Evidence of impaired microvascular function in pre-eclampsia: a non-invasive study

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Abstract

The clinical presentation of pre-eclampsia suggests that microvascular dysfunction may play a role in the maternal manifestations of the disease. Isovolumetric venous pressure (PVi) is an index of microvascular function, reflecting local plasma colloid osmotic (oncotic) pressure, and is abnormal in clinical conditions with microvascular dysfunction. We hypothesized that, in pre-eclampsia, post-capillary margination of neutrophils would increase post-capillary resistance, and therefore PVi. A small cumulative step strain-gauge plethysmography protocol was used to compare PVi in 18 women with pre-eclampsia, 16 normal pregnant women and 17 non-pregnant controls. Circulating levels of vascular cell-adhesion molecule-1 (VCAM-1), intercellular cell-adhesion molecule-1 (ICAM-1) and E-selectin, and neutrophil elastase, were measured to assess endothelial and neutrophil activation respectively. PVi was significantly greater in the pre-eclampsia group, relative to the normal pregnant and non-pregnant controls (P < 0.001, ANOVA, for both comparisons). PVi was significantly lower during normal pregnancy compared with the non-pregnant controls (P = 0.001). Plasma levels of neutrophil elastase, VCAM-1, ICAM-1 and E-selectin (P = 0.001) were significantly greater in the pre-eclamptics than the controls. Significant positive correlations were observed between PVi and neutrophil elastase (r = 0.71, P = 0.001), VCAM-1 (r = 0.52, P = 0.03), ICAM-1 (r = 0.67, P = 0.002), E-selectin (r = 0.69, P = 0.001), uric acid levels (r = 0.54, P = 0.02) and haematocrit (r = 0.64, P = 0.004) in pre-eclampsia. The relationship with the platelet count was negative (r = -0.65, P = 0.003). No significant correlations were observed between PVi and maternal age, gestational age, total protein, albumin, diastolic blood pressures, age, body mass index and infant birth mass in the normal pregnant and non-pregnant controls. These data suggest that microvascular dysfunction occurs in pre-eclampsia, and that it is related to alterations in endothelial cell and neutrophil activation.

Introduction

Pre-eclampsia is a hypertensive disorder occurring in the second half of pregnancy and is a leading cause of maternal and perinatal morbidity and mortality [1]. Generalized endothelial cell dysfunction underlies all the pathological manifestations of the disease [2,3]. Central cardiovascular parameters such as cardiac index, mean...
arterial blood pressure, central venous pressure and pulmonary capillary wedge pressure are often used in the assessment of patients with pre-eclampsia. However, these parameters largely reflect whole body circulatory function. Although pre-eclampsia is associated with profound changes in the cardiovascular system, many of the key abnormalities of the cardiovascular system occur at the level of the microcirculation, where nutritive exchange between blood and tissues occurs.

The clinical picture of the disease is suggestive of impaired tissue perfusion. Indeed, we have recently reported that resting tissue blood flow is reduced in pregnancies complicated by pre-eclampsia [4], and that this change precedes the onset of the disease [5]. Since pre-eclampsia often presents as a multisystem disease, and end-organ failure is common, it suggests the presence of an underlying microvascular dysfunction. The main function of the microcirculation is the exchange of fluid, oxygen and nutrients between blood and tissue. Pre-eclampsia is associated with defective tissue supply/extraction of oxygen [6]. This leads to a base deficit secondary to anaerobic metabolism, which correlates with maternal end-organ injury and adverse fetal outcome [7]. This is further evidence that microvascular dysfunction may be the common pathway for the clinical pictures seen in pre-eclampsia. Despite this supportive clinical evidence, there have been few previous reports of changes in microvascular function in pre-eclampsia [7a].

