Transmitral Doppler visualization was used to measure early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), E/A ratio, and E–wave deceleration time (DT). The resulting velocities were measured for the duration of 5–10 cardiac cycles, at a sweep speed of 100 mm/s. All the diastolic parameters were measured in three consecutive cardiac cycles, and the average of these measurements was calculated. An investigator blinded for the clinical data performed the echocardiography, while two cardiologists blinded for the data of the subjects analyzed the echocardiogram recordings.

### *CFR Measurement*

An Acuson Sequoia C256 Echocardiography System (Acuson Corp), equipped with a high–resolution transducer with second harmonic capability (5V2c), was used to perform transthoracic second harmonic Doppler echocardiography examination on each subject. A high–frequency, 5–7 MHz probe was used for the visualization of the LAD distal cross-section. The Nyquist limit was set to 0.16–0.50 m/sn in color Doppler imaging. After the vein was visualized using color Doppler imaging, pulse wave