



## Issues in the interpretation of serum endothelin levels in preeclampsia

Charles G. Coffey

PO Box 368, Golconda, IL 62938, United States



### ABSTRACT

In this paper are discussed reasons to suspect that measurements of serum endothelin levels in women with preeclampsia may not provide accurate estimations of the degree of systemic endothelin receptor activation and reasons to suspect that systemic endothelin receptor saturation studies should provide such estimations more accurately.

### Introduction

Not long after the discovery of endothelin [1,2], several studies demonstrated that serum levels of this substance were significantly elevated in women who had preeclampsia [3–6]. Additional further research on endothelin (much of it done without regard to preeclampsia) has demonstrated that interaction of the substance with its receptors in endothelial cells and in hepatocytes is capable of giving rise to many of the aberrancies known to occur in preeclampsia [7], from the classic triad of hypertension, proteinuria, and edema [8,9] to hyperuricemia and hypertriglyceridemia [10]. As such, endothelin has been suspected of playing a significant role in the pathogenesis of preeclampsia [11–18]. In this paper are discussed reasons to suspect that measurements of serum levels of endothelin in women with preeclampsia may be inadequate to assess the extent of maternal systemic endothelin receptor activation.

### Hypothesis

Usually when serum levels of a substance are measured, the blood samples are drawn from the antecubital veins. For most substances it can be expected that blood in almost any vessels in the body will have similar levels of the particular substance, so from which vessel to draw the blood is mainly a matter of convenience. In the case of measuring serum endothelin levels in preeclampsia, however, serum levels of blood drawn from the antecubital veins may represent something of a nadir for the following reasons: in patients with preeclampsia the source of additional systemic endothelin is likely from the placenta. Therefore, it would be expected to enter the maternal circulation almost entirely through the uterine veins. Given such a suspected single anatomic source for the additional systemic endothelin in the maternal circulation, it would be expected that serum levels would gradually drop as the blood travels from the uterine veins to the antecubital veins.

This would occur as a result of both dilution and attrition.

Dilution would occur as blood from the uterine veins enters larger vessels. Significant points of dilution would be where the uterine veins meet the portal vein, where the hepatic vein meets the inferior vena cava, and where the inferior vena cava meets the right ventricle.

Attrition would occur all along the movement of blood from the uterine veins to the antecubital veins, as endothelin receptors are present throughout the endothelium (and also on hepatocytes). Therefore, it would be expected that serum levels would drop by attrition as the blood progresses from the uterine veins to more distant points in the circulatory system. This attrition would be especially pronounced at the capillary level due to the greater surface area of the endothelium relative to blood volume. The endothelin molecules entering maternal circulation from the uterine veins would have to pass sequentially through three capillary systems (hepatic sinusoidal system, pulmonary alveoli, and the systemic capillary system) before any would reach the antecubital veins [19].

Another issue is that endothelin is different from most other blood borne substances, in that it is a paracrine factor.

Paracrine factors are substances which are released by the source cell to act upon receptors in adjacent cells (as opposed to endocrine factors, which act upon receptors in cells distant from the source cells) and thus would generally travel distances of microns to millimeters - not meters, from their source cells. Given that endothelin receptors are present throughout the circulatory system, that a significant number of endothelin molecules are consistently traveling all on the way from the uterine veins to the antecubital veins despite these dilutional and attritional factors, then it is likely that a near saturation of systemic endothelin receptors has been reached in women with preeclampsia.

### Conclusion

Preeclampsia may be characterized as a state of prolonged near

E-mail address: [gra88is@msn.com](mailto:gra88is@msn.com).

<https://doi.org/10.1016/j.mehy.2019.109400>

Received 29 March 2018; Received in revised form 21 July 2019; Accepted 13 September 2019

0306-9877/ © 2019 The Author. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

saturation of maternal systemic endothelin receptors, this being the result of what essentially is a continuous intravenous infusion of endothelin via the uterine veins. With most situations of continuous intravenous infusions of bioactive substances, in a matter of a few days a steady state will be reached. Women with preeclampsia may be experiencing such a steady state. Rather than studying only serum levels, systemic receptor saturation studies should provide more direct estimations of the degree of systemic endothelin receptor activation in pregnancies complicated by preeclampsia, as well as in normal pregnancies.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### References

