Therapeutic Advances in Cardiovascular Disease
(2008) 2(4) 261–275
DOI: 10.1177/1753944708092277

The role of the L-arginine-nitric oxide pathway in preeclampsia

Patricio López-Jaramillo, William D. Arenas, Ronald G. García, Melvin Y. Rincon and Marcos López

Abstract: Preeclampsia (PE) is a major cause of maternal and perinatal mortality, especially in developing countries. Its etiology involves multiple factors, but no specific cause has been identified. Evidence suggests that clinical manifestations are caused by endothelial dysfunction. Nitric oxide (NO), which is synthesized from L-arginine in endothelial cells by the endothelial nitric oxide synthase (eNOS), provides a tonic dilator tone and regulates the adhesion of white blood cells and platelet aggregation. Alterations in the L-arginine-NO pathway have been associated with the development of PE. Various studies, reporting decreased, elevated or unchanged levels of nitrite (NO_2) and nitrate (NO_3), two end products of NO metabolism, have been published. Our group contributed to those contradictory reports describing cases of PE with both elevated and decreased levels of NO_2 and NO_3. Apparently, diminished levels of NO could be related to deficiencies in the ingestion of dietary calcium associated to low levels of plasma ionic calcium, which is crucial to the eNOS' activity. Also, low levels of NO could be associated with the presence of eNOS polymorphisms or the presence of increased levels of ADMA, the endogenous inhibitor of NO. High levels of NO associated to low levels of cGMP suggest a decreased bioactivity of NO, which is probably related to an increased degradation of NO caused by a high production of superoxide in states of infection and inflammation. The present article analyses and reviews the reported paradoxical roles of the L-arginine-NO pathway in PE and gives a possible explanation for these results.

Keywords: preeclampsia, endothelium, nitric oxide, inflammation, infection

Introduction

Hypertensive pregnancy disorders are the main cause of maternal and perinatal morbidity and mortality. Preeclampsia (PE) is the most important among these pathologies [WHO, 2004; Walker, 2000] Preeclampsia, defined as the onset of hypertension and proteinuria after 20 weeks of gestation in previously normotensive non-proteinuric pregnant women [Walker, 2000], is a multiorgan disease, affecting the liver, kidneys, brain, and blood clotting system. Despite its importance, the etiology of PE is not well defined and multiple risk factors have been identified [Lopez-Jaramillo *et al.* 2001; Lopez-Jaramillo, 2000]. The impact of each of them varies in different populations, with considerable differences between developed and developing countries [Lopez-Jaramillo *et al.* 2005]. In Latin America, the high frequency of risk factors, such as inappropriate nutrition, young maternal age, and inadequate prenatal care programs, is reflected in the high incidence of PE [WHO, 2004, 1987] and elevated maternal mortality, which is 10–20 times higher than in developed countries [WHO International Collaborative Study of Hypertensive Disorders of Pregnancy, 1998].

Pregnancy is a physiological state in which there are important hemodynamic adaptations that are maintained by an increased peripheral vasodilation [Lopez-Jaramillo, 1996]. The vascular endothelial cells provide a tonic dilator tone, which is mainly maintained not only by the production of NO, but also by prostacyclin and endothelium-derived hyperpolarizing factor (EDHF). Furthermore, these substances inhibit the adhesion and migration of leukocytes and platelets to the vascular wall [Sladek *et al.* 1997; Moncada *et al.* 1991].

Nitric oxide is synthesized from the amino acid L-arginine by a family of enzymes denominated NO synthases (NOS). The endothelial NOS

Correspondence to:
Patricio López-Jaramillo
VILANO Group. Research Institute, Fundación Cardiovascular de Colombia, Floridablanca, Santander, Colombia and Research Department, Medical School, Universidad de Santander (UDES), Bucaramanga, Colombia
joselopez@fcv.org; jplopezj@hotmail.com

William D. Arenas, Ronald G. García, Melvin Y. Rincon
VILANO Group. Research Institute, Fundación Cardiovascular de Colombia, Floridablanca, Santander, Colombia

Marcos López
Free Radical Research Center, Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA