A Tale of Two Molecules: Nitric Oxide and Asymmetric Dimethylarginine

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Despite monumental progress in both molecular and interventional cardiology, atherosclerosis remains the leading cause of mortality and morbidity in the US, claiming more lives than the next 7 causes of mortality combined. Not only is this chronic disease the beginning of many familiar downstream clinical manifestations such as acute myocardial infarction, but research has demonstrated that the pathogenesis of atherosclerosis is intricately linked to many other cardiovascular abnormalities, from hyperhomocysteinemia to diabetes mellitus. Inflammation and oxidative stress, for instance, are common mediators for these diseases. Their interrelatedness has elicited much interest in finding a molecular marker with both prognostic and diagnostic values. Asymmetric dimethylarginine (ADMA) is one such molecule, recently gaining wider acceptance as a novel cardiovascular risk factor. As an endogenous competitive inhibitor of nitric oxide synthase (NOS), ADMA is elevated in the plasma of patients with hypercholesterolemia, hypertension, hyperhomocysteinemia, hyperglycemia, and insulin resistance. Not only is plasma ADMA concentration predictive of cardiovascular events, ADMA reduces the production of the anti-inflammatory and anti-atherogenic molecule, nitric oxide. As such, ADMA is both a disease marker and a mediator, whose pathophysiology merits attention. This article reviews the current knowledge of ADMA within the larger context of the NOS pathway.

Key Words: Nitric oxide • Asymmetric dimethyl-arginine • Endothelium • Nitric oxide synthesis (NOS)

The endothelium

The endothelium is a monolayer of cell that invests the lumen of all blood vessels. The normal endothelium acts like a Teflon coat, preventing circulating blood elements from adhering to the vessel wall. Strategically stationed between the smooth muscle cells and the circulating blood, endothelial cells play a seminal role in the intricate signal pathways that network our circulation to local tissues. To maintain these functions, endothelial cells synthesize and respond to a plethora of molecules. Most famous among them in the past decade has been nitric oxide (NO).

Nitric oxide

The pioneering work that led to the identification of NO as the endothelium-derived relaxing factor (EDRF) was no less celebrated than the molecule itself. As a parasympathetic molecule, acetylcholine was known to relax vascular smooth muscles, causing vasodilation. Intriguingly, when a vessel ring was removed for ex vivo studies in which acetylcholine was added, a contradictory vasoconstriction was observed in the vessel section. Moreover, vascular constriction was observed if acetylcholine was added directly to vascular smooth muscle cells. Robert Furchgott and colleagues explained these observations with a hypothetical EDRF, which was released from endothelial cells upon their stimulation by acetylcholine. Subsequent chemical characterization of EDRF by the laboratories of Louis Ignarro and Ferid Murrad led to the striking conclusion that NO, a com-
mon air pollutant, is indeed the EDRF. For their contributions, Furchgott, Ignarro, and Murad were awarded the Nobel Prize in Physiology and Medicine in 1998.

Because its nitrogen has an unpaired electron, NO is a free radical. As such, its in vivo half-life is on the order of microseconds, the molecule being rapidly oxidized to nitrate ($\text{NO}_3^-$). This short half-life gives NO just enough time to diffuse from the endothelium, where the gas is produced, to the neighboring smooth muscle cells, where the molecule induces its vasodilatory effect. Reduced NO bioavailability occurs through 2 mechanisms: decreased production and/or increased degradation. In the former, nitric oxide synthase (NOS) makes less NO because of reduced substrate, cofactors, the enzyme itself, and/or increased antagonists. In the latter, oxidative stress, characterized by an increase in superoxide anion ($\text{O}_2^-$), quenches NO, turning it into peroxynitrite (ONOO$^-$), which is then oxidized to the inactive nitrate.

