

Commentary

Live and let die: asymmetric dimethylarginine and septic shock

Rainer H Böger

Clinical Pharmacology Unit, Institute of Experimental and Clinical Pharmacology, University Hospital Hamburg-Eppendorf, Germany

Corresponding author: Rainer H Böger, boeger@uke.uni-hamburg.de

Published: 3 November 2006

This article is online at <http://ccforum.com/content/10/6/169>

© 2006 BioMed Central Ltd

Critical Care 2006, **10**:169 (doi:10.1186/cc5076)

See related research by O'Dwyer *et al.*, <http://ccforum.com/content/10/5/R139>

Abstract

Nitric oxide (NO) is an important mediator of host defence and of vascular tone. In septic shock, upregulation of inducible NO synthase leads to the production of vast amounts of NO, which contribute to pathogen elimination but also to inappropriate vasodilation and to loss of vascular resistance. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthases shown to contribute to the regulation of vascular tone. ADMA was recently identified as a marker of organ dysfunction and mortality in intensive care patients and as a novel cardiovascular risk factor. In the present issue of *Critical Care*, a study by O'Dwyer and colleagues identifies ADMA as a potential regulator of NO production in septic shock. Being an inhibitor of NO production, ADMA may at least partly counteract pathological hypotension, but at the same time may impair the NO-dependent host defence. A mechanism is proposed by which the interplay between ADMA and inducible NO synthase activity is mediated. ADMA levels should be determined in future studies evaluating the regulation of NO in the intensive care setting.

In the present issue of *Critical Care*, O'Dwyer and colleagues [1] report the results of a study in 47 patients with septic shock. Asymmetric dimethylarginine (ADMA) levels were elevated in these patients at the time of admission to the intensive care unit (ICU) as compared with a group of 10 healthy controls. ADMA levels in septic patients directly correlated with the Sequential Organ Failure Assessment scores, with the degree of acidaemia and lactaemia, and with vasopressor requirements. Interestingly enough, ADMA levels were higher in patients requiring vasoactive infusions than in those not requiring vasoactive infusions. ADMA levels further increased during the subsequent 7 days of ICU treatment. Nonsurvivors tended to have higher ADMA plasma levels on days 1 and 7 of ICU treatment as compared with survivors, although this trend was insignificant in the small patient group. The authors also demonstrated that a genetic polymorphism in the promoter region of the dimethylarginine dimethylaminohydrolase (DDAH) II gene was significantly

associated with ADMA levels in these patients, suggesting that the genetically anchored dysfunction of the enzyme that metabolises ADMA may importantly regulate ADMA levels.

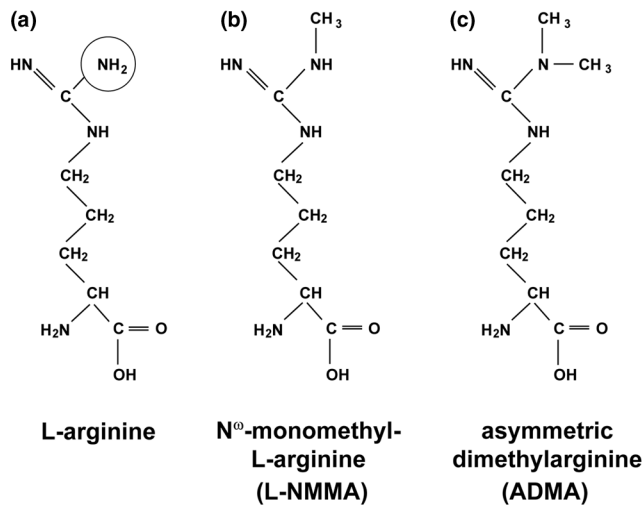
Standard therapy for patients with sepsis includes ICU admission, careful selection of antibiotic therapy, and, if needed, haemodynamic and ventilatory support [2]. Despite the use of these intensive therapies, however, mortality from sepsis has remained at levels between 35% and 50% [2].

Nitric oxide (NO) is referred to as a key mediator of vasodilatation and catecholamine resistance in septic shock [3,4]. Whereas in physiological conditions NO is mainly formed in the endothelium at low rates by the activity of the constitutive, endothelial isoform of the enzyme NO synthase, inflammatory stimuli such as bacterial lipopolysaccharides and cytokines released during sepsis result in a strong upregulation of an inducible isoform of NO synthase (iNOS). This isoform, once upregulated, releases huge amounts of NO during prolonged time intervals. The iNOS-derived NO contributes to pathogen elimination. NO-induced vasodilatation, however, also contributes to widespread vascular loss of tone and has been implicated in the cardiovascular failure in septic shock [5]. There has been controversy about the pathophysiological roles of iNOS and NO in the development of septic shock after a phase III trial with *N*^G-monomethyl-L-arginine, a nonselective NO synthase inhibitor, resulted in excess mortality [6]. Indeed, experimental studies have suggested that iNOS-derived NO plays an important role in host defence and organ protection [7].

