The Acute Effects of L-arginine on Hormonal and Metabolic Responses During Submaximal Exercise in Trained Cyclists

Scott C. Forbes, Vicki Harber, and Gordon J. Bell

L-arginine may enhance endurance performance mediated by two primary mechanisms including enhanced secretion of endogenous growth hormone (GH) and as a precursor of nitric oxide (NO); however, research in trained participants has been equivocal. The purpose was to investigate the effect of acute L-arginine ingestion on the hormonal and metabolic response during submaximal exercise in trained cyclists. Fifteen aerobically trained men (age: 28 ± 5 y; body mass: 77.4 ± 9.5 kg; height: 180.9 ± 7.9 cm; VO2max: 59.6 ± 5.9 ml·kg\(^{-1}\)·min\(^{-1}\)) participated in a randomized, double-blind, crossover study. Subjects consumed L-arginine (ARG; 0.075 g·kg\(^{-1}\) body mass) or a placebo (PLA) before performing an acute bout of submaximal exercise (60 min at 80% of power output achieved at ventilatory threshold). The ARG condition significantly increased plasma L-arginine concentrations (~146%), while no change was detected in the PLA condition. There were no differences between conditions for GH, nonesterified fatty acids (NEFA), lactate, glucose, VO2, VCO2, RER, CHO oxidation, and NOx. There was reduced fat oxidation at the start of exercise (ARG: 0.36 ± 0.25 vs. PLA: 0.42 ± 0.23 g·min\(^{-1}\), \(p<.05\)) and an elevated plasma glycerol concentrations at the 45-min time point (ARG: 340.3 vs. PLA: 288.5 \(\mu\)mol·L\(^{-1}\), \(p<.05\)) after L-arginine consumption. In conclusion, the acute ingestion of L-arginine did not alter any hormonal, metabolic, or cardio-respiratory responses during submaximal exercise except for a small but significant increase in glycerol at the 45-min time point and a reduction in fat oxidation at the start of exercise.

L-arginine (2-amino-5-guanidinovaleric acid) is a conditionally essential amino acid and has been purported to be ergogenic (Bailey et al., 2010; Bescós et al., 2012b; Paddon-Jones et al., 2004). It has been suggested that L-arginine can enhance endurance exercise performance by two primary mechanisms including an enhanced secretion of endogenous growth hormone (GH; Kanaley, 2008) and as a precursor for nitric oxide (NO). First, GH may influence endurance exercise performance by enhancing lipolysis (Møller et al., 1990) and fat oxidation (Gravholt et al., 1999). During submaximal exercise, GH administration increases plasma glycerol and nonesterified free fatty acids (NEFAs) in healthy (Hansen et al., 2005; Lange et al., 2002) and well-trained endurance cyclists (Hansen et al., 2005; Healy et al., 2006). These effects may in turn increase time to exhaustion during exercise by sparing skeletal muscle and liver glycogen (Bescós et al. 2012a; Phillips et al., 2011). Secondly, L-arginine may enhance endurance performance through a greater NO production (Bailey et al., 2010; Bescós et al. 2012a). Nitric oxide is a signaling molecule produced by the nitric oxide synthase (NOS) group of enzymes, which catalyze the oxidation of L-arginine, the essential NOS substrate (Bescós et al., 2012b; Moncada et al., 1989). NO production can elevate cyclic guanosine monophosphate (cGMP), resulting in the relaxation of smooth muscle and inducing vasodilation, and there is increasing evidence that interventions that influence NO bioavailability can also alter the O2 cost of exercise (Bailey et al., 2009, 2010; Koppo et al., 2009; Cermak et al., 2012), influence blood flow (Bode-Böger et al. 1994), nutrient delivery (Apostol et al. 2003, 2007; Schellong et al., 1997; McConell et al., 2006) and aid in metabolic waste product removal (Schaefer et al., 2002) and enhance performance. However, there is controversy as to the effectiveness of L-arginine ingested orally for increasing GH and NO bioavailability in humans at rest and during endurance exercise (Bailey et al., 2010; Koppo et al., 2009; Bescós et al., 2009; Liu et al., 2009; Olek et al., 2010; Linden et al., 2011; Forbes et al., 2011; Wideman et al., 2000). In animals and in some clinical populations, such as congestive heart failure, stable angina, and pulmonary hypertension, L-arginine ingestion has demonstrated positive effects on aerobic exercise performance and maximal aerobic power (VO2max; Maxwell et al., 2001; Bednarz et al., 2004; Mizuno et al., 1998; Nagaya et al., 2001; Ceremuzyński et al., 1997); however, in healthy, physically active or trained males, the research has shown either a positive effect (Bailey et al., 2010; Schaefer et al., 2002), no effect (Bescós et al., 2009; McConell et al., 2006; Sunderland et al., 2011), or a detrimental effect.
(Buchman et al., 1999) on performance. Thus there is much controversy as to whether L-arginine supplementation can benefit aerobic endurance performance. The purpose of this study was to evaluate whether L-arginine consumed orally before a bout of aerobic exercise would stimulate plasma GH above exercise alone, and to examine the subsequent metabolic (glycerol, NEFA, glucose, lactate, VO2, VCO2, RER, and fat and CHO oxidation) responses in endurance-trained individuals. It was hypothesized that the ingestion of L-arginine before submaximal aerobic exercise would increase circulating concentrations of GH which would promote an increase in circulating glycerol and NEFAs while lowering lactate concentration during exercise compared with aerobic exercise alone. A secondary hypothesis was to explore the possibility that L-arginine consumption before an aerobic bout of exercise increases markers of NO (nitrate + nitrite; NOx) production.