The movement of fluid and plasma proteins between the vascular and interstitial compartments is governed by the Starling forces, which can be described by the following equation:

\[ J_i = K_i ((P_v - P_i) - \sigma (P_i - P_t)). \]

\( K_i \) is the fluid filtration capacity; \( P_v \) and \( P_i \) are the hydrostatic pressures in the capillaries and the tissue respectively; \( \sigma \) is the osmotic reflection coefficient, an index of the vascular permeability to plasma proteins; and \( P_v \) and \( P_t \) are plasma and tissue oncotic pressures respectively. \( K_i \) reflects the product of the area available for fluid filtration and the permeability per unit surface area of the microvessels in the tissue being investigated [8]. The isovolumetric venous pressure (\( P_v \)) is equivalent to the equilibrium pressure at the microvascular interface, and is the congestion pressure that has to be applied to make the value of \( P_v \) equal and opposite to the local plasma oncotic pressure, that is \( \sigma P_i \). It is an important and useful indicator of altered microvascular function [9]. \( P_v \) has been shown to be abnormal in multisystem diseases, such as septic shock [10], dengue haemorrhagic fever in children [11] and diabetes, when organ failure occurs [12]. Venous congestion strain-gauge plethysmography allows non-invasive assessment of microvascular parameters, such as microvascular \( K_i \) and \( P_v \) [13].

We postulated that the up-regulation of cell adhesion molecules by endothelial cells [14] and by activated leucocytes [15], which occurs in pre-eclampsia, would result in increased post-capillary resistance and margination of white cells and adherence to microvascular endothelium. It has been proposed that the upstream perturbations resulting from the increased post-capillary resistance would alter the local haemodynamic forces governing microvascular exchange [16], thereby, we propose, enhancing fluid filtration, and increasing \( P_v \). The aim of the present study was to investigate whether \( P_v \) is altered in pregnancies complicated by pre-eclampsia, and to see if these changes correlate with evidence of endothelial cell and neutrophil activation.

**METHODS**

**Subjects**

We used an established small cumulative step strain-gauge plethysmography protocol [17] to compare the \( P_v \) values in the calves of three groups of women. They comprised 18 women with pre-eclampsia, 16 normal pregnant controls and 17 non-pregnant controls. All of the subjects were recruited from the maternity unit of the Chelsea and Westminster Hospital. Women with pre-eclampsia were recruited from the antenatal ward, normal pregnant women from the antenatal clinic and the non-pregnant volunteers were health workers from the unit. Controls were chosen to be similar to the pre-eclamptic group with regard to the latter’s booking body mass index (BMI) and, in the pregnant controls, gestational age. All the women were nulliparous, non-smokers and were not on any medication. None of the subjects received any intravenous infusion before or during the study. Women with a previous or current history of peripheral vascular disease, peripheral neuropathy or any other underlying medical disorders were excluded from the study.

Pre-eclampsia was defined according to the criteria of hypertension, proteinuria and the reversal of both after the pregnancy. Hypertension was defined as an absolute blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic, taken twice, 6 h apart. The first and fifth Korotkoff sounds were used to determine the systolic and diastolic components respectively. Proteinuria was defined as more than 0.5 g/l urinary protein excretion over 24 h [18]. The 24-h urine specimens were collected into plastic jugs containing phenyl mercuric acetate as preservative, and protein was measured by colorimeric reaction using an autoanalyser, as described by Watanabe et al. [19]. The obstetric records of all pregnant women were reviewed after delivery to confirm reversal of hypertension and proteinuria. The local ethics
committee approved the study and informed consent was obtained from each participant.

**Equipment and study protocol**

Microvascular parameters were measured using the Filtrass strain-gauge plethysmograph (Filtrass; DOMED, Munich, Germany) [20]. This system is based on the standard strain-gauge plethysmography procedure described by Gamble et al. [21]. The measuring device is mercury free with an integrated automatic calibration system that allows touch-free calibration, thus reducing artefacts due to investigator manipulation. The sensor is calibrated automatically in triplicate, by a computer-driven program at the start of each study. The relative merits of the Filtrass over the standard strain gauge in terms of the quality of calibration and reproducibility have been validated previously [21]. The Filtrass program is computer-assisted and allows the selection of pre-recorded protocols for measuring blood flow and other microvascular parameters, such as $K_f$ and $P_{Vi}$.

The study was performed in a quiet, temperature-controlled room ($23–24 \, ^\circ \text{C}$). Subjects rested for at least 30 min before the study. Observations were made in the left lateral position, to prevent aorto-caval compression, and with the right mid-calf supported at the level of the heart. Arterial blood pressure was measured non-invasively in the ipsi-lateral calf and arm, using a Dinamap Vital Sign Monitor (Type 1800; Critikon, Tampa, FL, U.S.A.). The average values of systolic, diastolic and mean arterial blood pressures were calculated from triplicate measurements.

