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Arginine in the Critically Ill: Can we Finally Push Past the Controversy?

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Abstract

Arginine is a conditional amino acid that has a wide breadth of metabolic activity and applications when supplemented. During critical illness, high stressed states, and increased metabolic demand arginine becomes an essential amino acid. It is during this time that supplementation benefits the host. Arginine supplementation during sepsis, however, has remained controversial as there is theoretical harm stemming from arginine serving as a substrate for nitric oxide production. In this review we discuss the literature both in support of and against the use of arginine in all critically ill patients, as well as, advocate for ongoing research to better understand appropriate dosage of arginine in relation to the arginine: asymmetric dimethylarginine ratio.

Keywords

Arginine, Sepsis, Nutrition, Asymmetric dimethylarginine, ADMA

Introduction

When Ernst Schultze, a Swiss chemist, first isolated arginine from lupin seedling extract in 1886 he probably did not anticipate its wide use in nutritional supplementation for medical purposes. Arginine is a conditional amino acid meaning its requirement is dependent the person's health status. Normally, a non-essential amino acid during periods of good health, arginine becomes an essential amino acid during periods of metabolic or traumatic stress as the endogenous supply is inadequate to meet physiologic demand [1-4]. Arginine supplementation has a wide breadth of applications ranging from better outcomes for plastic surgery free flap reconstruction and wound healing to treatment of preterm labor and pulmonary hypertension, with relatively low side effects (GI upset being the most common). Arginine, however, in the septic, critically ill patient has been a controversial supplement because of the *theoretical* adverse vasodilatory properties.

Therefore the purpose of this article is to discuss a) the role of arginine in health, b) arginine depletion in critical illness, c) the ramifications of arginine depletion, and d) the controversy surrounding arginine and sepsis. We intend to provide convincing evidence that arginine supplementation is not only beneficial in severe sepsis, but can be safely provided to patients with critical illness.

Arginine in health

As a non-essential amino acid, arginine can be synthesized from 3 primary sources. 1) Diet contributes 25-30% of total daily arginine, 2) endogenous arginine can be synthesized in the urea cycle by conversion of citrulline in the kidney, and 3) from protein turnover/breakdown. Circulating arginine levels are kept in balance by arginase-1, which serve as constitutive and inducible enzymes tasked with hydrolyzing arginine to ornithine and urea [5]. It should also be mentioned that circulating arginine differs from tissue arginine, which is tightly controlled by cationic amino acid transporter (CAT) [6]. These transporters can serve as constitutive, pH independent transporters (CAT1) or inducible, pH dependent transporter (CAT2). Although CAT1 could function during acidosis (sepsis) it functions as an exchange transporter, which is set up by intracellular gradient. CAT 2 looses 50% of its transport capabilities at lower pH [6-8].

Another physiologic component of arginine is a counter balance with asymmetric dimethyl arginine (ADMA), which will be discussed later in the manuscript. ADMA has vasoconstriction properties, and can block the iNOS enzymatic production of NO. The regulation of arginine: ADMA ratio is elaborate, but in brief, arginine bound to protein carriers can be methylated by protein arginine methylarginase (PRMT) to form methylagrinines (mono- and di-methylarginines). ADMA in turn, can be metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to generate citrulline, which can be converted back to arginine via argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) [9-11].

Citrulline can be a byproduct of the pathway described above or can be produced in the intestines from glutamine, and then converted to arginine with the same enzymes ASS/ASL in the urea cycle. Ultimately, the final outcome is endogenous arginine. One of arginine's fates is to serves as a substrate for nitric oxide (NO) production, which has local vasodilatory properties. This reaction

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is carried out by three isoforms of nitric oxide synthase (endothelial Nitric Oxide Synthase, inducible Nitric Oxide Synthase, neuronal Nitric Oxide Synthase). Arginine also serves as an intermediate amino acid during proline synthesis, which is required for wound healing and collagen synthesis [12-14]. Finally, arginine's role in immune-competence is that it serves as an intra-cellular substrate for NO production in macrophages to improve bactericidal activity, as well as, improves T cell function, proliferation, and maturation [15-21].