During the past decade knowledge has accumulated of endogenous compounds that inhibit NO synthase activity, and thereby regulate NO-dependent vascular function. The major molecule endogenously present in the circulation at concentrations sufficiently high to exert inhibitory effects on

ADMA = asymmetric dimethylarginine; DDAH = dimethylarginine dimethylaminohydrolase; ICU = intensive care unit; iNOS = inducible NO synthase; NO = nitric oxide.

Figure 1



Structural formulae. Schematic drawings of the structural formula of (a) L-arginine, the natural substrate of nitric oxide (NO) synthase, (b) N^G-monomethyl-L-arginine, the NO synthase inhibitor used in clinical trials, and (c) asymmetric dimethylarginine, the endogenous inhibitor of NO synthases. The circle in (a) indicates the terminal guanidino nitrogen group, where NO is cleaved by NO synthase.

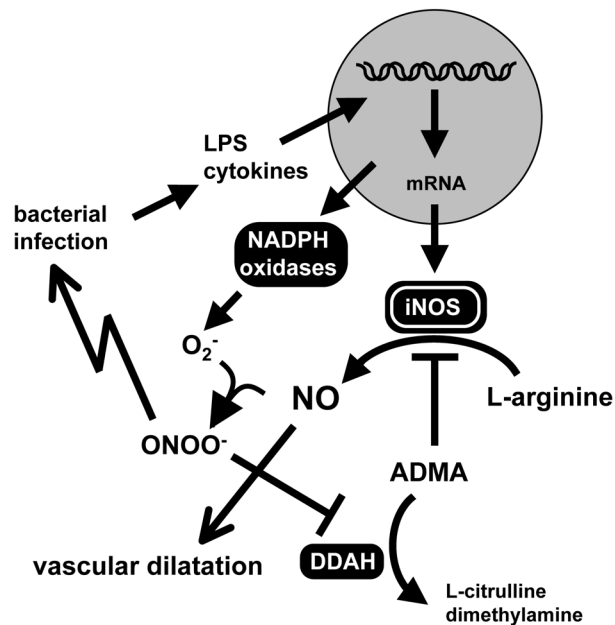
NO synthesis *in vivo* is ADMA. A structural analogue of N^G-monomethyl-L-arginine, the long-known NO synthase inhibitor, and of L-arginine, ADMA is the endogenous substrate of NO synthase (Figure 1). ADMA levels have been shown to regulate NO generation, endothelial function, and vascular resistance in animal models and in humans (for recent reviews, see [8-10]). Moreover, ADMA has evolved from prospective clinical trials as a novel cardiovascular risk marker [11].

Previous evidence has linked elevated ADMA levels to reduced kidney and liver function and to multiple organ failure in ICU patients [12]. Moreover, prospective clinical data point to the fact that ADMA may be a superior predictive marker of ICU death [13]. We have recently shown that ADMA levels are prospectively associated with organ dysfunction and with the postoperative complication rate in patients undergoing major elective surgery (unpublished data).

In the battle between the invading pathogen and the host organism, NO generation has to be kept in a delicate balance between 'live' (keeping NO within boundaries for cardiovascular homeostasis) and 'let die' (upregulating NO to a sufficient degree for pathogen defence). Here, upregulation of ADMA levels may be another long ignored but important regulator.

But what may be the mechanism behind the interrelation of iNOS activity and ADMA? Upregulation of iNOS leads to the release of huge amounts of NO and superoxide, which, by

Figure 2



Potential interrelation of nitric oxide generation and the pathophysiology of sepsis. Potential interrelation of nitric oxide (NO) generation by inducible nitric oxide synthase (iNOS) and by asymmetric dimethylarginine (ADMA) and the pathophysiology of sepsis. LPS, lipopolysaccharide; DDAH, dimethylarginine dimethylaminohydrolase.