Methods

Subjects

Fifteen aerobically trained males (mean ± SD age: 28 ± 5 y; body mass: 77.4 ± 9.5 kg; height: 180.9 ± 7.9 cm; body fat: 11.5 ± 3.5%; training experience: 5.9 ± 3.4 y; VO₂max: 59.6 ± 5.9 ml·kg⁻¹·min⁻¹; power output achieved during the VO₂max protocol: 440 ± 59 W) participated in this study. Participants were actively training at least three times per week during the 12-month period before the start of this study. Participants were verbally screened for food allergies, vegetarianism, or any medical condition that would prevent participation in this study and an investigator recorded this information. Participants were required to abstain from consuming any other type of nutritional supplement for at least 12 weeks before the start of the study to eliminate effects from other supplementation. In addition, all subjects completed a Physical Activity Readiness Questionnaire (PAR-Q) and provided written informed consent. A University Research Ethics Board for human subject research approved the study.

Experimental Protocol

This study used a randomized double-blind, cross-over design and the two conditions were separated by ~7 days. At the first visit subjects completed a medical history, anthropometric (height and body mass) and body composition measurements. Body composition was assessed with hydrostatic weighing according to the procedures previously published for our laboratory (Biondo et al., 2008); body density was calculated and subsequently % body fat was determined using the prediction formula of Siri (1956). In addition a 2-day food record was completed, analyzed, and returned to the participants so they could consume this exact diet 2 days before each experimental condition. The dietary records were analyzed to determine the total daily energy, carbohydrate, fat, and protein intake, using a computer software program (Food Processor II for Windows, version 6.11; Salem, Ore., USA). During this same visit each participant completed an exercise test to determine maximal oxygen consumption (VO₂max). The VO₂max was performed on a calibrated cycle ergometer (Monark, 828E, Sweden) and involved a graded, incremental exercise to volitional exhaustion. Subjects began cycling at 80 W and maintained a pedaling frequency of 80 rpm (rpm). Every 2 min the power output was increased by 40 W; after ventilatory threshold (VT) was reached, power output was increased by 40 W every min until VO₂max was attained. Ventilatory threshold during the tests were determined by a decrease and plateau in the minute ventilation to carbon dioxide production ratio (VE/VCO₂) before a systematic increase with increased power output and a respiratory exchange ratio (RER) greater than 1.05 (Bhambhani et al., 1985). Following the test, the ventilatory threshold was determined as the point at which VCO₂ production and VO₂ consumption deviated from linearity using the V-slope method (Wasserman et al., 1973). Attainment of VO₂max was indicated by a leveling (<0.100 L·min⁻¹) or decrease in VO₂ with increasing workload; a plateau in heart rate (<5bpm) and (or) attainment of age predicted maximum heart rate; a respiratory exchange ratio >1.1; and volitional fatigue (Thoden, 1991). During the test, expired air was collected and analyzed for O₂ and CO₂ using a calibrated metabolic system (ParvoMed True Max 2400, Utah). A two-point (ambient air and known gas standards of 16% O₂ and 4% CO₂) calibration was completed before and after each testing protocol. In addition, a 3 L syringe was used to calibrate flow before each testing condition. Heart rates were recorded every min from the receiver of a telemetric heart rate monitor (Polar Electro, Finland).

At least 72 hr following the initial assessment participants returned for the first of two experimental conditions (visit 2 and 3). During visit 2 and 3 (separated by ~7 days) subjects returned to the laboratory at 08:00 after a 10-hr overnight fast and no prior exercise to obtain a resting blood sample from a forearm vein. Following this, the participants were provided either L-arginine (Now Foods; Bloomingdale, IL); 0.075 g·kg⁻¹ of body mass (Forbes et al., 2011) or a placebo containing flour with 500 ml of water in a double-blind fashion. Resting blood samples (~10 ml per sample) were obtained via veni-puncture while exercise and postexercise blood samples were obtained using an intravenous cathelent inserted into a forearm vein kept patent with sterile saline (0.5 ml of 0.9% NaCl) in a seated position. Note that 2 ml of blood was drawn and discarded before obtaining each sample to ensure no saline was present in the sample used for analysis. Blood samples were taken at rest, immediately before exercise, every 15 min during exercise, and 15, 30, 60 min post exercise. Two aliquots of blood were removed for the measurement of hematocrit by microcentrifugation (International Micro Capillary Centrifuge—MB). The remaining blood samples were collected in EDTA-containing tubes, immediately put on ice, and within 2 min were centrifuged for 10 min at 1500 xg. The plasma
was aliquotted, immediately frozen at −20 °C and subsequently stored at −80°C until analyzed.