Arginine depletion in critical illness

Arginine intake from a typical diet is between 5 and 7 g/d, while endogenous production of arginine is estimated at 15 to 20 g. These values quickly deteriorate during critical illness such as trauma, sepsis, or other acute stress such as surgery. In fact, not only is de novo synthesis of arginine reduced to one third of the normal level (either by a decrease in citrulline conversion or preferential use in gluconeogenesis, etc.) but arginase, an enzyme responsible for arginine catabolism to urea and ornithine is up-regulated 4-fold [22-24]. Arginase exists in two isofroms and has a broad tissue distribution. A cytosolic form, arginase I (AI), is expressed in the liver and thought to be involved in ureagenesis. Arginase II (AII) has been thought to be more involved in the biosynthesis of polyamines, the amino acids ornithine, proline, and glutamate and in the inflammatory process [25]. Thus, the ramifications of withholding arginine supplementation from critically ill patients, especially at the height of their inflammatory process would be deleterious and will be discussed in the next section "Ramifications of arginine depletion".

During critical illness the expansion of immature myeloid derived suppressor cells (MDSCs which are immature granulocytes and monocytes) play an integral role in the "emergency myelopoietic" response that is aimed at preserving innate immunity. The body sacrifices lymphocyte production (i.e., adaptive immunity) to produce MDSCs (i.e., innate immunity) [26]. Acutely, their expansion is believed to be protective, but fight infections poorly. However, long term they cause persistent inflammation (via nitric oxide, myeloperoxidase and reactive oxygen species), have poor antigen presentation, elaborate pro-inflammatory cytokines, potentiate an acute cachexia-like state, and cause immunosuppression (via decreased T-cell proliferation through secretion of arginase-1 and inflammatory cytokines) [27-37].

Arginase, as discussed earlier, is an enzyme that reduces the circulating arginine levels thus making severe stress and critical illness an "arginine deficient" state [15,22,30,38-41]. While the endogenous supply of arginine is drastically decreased and even consumed by arginase, the cellular demand for arginine is increased because it is needed for T cell proliferation and activity required by an inflammatory condition. As stated above, during critical illness arginine becomes an essential amino acid that would benefit from supplementation, yet the fear of *theoretical*, (not clinically proven) catastrophic vasodilation with resultant hypotension and organ malperfusion in the setting of sepsis deters physicians from prescribing this essential amino acid to patients.

Ramifications of arginine depletion

Arginine deficiency is clinically relevant and phenotypically seen as the patient post severe stress (surgery, sepsis, trauma) has recurrent nosocomial infections, poor wound healing, deranged laboratory markers for inflammation, and been nil per os. During critical illness enzymes in the urea cycle can be bidirectional depending on the body's need for arginine, but at a high cost to an already catabolic patient: 2 molecules of adenosine triphosphate for every one arginine replenished. Therefore, the first ramification of arginine depletion in critical illness is a perpetual taxing energy drain that could be reversed with nutritional supplementation, and allow the body to conserve its energy for other vital needs.

Arginine is also used as a substrate for hydroxyproline synthesis that is necessary for collagen production and wound healing [12-14]. Perhaps one of the most influential researchers of arginine, Barbul *et al.* in the 1990's demonstrated that arginine supplementation increased wound healing by allowing the host to make more collagen [12,42,43]. The role of arginine supplementation in wound healing isn't just amplified collagen production by providing proline substrate, but can also provide local vasodilation through nitric oxide. The resultant vasodilation allows for locally increased blood flow and nutrients to cells undergoing repair. Thus post-operative patients and critically ill patients with large wounds with inadequate arginine heal slower with less tensile strength.

