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Review

The Role of Arginine in Infection and Sepsis

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ABSTRACT. Sepsis is a systemic response to an infection, with high morbidity and mortality rates. Metabolic changes during infection and sepsis could be related to changes in metabolism of the amino acid L-arginine. In sepsis, protein breakdown is increased, which is a key process to maintain arginine delivery because both endogenous *de novo* arginine production from citrulline and food intake are reduced. Arginine catabolism, on the other hand, is markedly increased by enhanced use of arginine *via* the arginase and nitric oxide pathways. As a result, lowered plasma arginine levels are usually found. Arginine may therefore be considered as an essential amino acid in sepsis, and supplementation could be beneficial in sepsis by improving microcirculation and protein anabolism.

L-Arginine supplementation in a hyperdynamic pig model of sepsis prohibits the increase in pulmonary arterial blood pressure, improves muscle and liver protein metabolism, and restores the intestinal motility pattern. Arguments raised against arginine supplementation are mainly pointed at stimulating nitric oxide (NO) production, with concerns about toxicity of increased NO and hemodynamic instability with refractory hypotension. NO synthase inhibition, however, increased mortality. Arginine supplementation in septic patients has transient effects on hemodynamics when supplied as a bolus but seems without hemodynamic side effects when supplied continuously.

In conclusion, arginine could have an essential role in infection and sepsis. (*Journal of Parenteral and Enteral Nutrition* **29:**S70–S74, 2005)

Sepsis is defined as a systemic response to an infection[1,2] and is a serious health problem that generally requires intensive care treatment.[3] There is growing evidence that metabolic changes in sepsis are related to changes in arginine metabolism, which may also indicate that arginine is an essential amino acid in sepsis. This would also make arginine supplementation a valid therapy. In this section, we will overview arginine metabolism in infection/sepsis and arginine supplementation in a pig model of sepsis and in septic patients.

Changes in Arginine Metabolism in Infection/Sepsis

Arginine metabolism (Fig. 1A). Arginine is a nonessential amino acid under normal conditions, derived from food intake (about 5–6 g daily),[4,5] from breakdown of protein proteins and *de novo* synthesized from citrulline in the kidney.[6,7] The main source of citrulline in the body is by conversion from glutamine in the gut.[8,9] Besides these anabolic arginine routes, arginine is catabolized through various pathways.[7] First, arginine is incorporated in body proteins. Second, arginine is substrate for synthesis of urea and ornithine by the enzyme arginase. Ornithine is an important substrate for polyamines and therefore important for cell growth and differentiation.[10] Third, arginine is the only substrate for synthesis of nitric oxide (NO) by the enzyme NO synthase (NOS), of which isoforms are known in neuronal cells (NOS1), in macrophages (NOS2), and in endothelial cells (NOS3).[11,12] This makes NO important as a neurotransmitter, as a component in the immune response and for vascular tension, respectively. Finally, arginine is a source for synthesis of creatine and agmatine.[7] Under normal conditions, about 1.2% of plasma arginine production is used for NO synthesis, whereas this percentage is about 15% for urea synthesis.[13]

Arginine metabolism in infection/sepsis (Fig. 1B). Infection is characterized by metabolic changes, which imply both anabolic and catabolic arginine routes. To increase arginine availability, body protein breakdown is increased,[14] and *de novo* arginine synthesis in the kidney in increased, at least in moderate inflammation.[15] In severe inflammation, *de novo* arginine production even seems reduced.[15] Food intake is often reduced, which further compromises arginine delivery. On the catabolic site, the demand for arginine for protein synthesis, like synthesis of acute phase proteins, is increased.[16] Moreover, arginase and NOS pathways are increased and therefore consume more arginine.[14,17–19] Although in moderate inflammation the balance between arginine anabolism and arginine catabolism can be maintained, arginine catabolism probably overrides anabolism in severe inflammation and, as a result, plasma arginine levels drop. Lowered plasma arginine levels are found in sepsis.[14,20–22]