forming peroxynitrite, can nitrosylate proteins and thereby damage tissues [14]. S-nitrosylation of DDAH II has been shown to downregulate this enzyme's activity, leading to accumulation of ADMA [15]. This may explain why ADMA levels were actually higher in patients with more vasopressor need in the study by O'Dwyer and colleagues [1]: vasopressor need identified patients with greater iNOS induction, which, in turn, may have resulted in DDAH nitrosylation – and thereby inactivation – which finally resulted in higher ADMA levels that blocked the activities of both constitutive and inducible NO synthases (Figure 2). Alternatively, compromised kidney and liver function secondary to tissue malperfusion may have led to reduced metabolic clearance of ADMA by DDAHs [12,13]. The study did not, however, report any data to support or refute any of these hypotheses. ADMA may interfere, by nonspecific inhibition of NO synthases, with critical physiological functions, eventually giving rise to a cascade of organ dysfunction that may be fatal to the critically ill patient [12].

With ADMA as a novel player in the game, understanding the role of NO in the 'live and let die' issue of septic shock has become even more complex. Measuring ADMA levels should certainly be considered in future studies on NO in critically ill patients.

Competing interests

RHB is named as an inventor on patents relating to endogenous inhibitors of the nitric oxide pathway and receives royalties from licenses thereof.

References

- O'Dwyer MJ, Dempsey F, Crowley V, Kelleher D, McManus R, Ryan T: **Septic shock is correlated with asymmetrical dimethyl arginine levels, which may be influenced by a polymorphism in the dimethylarginine dimethylaminohydrolase II gene: a prospective observational study.** *Crit Care* 2006, **10**:R139.
- Wheeler AP, Bernard GR: **Treating patients with severe sepsis.** *N Engl J Med* 1999, **340**:207-214.
- Kilbourn R: **The discovery of nitric oxide as a key mediator in septic shock.** *Sepsis* 1998, **1**:85-91.
- Boyle WA 3rd, Parvathaneni LS, Bourlier V, Sauter C, Laubach VE, Cobb JP: **iNOS gene expression modulates microvascular responsiveness in endotoxin-challenged mice.** *Circ Res* 2000, **87**:E18-E24.
- Alden KJ, Motew SJ, Sharma AC, Ferguson JL: **Effect of aminoguanidine on plasma nitric oxide by-products and blood flow during chronic peritoneal sepsis.** *Shock* 1998, **9**:289-295.
- Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, Brockway M, Anzueto A, Holzapfel L, Breen D, *et al.*: **Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock.** *Crit Care Med* 2004, **32**:21-30.
- Cobb JP, Hotchkiss RS, Swanson PE, Chang K, Qiu Y, Laubach VE, Karl IE, Buchman TG: **Inducible nitric oxide synthase (iNOS) gene deficiency increases the mortality of sepsis in mice.** *Surgery* 1999, **126**:438-442.
- Böger RH: **The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor.** *Cardiovasc Res* 2003, **59**: 824-833.
- Cooke JP: **Asymmetrical dimethylarginine: the Uber marker?** *Circulation* 2004, **109**:1813-1818.
- Vallance P, Leiper J: **Cardiovascular biology of the asymmetric dimethylarginine: dimethylarginine dimethylaminohydrolase pathway.** *Arterioscler Thromb Vasc Biol* 2004, **24**:1023-1030.
- Böger RH: **Asymmetric dimethylarginine (ADMA): a novel risk marker in cardiovascular medicine and beyond.** *Ann Med* 2006, **38**:126-136.
- Nijveldt RJ, Teerlink T, van Leeuwen PA: **The asymmetrical dimethylarginine (ADMA)-multiple organ failure hypothesis.** *Clin Nutr* 2003, **22**:99-104.
- Nijveldt RJ, Teerlink T, Van Der Hoven B, Siroen MP, Kuik DJ, Rauwerda JA, van Leeuwen PA: **Asymmetrical dimethylarginine (ADMA) in critically ill patients: high plasma ADMA concentration is an independent risk factor of ICU mortality.** *Clin Nutr* 2003, **22**:23-30.
- Cuzzocrea S, Mazzon E, Di Paola R, Esposito E, Macarthur H, Matuschak GM, Salvemini D: **A role for nitric oxide-mediated peroxynitrite formation in a model of endotoxin-induced shock.** *J Pharmacol Exp Ther* 2006, **319**:73-81.
- Leiper J, Murray-Rust J, McDonald N, Vallance P: **S-nitrosylation of dimethylarginine dimethylaminohydrolase regulates enzyme activity: further interactions between nitric oxide synthase and dimethylarginine dimethylaminohydrolase.** *Proc Natl Acad Sci USA* 2002, **99**:13527-13532.