Pre-eclampsia and the microcirculation: a novel explanation

Pre-eclamptic toxaemia (pre-eclampsia or PET) is the leading cause of maternal morbidity and mortality in the U.K. It results from failure of the maternal vasculature to effectively invade the trophoblast in the placenta and this subsequently causes placental under-perfusion. It has been proposed that circulating factors released from the placenta result in widespread endothelial dysfunction, leading to a spectrum of clinical manifestations, including hypertension, proteinuria, peripheral and cerebral oedema and infarction, eclampsia (seizures), pulmonary oedema, liver haemorrhage, renal failure and coagulopathy. Many of these symptoms can be attributed directly or indirectly to alterations in peripheral vascular resistance in these patients. This peripheral vascular resistance depends not only on the tone of the arterioles, but also on post-capillary resistance provided by the venular system. An increase in pre-capillary (arteriolar) resistance leads to hypertension, but reduced capillary pressure. An increase in post-capillary (venular) resistance on the other hand leads to hypertension, but also increased capillary pressure and, hence, can lead to oedema. It has been known for some time that pre-eclampsia is associated with both hypertension and peripheral oedema, and the latter has been attributed to increased permeability of capillaries due to some unknown circulating factor. Although a number of candidate molecules have been suggested, including vascular endothelial growth factor (VEGF), none have been clearly demonstrated to cause the endothelial dysfunction seen in pre-eclampsia, and the permeability coefficients (diffusive solute permeability, hydraulic conductivity and oncotic reflection coefficient) have never been measured in pre-eclampsia.

In this issue of Clinical Science, Anim-Nyame and co-workers [1] provide evidence that one of the microvascular disturbances seen in pre-eclampsia is an increase in post-capillary resistance without any evidence for a change in oncotic reflection coefficient, a measure of the permeability of blood vessel walls to protein. Furthermore, they have shown that the degree of increased post-capillary resistance is associated with increased circulating factors that are characteristically released by leucocytes when they stick to vessel walls. They have suggested that in pre-eclampsia there is an increase in adherent leucocytes, resulting in a partial occlusion of the 20–30 μm diameter post-capillary venules. This increases post-capillary resistance, microvascular pressure and, hence, filtration of fluid into the tissues. They have estimated post-capillary resistance by measuring the isogravimetric venous pressure (Pv), the minimum pressure required by a cuff to cause filtration of fluid from the microcirculation into the interstitium in a limb. Pv is an indirect measurement of the pressure required to overcome the colloid osmotic (or oncotic) pressure difference between the microcirculatory plasma and the surrounding tissue. When fluid is filtered across the blood vessel wall, the oncotic pressure in the microvasculature increases, and that in the interstitium decreases. This results in an increased colloid osmotic pressure difference between blood and tissue. As long as the reflection coefficient does not fall (i.e. as long as the protein permeability does not increase), a higher filtration rate will be measured as an increase in Pv. This higher filtration rate may be brought about either by an increased post-capillary resistance (and hence higher capillary pressure) or by an increase in the hydraulic conductivity of the vessels (i.e. how easily the vessels allow water to be driven across them by a pressure gradient). Anim-Nyame et al. [1] detected an increase in Pv in pre-eclampsia. There are three explanations for this finding: increased post-capillary resistance, increased water permeability or a combination of the two. Interestingly, they also detected a small increase in the capillary filtration coefficient (Kf), which is a product of the surface area available for exchange and the hydraulic conductivity of the vascular bed. It is known that the venous end of a blood vessel has a higher hydraulic conductivity than the arterial end. An increase in post-capillary resistance would increase the pressure in the venous end more than the arterial end of the capillary, since the microcirculation itself has a resistance to fluid flow, so this finding would also be explained by an increase in post-capillary resistance. Circulating levels of VEGF are increased in pre-eclampsia [2], and VEGF has also been shown to increase hydraulic conductivity without altering the oncotic reflection coefficient [3]. Their finding that the increase in Pv is correlated with increased circulating leucocyte markers is intriguing in that it suggests that this increase in Pv is associated with leucocytes plugging up the venous end of the microcirculation. It has recently been shown [4] that antioxidants, such as vitamin E or vitamin C, can reduce the risk of pre-eclampsia, and also that they reduce leucocyte adherence and margination to the venous circulation. Taken together, it is tempting to speculate that pre-eclampsia may be a result of activation of leucocytes, again due to some unidentified circulating factor, or as they pass into the venous side of the placental circulation. This would result in adherence or margination of the...
leucocytes when they next encounter the microcirculation (which would account for the increased likelihood of pulmonary oedema in pre-eclamptic patients for example). This margination would result in increased post-capillary resistance, increased capillary pressure, reduced blood flow, oedema and infarction. However, the evidence for this hypothesis is still somewhat circumstantial. In particular, a correlation between circulating markers and increased $P_{vi}$ does not prove a causal link between leucocyte margination and increased post-capillary resistance in pre-eclampsia. It could be that the increase in $P_{vi}$ results in the increase margination and activation of leucocytes. It is known that leucocytes adhere more easily to the vessel wall under conditions of reduced shear stress, which would be the case with increased post-capillary resistance, i.e. the flow would be sluggish. Furthermore, increased circulating levels of VEGF could account for both the increased $K_f$ and $P_{vi}$ by increasing hydraulic conductivity without changing reflection coefficient, even in the absence of increased post-capillary resistance. Although activation of leucocytes in pre-eclampsia has previously been shown by a number of investigators, this is the first time that a potential mechanism has been proposed for how leucocyte activation may result in the microvascular disturbances that underlie the clinical sequelae of pre-eclamptic toxemia.

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REFERENCES