Decreased NO bioavailability is the defining feature of endothelial dysfunction. In patients with atherosclerosis, endothelial dysfunction, indicated by reduced forearm blood flow following acetylcholine infusion, can be observed before any morphological changes typical of atherosclerosis. NO inhibits monocyte adhesion,1 platelet aggregation,2,3 and vascular smooth muscle proliferation,4 all of which are key pathological processes in atherosclerosis. As such, deficiency of NO increases vascular resistance and promotes atherogenesis;5 it also plays a key role in the progression of a constellation of cardiovascular abnormalities, including diabetes mellitus,6-8 hypercholesterolemia,9 and hyperhomocysteinemia.10

**Nitric oxide synthesis**

NO is converted from L-arginine by the enzyme NOS. The reaction involves the transfer of electrons from NADPH, via the flavins FAD and FMN from the reductase region (C-terminal) of NOS to its oxidase region (N-terminal), where L-arginine is converted to L-citrulline and NO.11 Other cofactors in this enzymatic reaction include calmodulin, zinc, and tetrahydrobiopterin. In conditions where the substrate and/or cofactors become limited, the electrons obtained from oxidizing NADPH would be directed to oxygen, instead of L-arginine. Subsequently, superoxide anion, rather than NO, is produced. Under this condition, NOS is said to be “decoupled,” in the sense that the enzyme’s reductase is short-circuited from the oxidase region by molecular oxygen. In other words, depending on substrate availability, NOS would produce either NO or superoxide anion (Figure 1).

Upon its release from NOS, NO diffuses across the endothelial cell membrane and travels to the neighboring smooth muscle cells, where the gas activates soluble guanylate cyclase (sGC). The cytosolic sGC converts gua-

![Figure 1. The nitric oxide synthase pathway. NOS generates either NO or superoxide anion, depending on the substrate availability. NO stimulates the enzyme soluble guanylate cyclase (sGC), which generates cGMP, leading to vascular relaxation. Superoxide anion quenches NO and inactivates it to nitrate. ADMA is an endogenous inhibitor of NOS and is itself degraded by the enzyme DDAH. Superoxide anion lowers the enzymatic activity of DDAH and thereby elevates the level of ADMA and reduces NO production.](image-url)
nine triphosphate (GTP) to cyclic guanine monophosphate (cGMP), which triggers a phosphorylation cascade that leads to the relaxation of the smooth muscle cells.

There are three isoforms of NOS; namely, neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS). Both nNOS and eNOS are constitutively expressed, with the latter predominantly found in the cardiovascular system. It must be noted that the expression of eNOS is nonetheless subject to change. A variety of agents can augment eNOS expression. These include cyclosporin, glucose at high concentration, low-density lipoprotein at low concentration, shear stress, and estrogen. In fact, the promoter region of the eNOS gene contains an estrogen response element, an observation that could in part explain estrogen’s cardioprotective effect.

Increase in endothelial intracellular calcium concentration following agonist stimulation (such as acetylcholine) activates eNOS because the enzyme requires the calcium-bound calmodulin as a cofactor. Indeed, the calcium-dependency of eNOS was confirmed by studies in which NO production and eNOS activity were both abrogated after calcium removal. iNOS, on the other hand, is calcium-independent because it binds tightly to calmodulin, and the binding interaction is irreversible; its regulation henceforth depends almost exclusively on the transcriptional level, for which the enzyme receives the term “inducible.”

The arginine paradox

NOS is an intracellular enzyme. Half-saturating arginine concentration (Km) was reported as 1.4 μM for nNOS, 2.83 μM for iNOS, and 2.9 μM for eNOS. Freshly isolated endothelial cells have been found to contain up to 2 μM of arginine. Given that the intracellular arginine concentration in endothelial cells is hundred-fold higher than the enzyme’s Km, eNOS should always be saturated. In other words, an increase in the substrate arginine’s concentration would not increase the production of NO. Intriguingly, numerous studies have indicated that intravenous or oral supplementation of arginine in humans augments endothelial NO production (a list of these studies can be found in the study by Flam et al). In fact, a recent study showed that infusion of L-citrulline could also enhance NO production, mimicking the effect of arginine infusion. Colocalization of
these proteins with NOS suggests that the local arginine level around NOS could be highly regulated. Accordingly, the total intracellular arginine concentration should be cautiously interpreted.