Microvascular parameters were measured using an established small cumulative venous congestion strain-gauge plethysmography protocol [9]. Briefly, the congestion pressure cuff, attached to a compressor pump built into the apparatus, was placed around the right thigh and enclosed in a rigid corset, to reduce filling volume and thus filling time. Changes in calf circumference in response to a rapid increase in cuff pressure were measured using a passive inductive transducer with an accuracy of $\pm 5 \, \mu \text{m}$. The protocol involved the application of a series of five-to-seven small (8–10 mmHg) cumulative congestion pressure [venous congestion pressure (VCP)] steps, each of 5 min duration. The maximum pressure used never exceeded the subject’s own diastolic pressure. VCPs in excess of the ambient venous pressure cause a change in limb volume, attributable to venous filling. At higher congestion cuff pressures, a slow steady-state volume change also occurs, reflecting fluid filtration (Figure 1a). The analysis procedure used enables differentiation between venous filling and filtration responses [17]. The fluid filtration at each pressure was plotted against the corresponding congestion pressure. The slope of the regression line represents fluid $K_f$ and the intercept of the slope on the cuff pressure axis represents $P_{Vi}$ (Figure 1b). $P_{Vi}$

<table>
<thead>
<tr>
<th>Figure 1</th>
<th>Stages in the analysis of data recordings</th>
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<tr>
<td>(a) Volume response (upper trace) to a step increase in VCP (lower trace). In the upper trace, the complete volume response is depicted by the upper curve. A steady-state volume change ($J_v$) is achieved about 90 s after the increase in VCP. After subtraction of the $J_v$ slope from the whole volume change record, the lower curvilinear response is obtained, which shows a steady-state volume ($V_a$), depicting the vascular compliance at that VCP. (b) Relationship between VCP and $J_v$ in a single study. The regression slope ($K_f$) is derived from the values depicted by the closed circles. The intercept on the obliqua-x axis reflects the value ($P_{Vi}$) that has to be exceeded in order to achieve net fluid filtration. (c) Relationship between VCP and the equilibrium volume ($V_e$). Curvilinear extrapolation of this slope to the abscissa gives an index of calf venous pressure ($P_v$); this is the value which has to be exceeded in order to induce a net change in volume.</td>
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</table>
is the congestion pressure that has to be exceeded to induce net fluid filtration at the level of the strain gauge [17]. The relationship between vascular filling ($V_v$) and VCP is curvilinear and the intercept on the abscissa reflects the calf venous pressure (Figure 1c) [22]. The recorded files were saved for subsequent ‘off-line’ analysis.

Biochemical assays

To investigate the relationship between $P_{V_i}$ and indices of neutrophil and endothelial cell activation, blood samples were obtained to assay circulating levels of neutrophil elastase [23], as a marker of neutrophil activation, and soluble cell adhesion molecules as markers of endothelial activation [24]. The cell adhesion molecules measured were E-selectin, vascular cell-adhesion molecule-1 (VCAM-1) and intercellular cell-adhesion molecule-1 (ICAM-1) [14]. The samples were centrifuged for 10 min at 6420 g and 4 °C, and the plasma was separated and stored at −70 °C until assayed. Neutrophil elastase was assayed using a commercial kit (1.12589 PMN Elastase, obtained from Merck, Darmstadt, Germany). This is a heterogeneous commercial kit (1.12589 PMN Elastase, obtained from Merck, Darmstadt, Germany). This is a heterogeneous enzyme immunoassay for the specific determination of human PMN elastase from polymorphonuclear leukocytes in complex with α-proteinase inhibitor in plasma [25]. The cell adhesion molecule assays were done in duplicate using a quantitative sandwich enzyme technique (R & D Systems, Minneapolis, MN, U.S.A.). Monoclonal antibodies specific to human soluble ICAM-1, VCAM-1 and E-selectin were used. Full blood count, plasma albumin, total protein, uric acid and creatinine concentrations were also measured using an autoanalyser.