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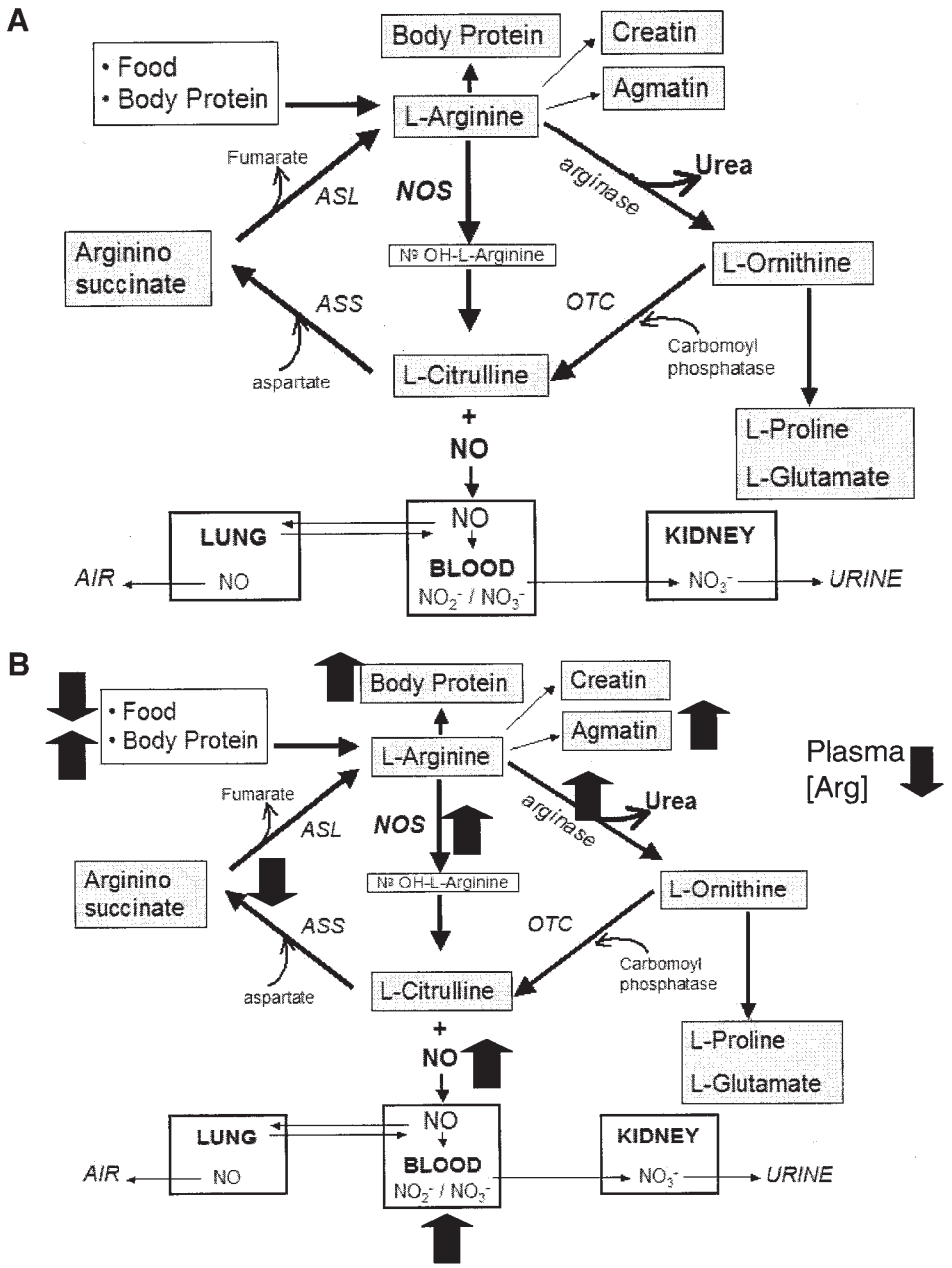

FIG. 1. *A*, Metabolic pathways of Arginine. Adapted from Luiking YC, Deutz NE. Isotopic investigation of nitric oxide metabolism in disease. *Curr Opin Clin Nutr Metab Care.* 2003;6:103–108, reproduced with permission from Lippincott Williams & Wilkins. B, Changes in catabolic and anabolic Arginine pathways during severe inflammation/sepsis, with a decrease in plasma Arginine level as a result.

Hypothesis: Arginine Is an Essential Amino Acid in Sepsis

Considering the changes in arginine metabolism in sepsis and the resultant drop in plasma arginine levels, arginine may be considered an essential amino acid in sepsis. Moreover, sepsis and inflammatory states may be considered as disease states with a specific arginine need, regarding the need for NO, for inflammatory proteins and for improved cell proliferation.