- [1] Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;322:411–5.
- [2] Masaki T, Yanagisawa M. Endothelins. *Essays Biochem* 1992;27:79–89.
- [3] Taylor RN, Varma M, Teng NNK, et al. Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. *J Clin Endocrinol Metab* 1990;71:1675.
- [4] Clark BA, Halvorson L, Sachs B, Epstein BH. Plasma endothelin levels in pre-eclampsia: elevation and correlation with uric acid levels and renal impairment. *Am J Obstet Gynecol* 1992;66(3):962–8.
- [5] Nova Alfredo, Sibai BahaM, Barton John R, Mercer Brian M, Mitchell Murray D. Maternal plasma level of endothelin is increased in preeclampsia. *Am J Obstetrics Gynecol* 1991;165(3):724–7. [Peer Reviewed].
- [6] Florijn K Willem, Frans HM, Visser Derkx Wil, Hofman Hans JA, Rosmalen Frans MA, Wallenburg Henk CS, Schalekamp Maarten ADH. Elevated plasma levels of endothelin in pre-eclampsia. *J Hypertens* 1991;9:S168. <https://doi.org/10.1097/00004872-199112006-00067>.
- [7] Coffey CG. Pre-eclampsia: excessive Activation of a G Protein-associated Receptor? *Med Hypotheses* 1995;44:406–8.
- [8] Greenberg SG, Baker SB, Yang DS, Clark KE. Effects of continuous infusion of endothelin-1 in pregnant sheep. *Hypertension* 1997;30(6):1585–90.
- [9] Filep JG, Sirois MG, Rousseau A, Fournier A, Sirois P. Effects of Endothelin-1 on vascular permeability in the conscious rat: interactions with platelet-activating factor. *Br J Pharmacol* 1991;104:797–804.
- [10] Coffey CG. Cellular bases for the lipid-related aspects of preeclampsia. *Med Hypotheses* 2003;60(5):716–9.
- [11] Smid Marcela, Li Feng, Smithies Oliver, Boggess Kim. 265: Endothelin-1 over-expression mimics preeclampsia in pregnant mice. *Am J Obstet Gynecol* 2015;212(1):S145. <https://doi.org/10.1016/j.ajog.2014.10.311>.
- [12] George Eric M, Granger Joey P. Linking placental ischemia and hypertension in preeclampsia: role of endothelin 1. *Hypertension (Dallas, Tex.: 1979)*, 2012;60(2):507–11. [Peer Reviewed].
- [13] George Eric M, Palei Ana C, Granger Joey P. Endothelin as a final common pathway in the pathophysiology of preeclampsia: therapeutic implications. *Curr Opin Nephrol Hypertens* 2012;21(2):157–62. <https://doi.org/10.1097/MNH.0b013e328350094b>.
- [14] Saleh Langeza, Verdonk Koen, Visser Willy, van den Meiracker Anton H, Danser A H Jan. The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. *Ther Adv Cardiovasc Dis* 2016;10(5):282–93. <https://doi.org/10.1177/1753944715624853>.
- [15] Verdonk Koen, Saleh Langeza, Lankhorst Stephanie, Smilde JE Ilse, van Ingen Manon M, Garrelts Ingrid M, Friesema Edith CH, Russcher Henk, van den Meiracker Anton H, Visser Willy, Danser AH Jan. Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin–angiotensin–aldosterone system suppression. *Hypertension* 2015;65(6):1316–23. <https://doi.org/10.1161/HYPERTENSIONAHA.115.05267>.
- [16] Jain Arjun. Endothelin-1: a key pathological factor in pre-eclampsia? *Reprod BioMedicine Online* 2012;25(5):443–9. <https://doi.org/10.1016/j.rbmo.2012.07.014>.
- [17] Arjun Jain, Role of ET-1 in the induction of placental endoplasmic reticulum stress in pre-eclampsia and intrauterine growth restriction, 2012.
- [18] Jain Arjun, Olovsson Matts, Burton Graham J, Yung Hong-Wa. Endothelin-1 induces endoplasmic reticulum stress by activating the PLC4P3 pathway: implications for placental pathophysiology in preeclampsia: implications for placental pathophysiology in preeclampsia. *The American Journal of Pathology* 2012;180(6):2309–20. [Peer Reviewed].
- [19] Wolff, et al. Endothelin-1 and big endothelin-1 levels in normal term pregnancy and in preeclampsia. *Regul Pept* 1996;67:211–6.