Nevertheless, the hypothesis that eNOS localization answers the arginine paradox raises one critical question. Membrane-bound eNOS is inactive. In caveolae, eNOS is associated with the protein caveolin-1, which prevents calmodulin from binding to eNOS when intracellular calcium concentration is low. The activation of eNOS requires, in addition to a rise in calcium level, phosphorylation of the enzyme by a serine kinase, and the enzyme’s depalmitoylation. This process releases eNOS from the membrane. That eNOS is inactive when localized and that the enzyme makes NO only when it leaves caveolae raise a question regarding the extent to which eNOS localization contributes to the arginine paradox. Further experiments are needed to answer this question. Here is an example using cell culture: Dr. William Sessa’s laboratory at Yale University has developed eNOS mutants that are kinetically indistinguishable from the wildtype. However, the mutants cannot be myristoylated; hence, they remain cytosolic. After transfecting these mutants to endothelial cells, we could expose the cells to pathological stimuli that are known to reduce NO production (stimulus such as oxidized LDL). We could then apply arginine to the medium to determine whether increasing the substrate would lead to greater amount of NO. If arginine fails to restore NO production in the transfected cells, we can conclude that eNOS localization does not contribute to the arginine paradox.

ADMA in cardiovascular diseases

While the precise role of eNOS localization in the NO pathway still remains unsettled, another mechanism for endothelial dysfunction in general, and arginine paradox in specific, focuses on asymmetric dimethylarginine (ADMA). As an endogenous, intracellular competitive antagonist of all isoforms of NOS, ADMA can reduce NO synthesis if its concentration increases. In other words, the level of ADMA could serve as a biochemical marker for NO availability. Given that NO deficiency is the defining feature of endothelial dysfunction – the critical step in the onset of many cardiovascular diseases – ADMA appears a promising candidate for cardiovascular risk evaluation.

Accumulating evidence from both basic and clinical investigations supports this concept. Vallance and colleagues were among the first to document ADMA’s clinical significance. They noted that in patients with end-stage renal disease, plasma ADMA accumulate due to reduced renal clearance. Reduced clearance of ADMA in renal failure is associated with endothelial vasodilator dysfunction, reversible by administration of L-arginine or by dialysis, which removes plasma ADMA.

In subsequent years, several laboratories independently demonstrated and confirmed the correlation between elevated plasma ADMA and nearly all major cardiovascular risk factors such as aging, hypertension, diabetes, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and hyperhomocysteinemia. In hypercholesterolemic humans, elevated plasma ADMA inversely correlated with endothelial-dependent vasodilation in the forearm vasculature. Consistent with the idea of a competitive antagonism between ADMA and L-arginine, intravenous infusion of L-arginine restored endothelial function and increased urinary nitrate excretion, which served as a surrogate parameter of NO production.

Plasma ADMA levels are also associated with other cardiovascular complications such as stroke, congestive heart failure, and peripheral arterial disease (PAD). The level of ADMA was found to correlate with the severity of atherosclerotic disease in patients with PAD. Intravenous infusion of L-arginine both reduced pain and improved walking distance. In addition, ADMA levels have been shown to correlate with carotid intima-media thickness in patients with end-stage renal disease, and more strikingly, in a group of 116 apparently healthy individuals.

Most recently, plasma concentrations of ADMA were reported a strong predictor of coronary events in non-smoking male subjects with a history of coronary heart disease. Of note, patients in the upper quartile of ADMA plasma levels had a 3.9-fold enhanced risk of an acute coronary event.

Furthermore, Zoccali and colleagues recently published a large, prospective clinical study of 225 patients with end-stage renal disease undergoing hemodialysis (mean duration of hemodialysis 42 months). In this study cohort, both fatal and non-fatal cardiovascular events were recorded during a mean follow-up period of 33.4 months. Strikingly, plasma ADMA levels emerged
as the second strongest predictor of all causes of mortality after age, outweighing conventional risk factors such as hypertension, diabetes, hypercholesterolemia, and smoking.

Commensurate with these human studies, animal and cell-culture works not only confirm the association between elevated ADMA and reduced NO, but also establish the causal relation between the 2 molecules. Exogenously added ADMA in concentrations between 1 and 10 μmol/L dose-dependently reduces endothelium-dependent NO-mediated vasodilation in isolated rat mesenteric vessels and cerebral vessels, inhibits NO production by cultured macrophages, and increases endothelial adhesiveness to monocytes.

ADMA is arguably the newest addition to an already sizable list of cardiovascular risk markers such as fibrinogen, LDL, triglyceride, interleukin-6, von Willebrand factor, plasminogen activator inhibitor-1 and C-reactive protein. However, unlike some of these markers, ADMA is more than a marker; it plays a pivotal role in cardiovascular physiology by regulating the amount of NO synthesized. Hence, understanding the regulation of plasma ADMA elevation could lead to novel therapeutic approaches and treatment modalities. Presently, the mechanism of increased ADMA level is not fully characterized. Plasma ADMA level reflects a dynamic balance between the molecule’s generation and its degradation. As such, increased ADMA is a consequence of increased generation and/or decreased clearance.

