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Microcirculatory blood flow derangements during severe preeclampsia and HELLP syndrome

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ABSTRACT

Objective: To evaluate the microcirculatory blood flow in severe preeclampsia and compare it with healthy pregnant and non-pregnant women controls, using a portable intravital-microscopy technique.
Methods: Using a side-stream dark field (SDF) device, we prospectively evaluated the sublingual microcirculatory blood flow before placental delivery in 40 women with severe preeclampsia (PE-group) complicated (n = 8) or not (n = 32) with HELLP syndrome, 40 healthy pregnant women (HP-group) matched by gestational and chronological age, and 20 healthy non-pregnant women (NP-group). Microvessels were classified as large or small using a cutoff value of 20 μm and those with continuous flow were considered as normal while sluggish, intermittent and stopped flows were considered as abnormal. We computed the proportion of well-perfused small vessels (PPV), and total and functional capillary densities (TCD and FCD) were calculated according to the total number and quantity of well-perfused small vessels per area unit, respectively.
Results: Total capillary densities were significantly higher in all pregnant women when compared to non-pregnant controls. The PE-group exhibited, however, significantly lower TCD compared with the HP-group. Meanwhile, significant decreases in PPV and FCD were observed in the PE-group, with deeper alterations in those with coexisting HELLP syndrome. These altered PPVs were significant although incompletely reversed after placental delivery in pregnancies complicated by HELLP syndrome, while capillary densities remained unaltered at least during very early post-delivery period.
Conclusions: Substantial distributive microcirculatory blood flow alterations and restricted capillary densities are observed in preeclampsia, suggesting a key role for microvascular dysfunction in the pathophysiology of this condition.

1. Introduction

Preeclampsia remains a leading cause of maternal mortality and a major contributor to maternal and perinatal morbidity in both developed and emerging countries [1–3]. A myriad of immunological, genetic, behavioral and environmental factors have been implicated in its pathogenesis [4], although generalized endothelial cell and microvascular dysfunction seem to underlie the pathological manifestations leading to major cardiovascular derangements [5,6]. In fact, the reduction of peripheral tissue blood flow preceding the onset of clinical preeclampsia [7–10] advocates for the key role of microvascular dysfunction as a common pathway for multiple pathophysiological mechanisms.

In normal conditions, tissue oxygenation is determined by diffusive and convective components of microcirculation and these in turn, are determined by the capillary density and the microvascular blood flow itself, respectively. These physiological components of the microcirculation are responsible for fine-tuning

Abbreviations: SDF, side-stream dark field; PE-group, preeclampsia group; HP-group, healthy pregnant group; NP-group, non- pregnant group; PPV, percentage of small-vessels perfused; TCD, total capillary density; FCD, functional capillary density; HI, heterogeneity index; MFI, microvascular flow index; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count syndrome.

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perfusion to meet local metabolic requirements and might contribute to the development of multiorgan dysfunction when altered. Exploring microcirculation had been restricted to the experimental laboratory until the advent of new imaging techniques capable of evaluating microcirculatory blood flow at the bedside [11]. Data from critically ill patients during the last decade suggest that microcirculatory alterations play a decisive role in the development of multiorgan failure, independently of macrohemodynamic parameters [12–14], but information about microvascular changes during preeclampsia remain partially unknown [9,10]. Microcirculatory dysfunction in preeclampsia has been suggested by a decrease in arteriolar and venular calibers of retinal vessels via fundus photography [15–17] and reduced capillary density as shown by cutaneous intravital microscopy [9,10]. These alterations precede the onset of clinical manifestations, thus reinforcing the possible role of microvascular dysfunction and abnormal microvascular development. Unfortunately, most of these observations were restricted to microvascular beds highly influenced by environmental factors and macrohemodynamic changes [9,10].

Recently, a small-size study by Cornette et al. [18] evaluated microcirculation in preeclamptic patients using a portable imaging technique. They did not find significant microvascular density abnormalities, challenging previous observations by intravital microscopy [9,10], although they observed significant microcirculatory flow distribution abnormalities in preeclamptic pregnancies complicated with HELLP syndrome. Thus, it is not clear if these observations confirm the absence of microcirculatory blood flow alterations during severe preeclampsia without HELLP syndrome, whether these are product of an underpowered observation, or whether these simply denote the inherent limitations of the imaging technique.

Pathophysiological mechanisms associated with preeclampsia are not completely understood and despite some microcirculatory abnormalities that have been described in the past, there is little information about diffusive and convective alterations during clinically established preeclampsia. Thus, we aim to explore microcirculation by direct visualization in women with preeclampsia with and without HELLP syndrome, comparing them with healthy pregnant and non-pregnant groups of women, hypothesizing that preeclampsia is associated with significant microvascular density and blood flow distribution alterations.