Although inflammation increases activity of the NOS2 enzyme and subsequently increases NO production, diminished NOS3 activity has also been shown.[23] This reduced NOS3 activity could contribute to diminished microcirculation, whereas increased NOS2 could be an adaptive response to limit tissue injury through compensation of reduced NOS3 NO production.[19] Shunting in sepsis accounts for the condition in which apparently adequate oxygen delivery is not successful in delivering oxygen to shunted microcirculatory units, whereas vasodilatation could recruit these shunted units.[24]

Arginine Supplementation

Human sepsis is a hyperdynamic state, which is characterized by prolonged endotoxin release and fluid support. Fluid support is needed to maintain blood pressure. For the same reason, vasopressor therapy is

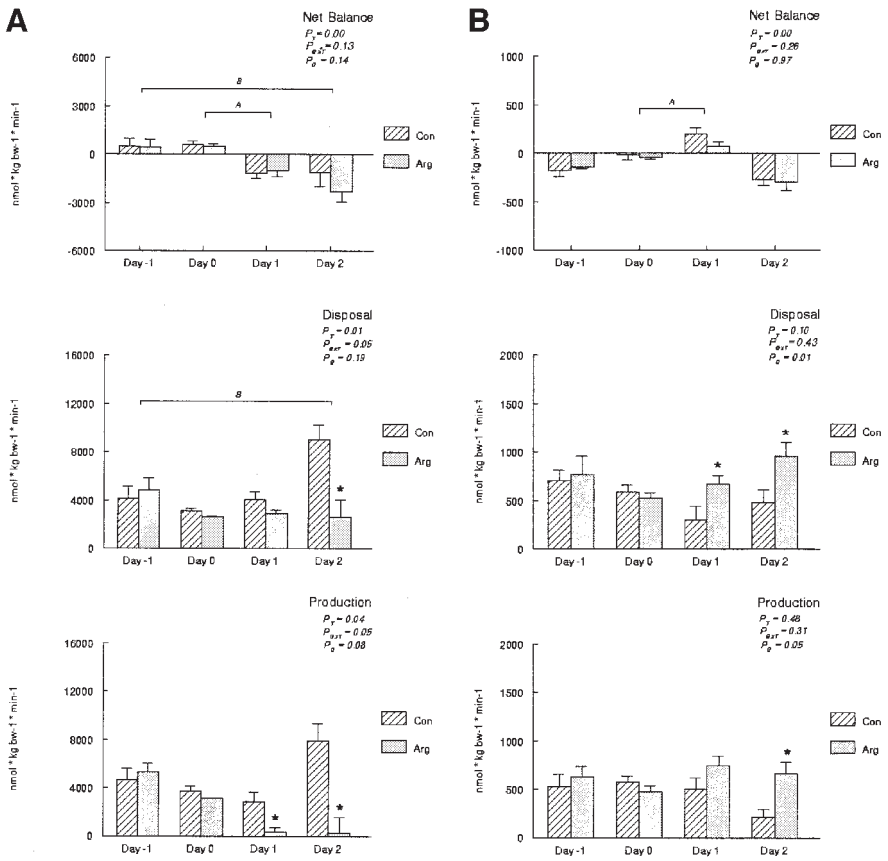

FIG. 2. *A*, Liver valine net balance, disposal (protein synthesis) and production (protein breakdown) in pigs before endotoxin infusion in the fed (day −1) or fasting state (day 0), during IV L-alanine (Con) or L-arginine (Arg) (day 1), and after intragastric L-alanine or L-arginine (day 2). Adapted from Bruins MJ, Soeters PB, Lamers WH, Deutz NE. L-arginine supplementation in pigs decreases liver protein turnover and increases hindquarter protein turnover both during and after endotoxemia. *Am J Clin Nutr.* 2002;75:1031–1044. Reproduced with permission by the *American Journal of Clinical Nutrition*, © Am J Clin Nutr, American Society for Clinical Nutrition. *B*, Hindquarter phenylalanine net balance, disposal (Protein synthesis) and production (protein breakdown) in pigs before endotoxin infusion in the fed (day −1) or fasting state (day 0), during IV L-alanine (Con) or L-arginine (Arg) (day 1), and after intragastric L-alanine or L-arginine (day 2). Adapted from Bruins MJ, Soeters PB, Lamers WH, Deutz NE, L-arginine supplementation in pigs decreases liver protein turnover and increases hindquarter protein turnover both during and after endotoxemia. *Am J Clin Nutr.* 2002;75:1031–1044. Reproduced with permission by the *American Journal of Clinical Nutrition*, © Am J Clin Nutr, American Society for Clinical Nutrition.

also given. Even though blood pressure is controlled, cardiac output and heart rate are both increased.[1,2]

Arginine Supplementation in a Pig Model of Sepsis

In a pig model of sepsis in our laboratory, we used 24-hour IV LPS (*E. coli* 055:B5, 3 μg kg bw^{-1} h^{-1}) infusion, and IV fluid support with 150 mmol/L NaCl (30 mL kg^{-1} h^{-1} during first 8 hours after start LPS; 20 mL kg^{-1} h^{-1} from 8 to 30 hours after start of LPS). We observed an increase in heart rate, temperature, and cardiac output in this model, with a rather stable mean arterial blood pressure.[14,25] Also, no mortality was observed in this model. This model therefore is considered suitable to study effects of L-arginine supplementation during sepsis.

