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Endothelin-1: a central factor in both preeclampsia and VEGF inhibition-induced hypertension

Preeclampsia (PE) is the most frequently encountered medical complication during pregnancy. It is characterized by a rise in systemic vascular resistance with a relatively low cardiac output and hypovolemia, combined with severe proteinuria. Despite the hypovolemia, renin-angiotensin system (RAS) activity is suppressed and aldosterone levels are decreased to the same degree as renin. This suggests that the RAS is not the cause of the hypertension in preeclampsia, but rather that its suppression is the consequence of the rise in blood pressure. Abnormal placentation early in pregnancy is widely assumed to be an important initial event in the onset of preeclampsia. Eventually, this results in the release of anti-angiogenic factors (in particular soluble Fms-like tyrosine kinase 1 or sFlt-1) and cytokines, leading to generalized vascular dysfunction. Elevated sFlt-1 levels bind and inactivate vascular endothelial growth factor (VEGF). Of interest, VEGF inhibition with drugs like sunitinib, applied in cancer patients, results in a preeclampsia-like syndrome, characterized by hypertension, proteinuria and renal toxicity. Both in cancer patients treated with sunitinib and in pregnant women with preeclampsia, significant rises in endothelin-1 occur. Multiple regression analysis revealed that endothelin-1 is an independent determinant of the hypertension and proteinuria in preeclampsia, and additionally a renin-suppressor. Moreover, studies in animal models representative of preeclampsia, have shown that endothelin receptor blockers prevent the development of this disease. Similarly, endothelin receptor blockers are protective during sunitinib treatment. Taken together, activation of the endothelin system emerges as an important pathway causing the clinical manifestations of preeclampsia. This talk will critically address this concept, taking into consideration both clinical and preclinical data. It will also discuss why sunitinib-induced hypertension is salt-sensitive, taking into consideration that VEGF is required for salt buffering in the skin.