Arginase inhibition improves endothelial function in patients with coronary artery disease and type 2 diabetes

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Background

Endothelial dysfunction, characterized by reduced bioavailability of nitric oxide (NO), plays an important role in the early development of atherosclerosis and vascular complications in type 2 diabetes.

NO is produced by the endothelial isoform of nitric oxide synthase (eNOS) from the amino acid L-arginine. Upregulation of arginase, metabolizing L-arginine to ornithine and urea, may result in reduced NO production by shunting L-arginine from the eNOS pathway to the arginase pathway.

Results

Nor-NOHA markedly increased EDV in patients with CAD+Diabetes and CAD, but not in the Control group. The increase in EDV was significantly higher in the CAD+Diabetes group than in the CAD group. The vasodilator response to SNP was enhanced by nor-NOHA in the CAD+Diabetes group, but not in the CAD or control group (data not shown).

Methods

36 male subjects were included in the study: 12 patients with coronary artery disease (CAD; age 64 ± 2), 12 patients with CAD and type 2 diabetes (CAD+Diabetes; age 68 ± 3) and 12 controls (age 60 ± 2). Forearm endothelium-dependent and endothelium-independent vasodilatation were assessed with venous occlusion plethysmography (see photos below) before and during 2 hours of i.a. infusion of the arginase inhibitor Nω-hydroxy-nor-L-arginine (nor-NOHA; 0.1 mg/min). In a separate protocol nor-NOHA was co-infused with the NO synthase inhibitor L-NMMA (20 mg/min). The expression of arginase was determined in internal mammary artery of patients undergoing bypass surgery.

Conclusions

Arginase inhibition improves endothelial function in patients with CAD and type 2 diabetes. This suggests that upregulation of arginase activity is a key mechanism behind endothelial dysfunction. Arginase activity may be a promising therapeutic target for the treatment of endothelial dysfunction among these patients.