Treatment of septic pigs with L-arginine (5.3 μmol kg bw^{-1} min^{-1}) from 8 hours after the start of LPS resulted in a rise of plasma arginine to 300 to 500 μmol/L and a concomitant rise of arginine appearance in plasma.[26,27] When compared with the isocaloric placebo L-alanine (10.6 μmol kg bw^{-1} min^{-1}), NO production was increased with L-arginine supplementation.[14,26] Protein kinetics in the liver of these animals indicated a relative reduction of both protein synthesis and protein breakdown, with stimulated protein synthesis as a net resultant at 24 hours after termination of LPS infusion (Fig. 2*A*).[27] Muscle protein synthesis and breakdown were maintained by L-arginine supplementation, whereas net muscle protein breakdown was reduced after 24 hours' LPS (Fig. 2*B*).[27] As a measure of gut function, the gut motility pattern, characterized by migrating motor complexes (MMCs), was monitored. LPS treatment increased the frequency and migration velocity of the MMCs,[28] which was normalized by L-arginine supplementation (Bruins et al, unpublished data).

Using the same pig model of sepsis, but with L-arginine supplementation started at 8 hours before LPS infusion, a similar rise in plasma arginine was observed, whereas NO production was already increased at the time LPS infusion started (Poeze et al, unpublished data). Similar changes in mean arterial blood pressure and cardiac output were observed. In addition, pulmonary arterial pressure was maintained

during L-arginine infusion, whereas pressure increased during LPS infusion alone (Poeze et al, unpublished data). Plasma flow to the gut and the liver increased when LPS was infused with L-arginine (Poeze et al, unpublished data).

Suggested Benefits of L-Arginine Supplementation From Pig Studies

From these pig studies, several arguments for arginine supplementation can be deduced. First, L-arginine can be given safely to pigs in our sepsis model with improvement of perfusion. Second, L-arginine prohibits the increase in pulmonary arterial blood pressure, improves muscle and liver protein metabolism, and restores the intestinal motility pattern. Finally, use of a selective NOS2 inhibitor reduced NO production, whereas it induced late mortality in a zero-mortality model (50% mortality after 48 hours).[29]

Suggested Arguments Against Arginine Supplementation in Sepsis

Arguments raised against arginine supplementation are mainly pointed at stimulating NO production, with concerns about toxicity of increased NO and hemodynamic instability with refractory hypotension.[30–32] When considering toxicity, formation of peroxynitrite by enhanced NO may cause tissue damage.[33] However, this increased peroxynitrite formation occurs mainly in conditions of reduced arginine availability.[34] Adequate arginine availability seems therefore warranted. Moreover, NO is considered cytotoxic because of inhibition of mitochondrial electron-transfer enzymes, which are involved in cell respiration, by inhibition of enzymatic substrate use and detoxifying enzymes and by inhibiting nuclear DNA synthesizing enzymes.[35] However, a phase III multicenter trial in septic shock patients using a NOS inhibitor was discontinued because of increased mortality.[36,37]

Arginine Supplementation in Septic Patients

LArginine supplementation in septic patients as a monotherapy is rare because L-arginine is often supplied as one of the components of immunonutrition.[38–40] Only 1 reference describes L-arginine bolus (200 mg kg^{-1}) administration in 7 patients with septic shock, given between 7 and 13 days of shock.[41] Although mean arterial blood pressure dropped and cardiac index increased, all changes were transient and noted 1 minute after administration of L-arginine. The authors describe no adverse effects. When considering a normal daily intake of 5–6 g, this bolus contains about a 3-fold daily load administered all at once. When considering the increase in plasma arginine with immunonutrition,[38] plasma arginine levels increase about 2.5-fold.

We recently started continuous L-arginine supplementation in septic-shock patients within 48 hours of diagnosis, using L-arginine doses ranging from 0.6 to 1.8 $\mu mol.kg^{-1}\ min^{-1}$ (Luiking et al, unpublished data). When considering hemodynamic parameters, no changes in mean arterial pressure, cardiac output, and pulmonary pressure have been observed.

DISCUSSION

Metabolic changes during sepsis indicate that arginine could be considered as an essential amino acid in sepsis and that sepsis could be an arginine-deficient state. Arginine supplementation could subsequently be beneficial in sepsis by improving microcirculation and protein anabolism. This hypothesis is further supported by the detrimental effects of selective NOS2 inhibition in the hyperdynamic pig model of sepsis. Moreover, arginine supplementation in septic patients has transient effects on hemodynamics when supplied as a bolus but has probably no hemodynamic side effects when supplied continuously.

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