The ultimate end point, and arguably the most important ramification of arginine depletion, is an immunosuppressed state as arginine deficiency leads to T-lymphocyte suppression and lack of proliferation [15-17]. Lack of T-lymphocyte expansion secondary to arginine depletion leads to reduced circulating CD-4 cells to help fight infection. Not only is there decreased proliferation, but even the T cells that remain in circulation have loss of function secondary to loss of the zeta chain peptide in the T cell receptor (TCR) [16,41,44,45]. Arginine serves as the backbone for the zeta chain which is essential for the TCR. Furthermore, limited arginine coupled with loss of T-cell expansion and its receptor function results in a complex, multi-level impaired immune response and incompetence contributing to an increased risk of nosocomial infections in the critically ill patients [16].

Controversy surrounding arginine and sepsis

Of all the pharmaconutrients currently being prescribed, arginine has prompted the most debate which revolves around the safety of its use in hemodynamically unstable severe sepsis patients. This form of shock is based off uncontrolled, decompensated vasodilation. Therefore, some propose that adding an agent that could shunt toward more NO production through the iNOS pathway could promote worsening hypotension, possibly refractory hypotension [2,46,47]. The theoretical increase in NO production in sepsis has been attributed to stimulation of NOS-2 by pro-inflammatory cytokines [15,48], was based on increases in plasma nitrate levels and increased NOS gene expression (not actual measurements of NO) [49-53].

This concern promulgated by Heyland *et al.* based on the results of their meta-analysis. Consistent with three other contemporary meta-analyses, it showed that enteral diets (containing a cocktail of immune modulating nutrients including arginine) compared to standard enteral diets decreased infections and length of hospital stay [54]. While none of the meta-analyses (including Heyland's) demonstrated a difference in mortality. Heyland *et al.* then performed a subgroup analysis in which medical ICU patients receiving arginine had increased mortality. The authors concluded that this increased mortality was due to the use of arginine in patients with severe sepsis. We have several concerns with their conclusions.

First, it is a subgroup analysis of a meta-analysis. Most experts would agree this subgroup analysis should only have been used to generate a hypothesis, not condemn arginine's use in ICU patients. Second, the observation was statistically driven by two studies that did not specifically include severe sepsis patients. One was by Dent *et al.* that remains unpublished and the second was by Bertolini *et al.* that was an interim analysis of only 39 patients (this study was not blinded, was actually a subgroup of larger multicenter trial designed to see if EN vs PN was better for critically ill none septic patients, and was poorly powered to truly see significant mortality differences) [55]. Third, the only study that specifically included patients with severe sepsis by Galban *et al.* demonstrated improved outcomes with no increased mortality [56]. In this study, "one hundred seventy-six (89 Impact patients, 87 control subjects) were eligible for intention-to-treat analysis. The mortality rate was reduced for the treatment group compared with the control group (17 of 89 vs. 28 of 87; $p < 0.05$). Bacteremia was reduced in the treatment group (7 of 89 vs. 19 of 87; $p = 0.01$) as well as the number of patients with more than one nosocomial infection (5 of 89 vs. 17 of 87; $p = 0.01$). The benefit in mortality rate for the treatment group was more pronounced for patients with APACHE II scores between 10 and 15 (1 of 26 vs. 8

of 29; p = 0.02)" [56]. Montejo and Galban followed this study up in 2003 with another report concluding, "Considering the beneficial effects and the absence of detrimental ones, the use of diets enriched with pharmaconutrients could be recommended in ICU patients requiring enteral feeding", but this was not included in Heyland's meta-analysis [57].

Heyland's contention has generated a lot of "expert opinion" concern and editorial chatter; because it is theoretically possible arginine supplementation could increase mortality in severe sepsis. This was even observed in a canine model of sepsis by Kalil *et al.* [58]. They provided parenteral arginine and observed that, "supplemental parenteral L-arginine, at doses above standard dietary practices, should be avoided in critically ill patients with septic shock," as there was increased mortality in the supplemented cohort. The doses used in the canine study (10 or 100 mg/kg/hr) in parenteral nutrition is equivalent to a supraphysiological dose of 200-300 mg/day for a human. This is well above the current nutritional recommendation of 15-30 mg/day and thus the clinical relevance of this a canine model is highly questionable.