**ADMA generation**

In endothelial cells, ADMA is generated from the proteolysis of ubiquitous proteins containing methylated arginine residue. In the nucleus, transcriptional regulators are often methylated by enzymes called methyl transferases. In particular, protein arginine methyl transferase (PRMT) transfers a methyl group to one of the guanidino nitrogens on an arginine residue. Either one or two methyl groups can be added to arginine, subsequently resulting in monomethylarginine (NMMA) and dimethylarginine, respectively. In the case of dimethylarginine, both methyl groups can occupy the same guanidino nitrogen, giving rise to asymmetric dimethylarginine (ADMA). Alternatively, the 2 methyl groups can be distributed symmetrically such that each guanidino nitrogen is only methylated once. This configuration gives rise to symmetric dimethylarginine (SDMA). Both NMMA and ADMA block the activity of NOS; SDMA, however, is inactive to NOS, presumably because its guanidino group is too large to fit into the active site of NOS (Figure 2).

**ADMA clearance**

Renal excretion is one common way by which ADMA, NMA, and SDMA are removed. This observation might in part explain the rise in plasma ADMA in patients with renal failure. In that particular context, the kidney acts as a sink for ADMA. Once the sink has malfunctioned, ADMA accumulates in the source - the endothelial cells - where it reduces the production of nitric oxide.

The degradation of ADMA and NMA, but not SDMA, occurs via an additional pathway. The enzyme dimethylarginine dimethylaminohydrolase (DDAH) metabolizes ADMA to dimethylamine and citrulline. Currently, two DDAH isoforms have been identified. DDAH-I is found mostly in neural tissue, while DDAH-II predominates in peripheral and vascular tissues. DDAH is an intracellular protein. Its distribution does not seem to be localized within any intracellular compartments, nor is the enzyme membrane-bound. Interestingly, red blood cells also contain DDAH, suggesting a possible role of erythrocytes in regulating...
plasma level of ADMA.

The role of DDAH in a variety of disease states has been intensely investigated. Given the enzyme’s role in removing ADMA, reduction of DDAH enzymatic expression or activity would elevate ADMA and subsequently reduce NO – the hallmark of endothelial dysfunction. Indeed, John Cooke’s laboratory has shown that an impairment of DDAH activity almost always accompanies a rise in plasma ADMA. In fact, a 30-50% reduction in DDAH enzyme activity was observed in hyperhomocysteinemia, hypercholesterolemia, and hyperglycemia, both in vitro and in vivo. In several papers, Cooke’s colleagues have also shown a strong negative correlation between DDAH activity and plasma ADMA level. Taken together, this line of evidence suggests that DDAH plays a key role in regulating the concentration of ADMA. As such, it becomes imperative to identify how DDAH activity is lowered.

DDAH is an oxidant-sensitive enzyme. At its active site, a cysteine residue initiates the first chemical reaction that leads to formation of the enzymatic reaction intermediate. This cysteine residue is vulnerable to oxidative attack from many intracellular oxidants, including homocysteine and superoxide anion (O$_2^-$). An imbalanced cellular oxidative state might oxidatively modify the cysteine residue of DDAH. In the case of homocysteine, a disulfide bond actually forms between the oxidant and the cysteine residue of DDAH. This and other oxidative interaction with the cysteine residue drastically lowers the activity of DDAH. Administration of antioxidants such as pyrollidine dithiocarbamate and polyethylene glycol conjugated superoxide dismutase have been shown to restore the enzymatic activity of DDAH in endothelial cell culture.

There is already a sizable list of pathways activated by oxidative stress that render cells in a pro-inflammatory state. The vulnerability of DDAH to oxidative stress presents another mechanism whereby oxidative stress aggravates endothelial dysfunction. Pathological conditions that elevate oxidative stress lower the activity of DDAH, leading to higher cellular and plasma levels of ADMA, which in turn reduces the production of NO.

