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## Endothelial Arginase Inhibition Prevents Vascular Dysfunction and Stiffness in Obesity

Bhatta A, Yao L, Xu Z, Toque HA, Chen J, Atawia RT, et al. Obesity-induced vascular dysfunction and arterial stiffening requires endothelial cell arginase 1. **Cardiovasc Res. 2017;113:1664-76. http://doi.org/gb4jqs**

It is well known that cardiovascular diseases are associated to metabolic disorders as obesity, hyperglycemia and dyslipidemias. The main cause of morbidity and mortality in these pathological conditions is vascular dysfunction, characterized by impaired endothelial-dependent vasodilating capacity, decreased vascular compliance and reduced coronary blood flow. The pathophysiology of cardiovascular disorders accompanying metabolic alterations is complex and includes increased plasma glucose levels, proinflammatory cytokines and reactive oxygen species (ROS), together with reduced bioavailability of nitric oxide (NO). These mechanisms are strongly interrelated and, generally, potentiate each other. Specifically, NO is synthetized from the amino acid L-arginine, which is catalyzed by nitric oxide synthase (NOS) into NO and L-citrulline. Reciprocally, NO synthesis can be regulated by the enzyme arginase, which competes with NOS for the same substrate, L-arginine. Arginase catalyzes the hydrolysis of arginine to urea and ornithine, which ultimately metabolizes into proline and polyamines. Thus, the deleterious effects of increased arginase can occur through both pathways, reduction of NO and enhanced proline and polyamines. Human and animal studies have demonstrated that increased arginase is involved in coronary vascular function impairment and in general cardiovascular dysfunction, in conditions such as hypertension, aging, atherosclerosis, hyperglycemia and inflammation.

In this study, Bhatta et al. aim to demonstrate that the expression of arginase-1 in vascular endothelial cells is implicated in increased vascular stiffness and dysfunction in obesity. They used an experimental mice model with type 2 diabetes and metabolic syndrome due to an elevated fat and fructose diet. After six months, the diet had promoted increased body weight and blood glucose and post-prandial insulin levels. In addition, mice developed a significant increase in blood pressure, together with greater vascular fibrosis and stiffness, lower plasma levels of L-arginine and increased ornithine. In vitro studies in isolated vessels confirmed in vivo findings, showing enhanced activity of vascular arginase, higher levels of oxidative stress, decreased NO and impaired endothelial-dependent vascular relaxation. Interestingly, despite maintaining high body weight and cholesterolemia levels, all these vascular levels were not observed in endothelial arginase knock-out mice or those receiving a specific inhibitor of his enzyme. The authors conclude that cardiovascular dysfunction observed in obesity is produced as a consequence of increased expression and activity of vascular endothelial arginase-1, leading to reduced L-arginine and NO and enhanced oxidative stress.

*Arginase is a hydrolase enzyme of the urea cycle, expressed in the cytoplasm and mitochondria of blood vessel endothelial and smooth muscle cells. Elevated blood glucose and ROS levels are among the mechanisms that stimulate its synthesis. The deleterious effects of increased arginase can be acute, due to loss of NO vasodilation, or chronic, by increased production of proliferative substances, as proline and polyamines. These substances may promote enhanced cellular proliferation and fibrosis leading to the vascular stiffness and dysfunction accompanying hypertension. Arterial stiffness is an important cardiovascular risk factor, as shown in diabetic patients before the manifestation of systems on the cardiovascular apparatus. The role of arginase as an integrative mechanism of different cardiovascular risk factors in the genesis of endothelial dysfunction is increasingly better known and, in this case, it has also been shown in obesity, a highly growing and prevalent disease.*