2. Materials and methods

We conducted a prospective observational study in a 20-bed high-dependency obstetric unit and the antenatal consultation clinic in a University Hospital (Fundación Valle del Lili. Cali, Colombia). Our institutional Ethics and Biomedical Research Committee approved this study (Protocol number: 627; Chart number: 037; 2.013. Renewal No. 072–2.015). An informed consent was obtained from all the pregnant participants. Sublingual microcirculation was explored in three groups: (a) pregnant women complicated by severe preeclampsia with (or without) HELLP syndrome: PE-group; (b) healthy pregnant women matched by gestational and chronological age: HP-group; (c) healthy non-pregnant women: NP-group.

Preeclampsia was defined as a new onset of blood pressure >140/90 mm Hg on two separate opportunities at least 4 h apart accompanied by proteinuria $\geq$300 mg/24 h, or $\geq$2+ on urine dipstick, or urinary protein to creatinine ratio >30 mg/mmol [19]. Severe preeclampsia was defined as severe hypertension (systolic pressure >160 and/or diastolic pressure >110 mm Hg), and/or symptoms (epigastric/right upper quadrant pain, cerebral or visual disturbances, pulmonary edema), and/or with biochemical, and/or hematological impairment [19]. HELLP syndrome was defined as the presence of hemolysis based on examination of a peripheral blood smear and/or elevated lactate dehydrogenase (LDH $\geq$ 600 U/L), associated with elevated liver enzymes (aspartate aminotransferase, AST $\geq$ 70 U/l), or thrombocytopenia (platelets count <100,000/mm^3) after ruling out other causes of hemolysis and thrombocytopenia [20].

A healthy pregnancy was determined by comprehensive examination and laboratory testing according to the attending obstetrician criteria during the antenatal clinical consultation. Pregnant women with chronic or suspected chronic hypertensive disorders were not included in the study. A two-weeks postpartum follow-up was carried out in healthy pregnant controls in order to discard the development of preeclampsia after inclusion. Healthy non-pregnant volunteers were women in childbearing age with no hypertension and/or no antecedents of hypertensive disorders.

2.1. Study protocol

During a ten-month period (July 2013–April 2014), all patients with pregnant hypertensive disorders were screened and evaluated by two independent evaluators (M.F.E., and J.C.). After obtaining written informed consent from each pregnant participant, patients fulfilling the criteria for severe preeclampsia (PE-group) were enrolled, while healthy pregnant women were weekly searched at the antenatal consultation clinic and selected according to each preeclamptic case included, matching them by gestational and chronological age (HP-group). Finally, twenty healthy women volunteers, usually health workers from the intensive care unit and the obstetric high-dependency unit served as non-pregnant age-matched controls (NP-group).

Patients with preeclampsia were managed according to international guidelines [19]. All hemodynamic measurements were performed at lateral decubitus in resting conditions and maintaining a fasting period at least of 120 min. In all cases, arterial pressure recorded before placental delivery was obtained by sphygmomanometry, while in some post-placental delivery measurements, invasive pressure by intra-arterial cannula (radial artery) was registered. Sublingual microcirculation was explored using the Sidestream dark-field (SDF) imaging device before placental delivery in both PE and HP groups. In PE-group, images were recorded at the most severe point of the disease (usually, at the peak of hypertension or when clinical deterioration or symptoms impairment were detected). A new set of images was obtained within 12 h of delivery in those patients whose pregnancy was ended or 48 h after the first set of measurements when a delayed delivery was planned (according to the decision of the attending physician). General demographics, laboratory parameters, and cumulative magnesium sulphate doses at inclusion were also recorded.

2.2. Microcirculation measurements

We used a Sidestream dark-field (SDF) imaging device (Micro Scan; MicroVision Medical, Amsterdam, the Netherlands) to explore microcirculation in the PE, HP and NP groups. This portable video-microscope device uses a stroboscopic green light (around 530 nm wavelength), which is delivered to the tissues by multiple light-emitting diodes (LEDs). This wavelength of light is absorbed by the hemoglobin of red blood cells, allowing their observation as dark cells flowing in the microcirculatory net while the light reflected by superficial layers does not reach the optics. As a result of the peripheral location of LEDs and the synchronization between the light emission and camera frame rate, SDF provides a detailed visualization of open capillaries using a 5x objective and providing an on-screen magnification of x380 [21] (Fig. 1).

After gentle removal of secretions with gauze, the SDF device was softly applied to the lateral side of the tongue covering an area

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