**ADMA assay in biological samples**

Literature on ADMA has been on a rapid rise over the last few years. Concurrent with our increasing appreciation of this molecule’s clinical importance rests the question of how to quantify ADMA. There are two challenges that any ADMA assay must overcome. First, the detection must be sufficiently sensitive to distinguish ADMA from its endogenous isomer, SDMA. Second, the assay must possess sub-micromolar sensitivity, because plasma level of ADMA is usually in the range of 0.5 to 3 µM.

Virtually all of the laboratories around the world currently investigating ADMA measure the molecule using high pressure liquid chromatography (HPLC). Briefly, the method involves pre-concentration of ADMA using solid-phase extraction, with a strong cation exchange column (available from Varian Inc., Palo Alto, USA). Solid-phase extraction removes most of the chemical components from the sample (which could be plasma, urine, or culture medium), leaving only moderately basic compounds, which include ADMA, SDMA, and arginine.

The concentrated sample is labeled with the fluorochrome, o-phthaldialdehyde or naphthalene-2, 3-dicarboxaldehyde. After the labeling (or the “derivatization”), components within the sample are separated using reverse-phase HPLC with a nucleosil phenyl column. A fluorescence detector then quantifies each sample component as it exits the column.

HPLC separates compounds based on their structural dissimilarity, and the time a compound takes to exit the column is in part determined by its relative hydrophobicity compared to other compounds present in the sample. Because ADMA is among the most hydrophobic chemicals in the concentrated sample, it is among the last compound to exit the column. The literature reports an elution time between 20 to 50 minutes for ADMA. The total time of the assay also includes the time spent on solid phase extraction and on cleaning the column after each sample run. In sum, one sample takes at least 40 minutes to process. As such, HPLC is very time- and labor-intensive, and is prone to human and mechanical errors.

HPLC’s intrinsic variability notwithstanding, there is no unified and consistent protocol of measuring ADMA using HPLC. Different mobile phases, column types, and derivatization times are usually employed in various laboratories. As such, there is often a significant difference between the control groups from 2 different
A study, initiated by Dr. Böger from Germany, is currently under its way to collect data from the major ADMA laboratories around the world and to compare their differences. Results from this study would certainly stimulate more communication and collaboration among laboratories investigating ADMA.

Other methods to quantify ADMA have also been published and proposed. A French group has reported successful separation and quantification of ADMA and SDMA using laser-induced fluorescence capillary electrophoresis (LIF-CE). This technique separates compounds based on difference in their charge-to-mass ratio. However, ADMA and SDMA have the same molecular mass, and their charge difference under any pH is so subtle that separation would be difficult under any buffer system. In fact, 2 groups from Stanford University have failed to measure ADMA using the reported LIF-CE protocol, but are currently working on a modified protocol that introduces organic additive into the buffer system to enhance the electrochemical difference among the chemicals (unpublished data). Several private firms have also started developing immunoassay for detecting ADMA. Such an approach relies on an ADMA-specific antibody to identify and quantify the molecule. If realized, this technique would enable ADMA detection using enzyme-linked immuno-sorbent assay (ELISA), which offers both high sensitivity (at the level of nanomole) and high throughput (96 samples in a few seconds).

The field of ADMA is a wonderful example of how interdisciplinary approach could accelerate and catalyze progress in today’s medicine. The number of analytical chemistry laboratories looking at ways to improve ADMA measurement is growing as rapidly as the number of clinical and basic laboratories investigating the pathophysiology of ADMA. These trends only underscore ADMA’s diagnostic and prognostic values.

ADMA: a critical appraisal

NO plays a critical role in maintaining vascular tone and integrity. When NO becomes deficient, the endothelium becomes adhesive, attracting monocytes and other blood elements to adhere and infiltrate through the endothelium. In the presence of oxidized LDL in the sub-endothelial subspace, the infiltrated monocytes become foam cells, setting the stage ready for the development of fatty streak and early lesions of atherosclerosis.

ADMA is among most potent and abundant endogenous inhibitors of eNOS. Today some doubts remain regarding the relevance of ADMA to the NO pathway. Most of the critics of ADMA argue that ADMA’s plasma level is too low, and the extent of its variation between normal and pathological condition is insignificant, to effectively compete with arginine, which has a ten-fold higher concentration in the plasma. The same ADMA-to-arginine ratio also holds true within the endothelial cells. However, as we have pointed out earlier, caution must be taken when interpreting intracellular concentrations, because the numbers reflect only the average, but not the local concentration of ADMA and arginine, which, given the localization of eNOS, are biochemically more relevant.