Statistical analysis

All the normally distributed data are presented as the means±S.D. Statistical differences between the groups were compared using analysis of variance with Bonferroni correction for multiple comparisons. The relationships between $P_{V_i}$ and the clinical parameters, markers of neutrophil and endothelial cell activation were determined using Pearson correlation coefficients. Multiple regression analysis was performed to determine which of the parameters were independently related to $P_{V_i}$ and to assess associations between blood flow and measured clinical and biochemical variables. Statistical significance was assumed at a $P$ value less than 0.05. The Statistical Package for Social Sciences (SPSS, version 10) was used for these analyses.

RESULTS

The clinical and demographic characteristics for the three groups are shown in Table 1. There were no significant differences in maternal age or booking BMI between the three groups or in gestational age between the two pregnant groups. Babies born to the normal pregnant and pre-eclamptic groups were similar in mass ($P = 0.12$). Women with pre-eclampsia had higher systolic and diastolic blood pressures ($P < 0.001$), serum uric acid levels ($P < 0.001$) and lower platelet counts ($P = 0.001$) than the pregnant control group. Plasma albumin concentrations were significantly lower in the pregnant groups compared with the non-pregnant controls, the concentrations being lower in pre-eclampsia compared with normal pregnancy ($P = 0.01$). Total plasma total proteins were similar in the three groups ($P = 0.61$) (Table 1). Haematocrit was significantly increased in the pre-eclampsia compared with the controls ($P = 0.001$) (Table 1).

$P_{V_i}$ values were significantly higher in the pre-eclampsia group compared with the normal pregnant and non-pregnant controls ($22.35 ± 9.1, 9.29 ± 0.7$ and $15.47 ± 0.6$ mmHg respectively; $P < 0.001$, ANOVA for both comparisons). In contrast, $P_{V_i}$ values were significantly lower in the normal pregnant women compared with the non-pregnant controls ($P = 0.001$; Figure 2). Microvascular $K_v$, measured as ml/min/mmHg (defined as $K_v$ units ($K_v$U)), was also significantly increased in pre-eclampsia ($6.4 ± 1.2 K_v$U), compared with the normal pregnant and non-pregnant controls ($4.5 ± 0.7$ and $3.1 ± 0.59 K_v$U respectively; $P < 0.001$, ANOVA with Bonferroni correction). Circulating levels of VCAM-1, ICAM-1, E-selectin and neutrophil elastase were significantly greater in the women with pre-eclampsia when compared with the controls ($P < 0.001$; Table 1). There was no significant correlation between gestational age and $P_{V_i}$ values in all three groups of women. Moreover, there was no significant correlation between the values of $K_v$ and $P_{V_i}$ in any of the groups ($r = 0.04$, $P = 0.85$; $r = 0.08$, $P = 0.74$; and $r = 0.01$, $P = 0.84$ for pre-eclampsia, normal pregnancy and non-pregnant controls respectively; Figure 3).