In exposing the study flaws in the negative trails we can now accept that the conclusion derived from their observation likely should not reflect arginine's use in critical care and sepsis. In fact, there have even been rebuttals to these trials. Recently, in an attempt to quell the controversy raised by Kalil's canine study, Luiking *et al.* took 8 critically ill patients with a diagnosis of septic shock and infused varying doses of L-Arginine-HCl in three stepwise-increasing doses (33, 66 and 99 μmol/kg/h). She reported "septic patients demonstrated elevated protein breakdown at baseline ($P < 0.001$ compared with healthy controls), whereas protein breakdown decreased during arginine infusion ($P < 0.0001$). Mean arterial pressure, mean pulmonary pressure and regional gastric mucosal carbon dioxide (PrCO2- measured by tonometry) did not change during arginine infusion ($P > 0.05$), whereas stroke volume (SV) increased ($P < 0.05$) and arterial lactate decreased ($P < 0.05$)" [59]. Thus Luiking showed that supraphysiologic arginine supplementation (give the comparative dose provided in these patients) not only decreased endogenous protein catabolism, but also reversed septic shock (as reflected by increased SV and lactate clearance) without compromising systemic hemodynamics or gut mucosal perfusion [59]. Though the power of this study is not very large, it seriously questions the validity of the Kalil's canine model and their conclusions, as there was no hypotension noted in humans.

Luiking suggests that arginine supplementation may increase NO, but it is not clinically detrimental as no refractory hypotension incurs after supplementation. In fact, on a cellular and microvascular level arginine supplementation in the septic, arginine-deplete state could be paramount for adequate end organ perfusion. The difference between local and systemic vascular tone can be described by varying concentrations of ADMA. ADMA also serves not only a potent vasoconstrictor, but also blocks the enzymatic production of NO. During times of septic shock the systemic results of ADMA may be to block NO production, but locally NO causes controlled vasodilation in an attempt to mitigate the increasing oxygen debt and modulate perfusion. This hypothesis of controlled, local microvasculature vasodilation being beneficial in critical illness and sepsis was tested in several animal and human studies as described below.

In 1979, Freund *et al.* suggested that decreasing arginine levels can be used as a predictor of severity and outcome of sepsis [60]. Reinforcing this original concept, in 2011, Gough *et al.* published that out of 109 septic patients and 50 controls, a ratio of arginine: ADMA was predictive of in hospital and 6 month mortality. "A declining arginine-to-dimethylarginine ratio was independently associated with hospital mortality (odds ratio, 1.63 per quartile; 95% confidence interval, 1.00-2.65; p = 0.048) and risk of death over the course of 6 months (hazard ratio, 1.41 per quartile; 95% confidence interval, 1.01-1.98; p = 0.043)" [61]. They concluded that this ratio is indicative of severe sepsis and clinical outcomes, as well as, provides the rationale for arginine supplementation for this patient group.