Cellular compartmentalization theory addresses the critics’ concerns; however, it does so by simply citing the unknown – the cell biology of eNOS, ADMA, and arginine. Another more direct piece of evidence supporting the role of ADMA comes from a standard practice in a pharmacology laboratory. Monomethylarginine (L-NMMA) and L-nitro-arginine methylester (L-NAME) are 2 commonly used agents to induce systemic vasoconstriction in humans and laboratory animals. They are usually administered with a low dose that would elevate their plasma concentrations 3- to 4-fold, which are still below 5 μM. The systemic effects of these eNOS inhibitors have been well documented for many years. Given that they share similar pharmacokinetic profile with ADMA, ADMA should likewise affect eNOS at micromolar quantity. More importantly, this line of logic suggests that eNOS’ access to arginine might not be as straightforward as vascular biologists once thought. Many factors could upset arginine’s availability to eNOS, from a decrease in arginine itself (possibly caused by increased arginine turnover by arginase) to an increase in eNOS inhibitor such as ADMA, which could be caused by oxidative stress and DDAH dysfunction.

If the level of ADMA is clinically important, the factors that influence DDAH enzymatic activity are also critical, for the latter directly regulates the former. Accordingly, a clinical study has been launched in Europe to investigate the relation between DDAH single nucleotide polymorphisms and a variety of cardiovascular
diseases. In the preliminary data, DDAH actually emerged as a stronger predictor for the onset of Type 2 diabetes than markers such as triglyceride and cholesterol. Meanwhile, the laboratory of John Cooke at Stanford University has also developed transgenic mice over-expressing human DDAH I gene. Recently, we have shown that acute peritoneal injection of ADMA instantly attenuates insulin sensitivity in mice. Meanwhile, the insulin sensitivity of transgenic mice over-expressing DDAH is not significantly different from that of mice receiving the control treatment. Presumably, this is due to the transgenic mice’s enhanced ability to degrade the exogenously added ADMA. Taken together, this line of initial evidence suggests that DDAH dysfunction in particular, and very possibly endothelial dysfunction in general, could lead to insulin resistance and Type 2 diabetes. A recent clinical study corroborated this hypothesis by showing that eNOS polymorphism is associated with Type 2 diabetes and insulin resistance syndrome. While this concept still requires more rigorous proof, these studies embody the now decades-old belief that metabolic abnormality is also a vascular disease.

The etiology of atherosclerosis is certainly multifaceted. ADMA and DDAH might also have yet-unknown interactions with other components of the NOS and inflammatory pathways, such as interleukin-8, protein kinase C and phosphoinositol-3-kinase. Treatments that aim to restore one pathway might bestow the benefits at the expense of another pathway. Hence, future studies should be directed to untangling these intricate interactions and based on these mechanistic understanding, to design better clinical guidelines and therapeutic interventions.

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雖然在分子心臟學與介入心臟學巨大的進步，動脈粥狀硬化仍在美國居患病率及死亡率的首要原因，且遠超過排行其下七項疾病之總數。動脈粥狀硬化為慢性疾病，它不僅是許多眾所周知的臨床疾病的初始，例如急性心肌梗塞，研究亦顯示血管硬化的病理也與其他心血管疾病，從高同氨酸症到糖尿病，都有錯綜複雜的關係。例如發炎反應，或氧化傷害，即為這些疾病的共通媒介。其中的一氧化氮（NO）與非對稱性二甲基精氨酸（ADMA）在血管硬化的病理變化過程中，扮演了極重要之角色。當發生發炎反應，或氧化傷害時，中間的媒介分子不只使血管產生病變，同時也扮演了預後的因子。由於ADMA具有診斷及預後的指標，因此最近被廣泛接受成為心臟血管疾病之新發現的危險因子之一。ADMA是體內一氧化氮合成酵素（NOS）的內源性抑制分子，因此在高血脂、高血壓、高同氨酸症、高血糖及胰島素阻抗的情況之下，血清中的ADMA值是偏高的。ADMA會減少抗發炎及抗硬化分子的產生，因此也同時具有診斷及預後之價值。本文將探討ADMA、NOS生化路徑及相互關係之最新研究。

關鍵詞：一氧化氮、非對稱性二甲基精氨酸、一氧化氮合成酵素、內皮細胞。