Editorial

When the endothelium cannot say ‘NO’ anymore

ADMA, an endogenous inhibitor of NO synthase, promotes cardiovascular disease

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The endothelium is one of the biggest organ systems in our body. This is not so apparent on first view, as it is spread throughout the body mostly in tiny arterioles and capillaries. If you should be asked to define the endothelium's 'personality', you would certainly come to the notion that this organ is characterized by a negative attitude: If vasoconstrictors attempt to constrict our arteries, the endothelium says 'NO'; if platelets tend to adhere to the vessel wall, the endothelium says NO'; if monocytes try to invade the vascular wall by penetrating the endothelial lining, the endothelium says 'NO' again; finally, if oxygen radicals sound the charge against the vasculature, it is the endothelium once more that sends out a burst of 'NOs to neutralize the offense.1

In the belligerently sounding setting of what we use to call 'vascular homeostasis', the endothelium with its major mediator, nitric oxide (NO) is one of the most valuable protective factors. It is a lack of NO or a deficiency of NO's actions in the vascular wall that lies behind most of the cardiovascular diseases that we face today: coronary heart disease, hypertension, chronic heart failure, vasculopathies associated with diabetes mellitus, hyperhomocysteinemia, and atherosclerosis in general, to name the best known among them.

But, many researchers have asked for years, what may be the molecular reason for NO deficiency in diseased arteries? Several hypotheses have been generated, among them downregulation of endothelial nitric oxide synthase (which was recently disproved), reduced sensitivity of effector systems against NO (which would not explain the selective defect of relaxations responses to endogenous NO seen in most experimental systems), and increased generation of oxygen-derived free radicals, leading to early inactivation of NO.1

In 1992, Vallance and co-workers2 reported data showing that an endogenous inhibitor of NO synthase circulates in human blood. This compound, which was identified to be asymmetrical dimethylarginine (ADMA), acts as a competitive inhibitor of NO synthase at concentrations that can be found in pathophysiological settings. ADMA has been shown to induce endothelial dysfunction in animal models and in humans. Its levels are elevated by a variety of cardiovascular risk factors like hypercholesterolemia, hyperhomocysteinemia, and hypertension (for review, cf.3). Most recently, evidence has been gathered by several groups of researchers to suggest that ADMA is a novel cardiovascular risk factor. In 1999, Miyazaki et al.4 found a significant correlation between ADMA and intima-media thickness in 116 apparently healthy subjects in a multivariate regression analysis including several established cardiovascular risk factors. ADMA prospectively predicts cardiovascular events and total mortality.5 In a nested case-control study including 150 healthy, non-smoking men from eastern Finland, they found that independently of other risk factors, elevated ADMA was associated with a significantly increased cardiovascular risk.6

In this issue of the Journal, Lu and co-workers7 present the results of a prospective clinical study in which they addressed the question whether ADMA may allow to predict outcome after percutaneous coronary intervention. One hundred and fifty-three consecutive patients with stable angina pectoris who underwent elective coronary angioplasty were included in the study. Patients were stratified into tertiles of pre-procedural ADMA and followed for a median of 16 months. The main end-point was an aggregate of major cardiovascular events.

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including cardiovascular death, myocardial infarction, and repeat revascularization of the target vessel.

A total of 51 major cardiovascular events occurred during follow-up. Interestingly, there was a clear increase in risk with increasing ADMA, which was independent of other potential confounding factors in a multifactorial Cox’s regression analysis (including age, smoking, hypercholesterolaemia, use of stent, and others).

This study is the second prospective study focussing on the association between ADMA and cardiovascular disease. It adds to previously published data showing that ADMA acts as a novel cardiovascular risk factor. The remarkable point with this study is that ADMA levels were within a range that many would consider as ‘normal’; patients in the lowest tertile of ADMA had a median circulating concentration of 0.42 µmol/l, as opposed to 0.75 µmol/l in the highest tertile. How could such small changes in circulating ADMA concentration possibly affect outcome after percutaneous intervention? Even more, in the light of L-arginine plasma concentrations of about 80 µmol/l and the knowledge that the eNOS’s Km value is about 3 µmol/l, how could ADMA affect NO synthase activity at all?

Firstly, there is abundant evidence from pre-clinical studies showing that inhibition of NO synthase accelerates and provision of L-arginine slows or even reverses atherosclerosis. Administration of synthetic NO inhibitors promotes lesion formation in various animal models of atherosclerosis, most probably by shifting the balance between NO and oxygen-derived radicals towards oxidative stress. By contrast, there is a high degree of concordance between studies showing that supplementation with L-arginine improves morphological and functional features of atherosclerotic arteries from animals, and improves the symptoms of atherosclerotic vascular disease in humans. Thus, endothelial NO is likely to modulate the atherogenic process in a way that can be influenced by exogenous L-arginine. This, in turn suggests the presence of a competitive inhibitory mechanism affecting NO synthase activity in atherosclerosis. As to the development of restenosis after angioplasty, enhancing NO’s bioavailability by transfecting the endothelial NO synthase gene into lesional areas has been shown to retard the development of restenosis; likewise, application of L-arginine into lesions had a similar effect.

Secondly, in vitro data suggest that the IC_{50} of ADMA for endothelial NO synthase is 3.9 µmol/l.12 Relatively low concentrations of ADMA may therefore affect NOS activity to a certain degree. Moreover, there is evidence that intracellular ADMA concentration is several-fold higher than concentrations circulating in plasma. ADMA may interact with L-arginine not only at the level of NO synthase, but also at the level of the cellular uptake mechanism (y^+ transporter).

Thirdly, the difference in median ADMA concentrations between the highest and lowest tertile, as small as it may appear in absolute numbers, corresponds to an 80% increase in the levels of this potential risk factor. In comparison to other novel risk factors like homocysteine, where differences between cases and controls were only 5–12% (11.1 vs 10.5 µmol/l in the Physicians’ Health Study),13 12.7 vs 11.3 µmol/l in the prospective Tromsø Study),14 or high-sensitive CRP, where differences of some 34% between cases and controls (1.51 vs 1.13 mg/l in the Physicians’ Health Study)15 conferred a significant increase in cardiovascular risk, it appears much easier to explain how ADMA might affect cardiovascular risk.

The mechanism by which ADMA is elevated in some patients may relate to oxidative stress. ADMA is inactivated by an enzyme named dimethylarginine dimethylaminohydrolase (DDAH); most investigators agree that DDAH plays an important role in the regulation of ADMA levels. DDAH activity is downregulated by oxidative stress, as it is associated with high cholesterol, high glucose, and high homocysteine levels.16 In these settings, accumulation of ADMA can be prevented by addition of antioxidants in experimental models. Inhibition of DDAH, in turn, leads to elevated ADMA levels, which in turn promote further generation of oxidants, possibly by uncoupling NO synthase. This vicious circle provides an integrative explanation for the interrelation between lack of NO, excess of oxygen-derived free radicals, and progression of vascular lesion formation.

References