Finally, Visser *et al.* had two reports (2012 and 2014) that tested the above hypothesis and demonstrated that elevated arginine and lower ADMA resulted in improved mortality in septic patients. A lower ratio of arginine to ADMA resulted in poor organ perfusion and decreased cardiac output [62,63]. The 2012 report demonstrated that the "arginine: ADMA ratio showed an association (OR 0.976, 95% CI 0.963, 0.997, P = 0·025) and a diagnostic accuracy (area under the curve 0.721, 95% CI 0.560, 0.882, P = 0·016) for hospital mortality, whereas the arginine or ADMA concentration alone or APACHE II-predicted mortality failed to do so" [63]. The conclusion was that the imbalance of arginine and ADMA is directly related to circulatory failure, organ failure, disease severity, and predicts mortality. The mechanism that Visser proposes is that the imbalance of "arginine: ADMA ratio contributes to endothelial and cardiac dysfunction resulting in poor organ perfusion and organ failure, thereby increasing the risk of death" [63]. The research is profound and the possible implications of supplementing arginine could restore the arginine: ADMA ratio, therefore, provide mortality benefit in septic patients. Further research, however, must continue to determine if there is a direct correlation, not just theoretical, with correcting the arginine: ADMA ratio, and at what dose or plasma concentration. Perhaps arginine supplementation should not be just a set number of grams a day, but be a part of goal directed therapy to restore the arginine: ADMA ratio to a pre-determined set point.

Paralleling the human studies above, Arora *et al.* in 2012, published a study using rodents as a 40% hemorrhagic shock model and demonstrated that arginine supplementation improved global perfusion. They also suggested that overriding ADMA seemed to be the primary mechanism [64]. Whether this model is clinically relevant to sepsis in humans as a way to improve perfusion is arguable as the mechanism for shock is drastically different, but what it does suggest is that the potent vasoconstriction of ADMA without the counter balance effects of arginine can be deleterious.

Ultimately, it is difficult to determine if single supplemental arginine correlates with direct outcomes for septic patients. Most studies evaluating outcomes with single agent use of arginine are animal studies, whereas, in humans arginine is typically provided along with other diverse immunomodulatory formulas. Six years ago, Luiking *et al.* took 33 patients (10 septic shock patients, 7 critically ill, and 16 healthy elderly patients) and studied citrulline and arginine metabolism after a 2 hour stable isotope infusion of phenylalanine, tyrosine, arginine, citrulline, and urea was then started for simultaneous measurement of protein and arginine metabolism. NO production was calculated as the conversion rate of arginine to citrulline; de novo arginine production was calculated as the conversion rate of citrulline to arginine.

In this intricate tracer study of septic patients compared to controls, Luiking *et al.* in 2009, demonstrated that not only is arginine production and availability (as a measure of the isotope conversion) greatly reduced, but so was NO production (as evidenced by decreased citrulline production from NO synthase conversion of arginine) [65]. In another investigation, using a similar purified strategy to determine if arginine supplementation equates to increase NO production, Kao *et al.* used tracer technology to again evaluated arginine in sepsis. They concluded "whole-body arginine production and NO synthesis were similar in patients with sepsis/septic shock and healthy controls. Despite increased proteolysis in sepsis, there is a decreased arginine plasma concentration, suggesting inadequate de novo synthesis secondary to decreased citrulline production" [47]. Additionally, as revealed earlier, Luiking in 2015 went on to study supraphysiologic dose of intravenous arginine supplementation in septic patient, and noted that there were no untoward hypotensive alterations in hemodynamics [59]. These three studies represent the future direction of arginine supplementation, and reflect that arginine supplementation is safe in critical illness and septic shock.

In conclusion, arginine plays an intricate role in wound healing, NO production, and T-lymphocyte function, proliferation, and maturation. All three of these physiologic roles are important to a critically ill patient,

and especially to septic patients. The complex metabolic alterations noted in sepsis that contribute to reduced citrulline and arginine availability would suggest that supplemental arginine may, in fact, be beneficial in the highly stress, septic population. Ultimately, just because arginine can be a substrate for NO production (which can be a significant vasoactive agent) doesn't necessarily mean it will affect the systemic circulatory system. In fact, based off the last three studies discussed in this article, supplemental arginine and citrulline 1) does not alter NO production, 2) confirms that sepsis is an arginine deficient state, 3) does not cause hemodynamic changes (even when supraphysiologic doses are used), and 4) can improve morbidity and mortality in the critically ill. A prospective trial of arginine supplementation with a targeted arginine: ADMA is needed.

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No conflict of or competing interests have been declared.

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