## Summary

Asymmetric dimethylarginine (ADMA) is characterized as an endogenous inhibitor of the nitric oxide synthase (NOS). Its plasma concentration is increased in humans with hypercholesterolemia, hypertension, atherosclerosis, chronic renal failure, and chronic heart failure. Increased ADMA levels are associated with reduced NO synthesis as assessed by impaired endothelium-dependent vasodilatation. In several prospective and cross-sectional studies, ADMA evolved as a marker of cardiovascular risk and becoming a goal for pharmacotherapeutic intervention.

The mechanism by which ADMA inhibits the enzyme NOS was investigated in vitro with a purified, recombinant bovine endothelial NO synthase. The result of a competitive inhibition of the NOS explains in part the L-arginine paradox and provides a possible mechanism for the improvement of endothelium-dependent vascular function in subjects with high ADMA levels after administration of L-arginine.

For analyzing ADMA with high sensitivity and specifity a method based on gas chromatography-mass spectrometry was developed. The method required the synthesis of an adequate internal standard and was validated for cell culture supernatants, small volumes of plasma and cell lysates. In vitro experiments with endothelial cells for investigation the effect of different substances on ADMA and on the dimethylarginine dimethylaminohydrolase (DDAH), the ADMA metabolising enzyme, were realized using this validated method. HMG-CoA-reductase inhibitors, LDL and oxLDL, PPAR-agonists and angiotensin II influenced the concentration of ADMA in different ways, but only the change under the use of PPAR $\alpha$ -agonists could be explained with an alteration of the expression and activity of the DDAH. The experiments gave evidence for angiotensin II-receptor antagonists as a new therapeutic possibility to lower ADMA concentrations without the ability of declaring the mechanism of action.

HMG-CoA-reductase inhibitors (statins) lower effectively the cholesterol concentration in patients with hypercholesterolemia and exert different pleiotropic effects including the increase of the expression of the NOS in vitro. Further experiments with endothelial cells and the simulation of the different half-lives of atorvastatin and simvastatin showed the importance of recognizing the different pharmacokinetic properties of the statins judging about their effects. Atorvastatin seems to influence the NOS expression more effectively compared to other statins with shorter half-lives.