There were significant positive correlations between $P_{V_i}$ and neutrophil elastase, ($r = 0.71$, $P = 0.001$), VCAM-1, ($r = 0.52$, $P = 0.03$), ICAM-1 ($r = 0.67$, $P = 0.002$) and E-selectin ($r = 0.69$, $P = 0.001$) in the pre-eclampsia group (Figures 4a–4d). However, no significant relationships were observed between $P_{V_i}$ and either the clinical and haematological parameters, or the markers of neutrophil and endothelial cell activation in the normal pregnant and non-pregnant controls. Significant positive correlations were also found between $P_{V_i}$ and both uric acid levels ($r = 0.54$, $P = 0.02$) and haematocrit ($r = 0.64$, $P = 0.004$). Platelet count was inversely related to $P_{V_i}$ ($r = 0.65$, $P = 0.003$). In contrast, no significant relationships were observed between $P_{V_i}$ and total protein ($r = 0.44$, $P = 0.08$), albumin ($r = 0.33$, $P = 0.17$), systolic and diastolic blood pressures ($r = 0.23$, $P = 0.35$ and $r = 0.14$, $P = 0.59$).
Table 1  Clinical and biochemical parameters for the three groups of women
Values are expressed as the means ± S.D.; P values < 0.05 were considered statistically significant (ANOVA with Bonferroni correction). N/A, not applicable.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-pregnant controls (n = 17)</th>
<th>Normal pregnant (n = 16)</th>
<th>Pre-eclampsia (n = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.5 ± 1.0</td>
<td>29.4 ± 1.5</td>
<td>28.3 ± 1.1</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 1.6</td>
<td>23.7 ± 0.9</td>
<td>24.4 ± 0.8</td>
<td>0.57</td>
</tr>
<tr>
<td>Parity</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>N/A</td>
<td>35.5 ± 0.4</td>
<td>35.8 ± 0.5</td>
<td>0.88</td>
</tr>
<tr>
<td>Birth mass (kg)</td>
<td>N/A</td>
<td>3.34 ± 0.56</td>
<td>2.97 ± 0.41</td>
<td>0.12</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>113/63</td>
<td>109/62</td>
<td>140/93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelet count (× 10⁶)</td>
<td>257.8 ± 11.9</td>
<td>221.1 ± 14.9</td>
<td>142.1 ± 8.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.32 ± 0.08</td>
<td>0.31 ± 0.01</td>
<td>0.35 ± 0.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Uric acid (mmol/l)</td>
<td>0.24 ± 0.1</td>
<td>0.21 ± 0.01</td>
<td>0.35 ± 0.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>74.2 ± 0.9</td>
<td>70.4 ± 1.16</td>
<td>64.1 ± 0.54</td>
<td>0.6</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>38.76 ± 1.1</td>
<td>26.5 ± 0.67</td>
<td>24.5 ± 0.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neutrophil elastase (µg/l)</td>
<td>76.5 ± 10.2</td>
<td>103.8 ± 15.7</td>
<td>216.83 ± 19.1</td>
<td>0.001</td>
</tr>
<tr>
<td>VCAM-1 (µg/l)</td>
<td>116.5 ± 13.4</td>
<td>150.8 ± 15.4</td>
<td>321.5 ± 27.2</td>
<td>0.001</td>
</tr>
<tr>
<td>ICAM-1 (µg/l)</td>
<td>174.4 ± 15.3</td>
<td>197.2 ± 18.1</td>
<td>391.1 ± 28.0</td>
<td>0.001</td>
</tr>
<tr>
<td>E-selectin (µg/l)</td>
<td>32.1 ± 3.9</td>
<td>27.7 ± 4.7</td>
<td>60.7 ± 7.4</td>
<td>0.001</td>
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</table>

DISCUSSION

The present study sought support for the hypothesis that the haemodynamic changes resulting from post-capillary margination of neutrophils, which occurs as a result of up-regulation of neutrophil and endothelial cell-adhesion molecule expression in pre-eclampsia, might correlate with the resulting increase in post-capillary resistance and therefore $P_V$, through the enhancement of fluid filtration. The results showed that $P_V$ was significantly increased during pre-eclampsia, and that these changes did correlate with markers of neutrophil and endothelial cell activation.

Whereas these data provide evidence to support the hypothesis regarding the relationships between neutrophil margination and $P_V$ in pre-eclampsia, there are other factors, which, by influencing $P_V$, could explain these observations. Firstly, the reduced maternal plasma
volume, which is a characteristic feature of pre-eclampsia, is believed to be secondary to increased microvascular permeability [26]. We have previously reported a highly significant \( P < 0.001 \) increase in permeability \( (K_f) \) in pre-eclamptic patients, relative to matched pregnant and non-pregnant controls [27]. The rise in \( K_f \) will cause an increase in protein concentration at the microvascular interface, especially in the light of the reduced blood flow rate following the increased pre-capillary resistance, which is known to occur in pre-eclampsia [4,5]. However, the lack of correlation between \( K_f \) and \( P_V \) in the present study suggests that the increased \( K_f \) is unlikely to solely explain the elevated values of \( K_f \) in pre-eclampsia. The reduced blood flow in the pre-eclamptics [4,5] is likely to enhance the interaction between the activated neutrophils and endothelial cells. The fact that protein concentration is decreased in both pregnant groups and not preferentially in the pre-eclamptics may be taken to imply that a decrease in the osmotic reflection coefficient \( (\sigma) \) does not accompany the increase in \( K_f \). Moreover, since the level of pitting oedema was similar in both groups of pregnant women, it seems unlikely that there were differences in the interstitial values of either oncotic or hydrostatic pressure. While this suggestion is at variance with the observations of Oian et al. [7a], the differences may reflect the levels of severity of pre-eclampsia in the two studies and the fact that the interstitial measurements in [7a] reflected changes in the subcutis of the ankle, not the interstitium of skeletal muscle. Furthermore, the increase in the values of \( K_f \) and \( P_V \) in the pre-eclamptic group may imply an up-regulation of the rate of lymphatic drainage in this group, thereby minimizing interstitial fluid retention, despite the increase in \( K_f \) [28]. In addition, the observation of a significant correlation between \( P_V \) and plasma uric acid levels suggests that \( P_V \) might provide an index of the severity of pre-eclampsia. However, it should be noted that the clinical utility of uric acid concentration, as an index of the severity of pre-eclampsia, is not universally accepted [29].

The haemodynamic consequence of post-capillary margination of neutrophils, which occurs preferentially, although not exclusively, on the venular endothelium [30], is an increase in post-capillary resistance [31]. The increased resistance raises local microvascular hydrostatic pressure further reducing the blood flow in the upstream capillary bed. This is consistent with our previous

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**Figure 4** Relationships between \( P_V \) and plasma concentrations of (a) neutrophil elastase, (b) VCAM-1, (c) ICAM-1 and (d) E-selectin in non-pregnant controls (▼), normal pregnant women (○) and pre-eclamptics (●). mg = μg.
observation that resting blood flow is reduced in pre-eclampsia [4]. Moreover, these changes precede the onset of the disease [5]. The combination of a reduction in microvascular blood flow and an increased intravascular pressure would increase $P_V$, by enhancing filtration of water from the microvessels, giving rise to an increase in local oncotic pressure [9,32].

The possibility of a causal relationship between post-capillary margination of neutrophils and $P_V$ was first investigated in man by studying the effects of cigarette smoke inhalation with, and then without, prophylactic vitamin C administration. The human studies were based on observations in an animal model that showed that cigarette smoke exposure caused a marked increase in post-capillary white-cell margination, which could be prevented by prior treatment with vitamin C [33]. In the human studies, smoking a single cigarette caused a highly significant increase in $P_V$. Moreover, this increase could be blocked by the prophylactic administration of vitamin C [34]. This inhibition of neutrophil margination by vitamin C may help to explain the observation that the prophylactic administration of vitamins C and E significantly reduced the risk of pre-eclampsia [35].

Although neutrophil–endothelial cell interaction may be an important factor in the haemodynamic changes at the microvascular interface, other rheological factors may also play a role in increasing post-capillary resistance in pre-eclampsia. The observation of a significant direct correlation between $P_V$ and haematocrit and an inverse relationship with platelet count are certainly consistent with this idea. Moreover, platelet aggregation and post-capillary microthrombi formation could certainly contribute to increased post-capillary resistance. In the present study, it was noted that both $P_V$ and total plasma protein concentration fell during normal pregnancy compared with the non-pregnant controls. This observation is compatible with the notion that $P_V$ reflects the pressure required to overcome the plasma oncotic pressure. We observed that $P_V$ increased in the pre-eclampsics, despite the fact that their total protein concentrations were similar to those in the pregnant controls. We believe that this reflects a change in the equilibrium oncotic pressure at the microvascular interface, rather than the systemic value [9,34]. We suggest that the increased $P_V$ in pregnancies complicated by pre-eclampsia reflects impaired nutritive exchange at the microvascular interface. Such an explanation is compatible with the multisystem manifestations of this disease and also the end organ failure, which occurs in the most severe cases. Although we have used maternal circulating levels of neutrophil elastase as a marker of neutrophil activation, this may not be as specific as cellular expression of adhesion molecules, such as CD11b/18 [15]. We are currently investigating the relationship between $P_V$ and the $\beta_2$-integrins CD11a/18, CD11b/18 and CD11c/18.

In summary, our data support the hypothesis that an increase in $P_V$ occurs in pre-eclampsia and that this is related to neutrophil and endothelial cell activation. If the changes in $P_V$ can be shown to precede the clinical onset of the disease, then its measurement may provide a test for the early detection of the disease.

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REFERENCES


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