Sixty minutes following supplementation the exercise protocol began. The protocol consisted of a standardized warm up at 40 W for 5 min followed by 60 min at a power output equivalent to 80% of the power output achieved at VT, as determined during the VO2max protocol. To maintain hydration status, subjects drank ad libitum during and following the exercise bout and were required to consume this identical volume of water during the second experimental condition. Heart rate (HR) was recorded from a HR monitor throughout the test. Blood pressure from an automated device (Automatic Plus Blood Pressure Monitor, Life Brand, Toronto, Ontario) at rest, immediately before exercise, and during recovery and manual blood pressure was obtained during exercise. The ratings of perceived exertion (RPE) using the Borg 6–20 scale was used to estimate effort during exercise at 15, 30, 45 and 60 min. Expired-gas samples for determination of VO2, carbon dioxide output (VCO2), and RER (the ratio between VCO2 and VO2) were collected for 6-min periods at the beginning of exercise (1–6 min), middle (27–33 min), and end (54–60 min). Whole-body rates of CHO and fat oxidation (g·min⁻¹) were calculated during the steady-state cycling from the rates of CO2 production (VCO₂) and O2 consumption (VO₂) using the nonprotein RER values according the following equation (Péronnet and Massicotte, 1991):

\[
\text{CHO oxidation (g·min}^{-1}\) = \[4.585 \times \text{VCO}_2 (\text{L·min}^{-1})\] – \[3.226 \times \text{VO}_2 (\text{L·min}^{-1})\]
\]

\[
\text{Fat oxidation (g·min}^{-1}\) = \[1.695 \times \text{VO}_2 (\text{L·min}^{-1})\] – \[1.701 \times \text{VCO}_2 (\text{L·min}^{-1})\]
\]

**Blood Analysis**

All samples from the same subjects were assayed in the same order and in duplicate. L-arginine concentrations were determined spectrophotometrically (Bergmeyer 1974) by the oxidation of NADH using octopine dehydrogenase. GH, glycerol, NOx were measured using commercially available enzyme-linked immunoassay kits (GH: Diagnostics Biochem., Canada Inc., London, Ontario; glycerol and NOx: Cayman Chemical Company). Plasma glucose and lactate were determined spectrophotometrically (Sigma Chemical Inc. USA). Plasma NEFA was determined by an enzymatic colorimetric procedure (NEFA-C test; Wako, USA). The intra-assay coefficient of variation (CV) for the duplicate samples for heamatocrit, L-arginine, GH, NEFA, glycerol, glucose, lactate, and NOx was 1.2%, 3.1%, 9.8%, 7.8%, 4.2%, 5.0%, 8.2%, 4.3%, respectively.

**Statistical Analysis**

A two-factorial (condition: ARG vs. PLA; and time) repeated-measures ANOVA was used to determine whether there were any differences between the two experimental conditions and over time for each dependent variable. Paired t tests were used to determine whether there were any differences between peak heart rate and RPE between the two conditions. Significant F ratios were further analyzed with a Tukey’s paired-wise comparison. Statistical analyses were completed using Statistica, version 8.0 (StatsSoft Inc., Tulsa, OK). All results are expressed as means ± SD, unless otherwise noted. Statistical significance was set at \(p \leq .05\).

**Results**

All of the participants completed the study with no observed or reported side effects. Resting values for all the dependent variables ([L-arginine], [GH], [NEFA], [glycerol], [lactate], [glucose], [glycerol], [NOx], blood pressure, HR) were not significantly different between conditions.

The average macronutrient breakdown from the food records were 116 ± 17 g d⁻¹ (1.5 ± 0.3 g kg⁻¹·d⁻¹) of protein, 538 ± 82 g d⁻¹ (7.0 ± 1.0 g kg⁻¹·d⁻¹) of carbohydrate, and 75 ± 9 g d⁻¹ (1.0 ± 0.1 g kg⁻¹·d⁻¹) of fat. There was no significant difference over time or between conditions for hematocrit (average hematocrit: PLA: 48 ± 5; ARG: 47 ± 4). L-arginine plasma concentrations significantly increased in the ARG condition (146%) while there was no change over time for the PLA condition (Figure 1). There were significant increases in plasma GH (Figure 2A), NEFA (Figure 2B), lactate (Figure 2C), and a significant decrease in glucose over time (Figure 2D); however, there were no differences between conditions. There was no significant difference over time or between conditions for NOx (Figure 2E). There was a significant increase over time and a difference between ARG and PLA 45 min into the bout of exercise for plasma glycerol (Figure 2F).

Diastolic and systolic blood pressure changed over time; however, there were no significant differences between conditions. Cardio-respiratory data are shown in Table 1. The average power output at ventilatory threshold was 283 ± 67 W and the mean VO2 was 60% of VO2max during the exercise protocol, with no differences between conditions. There were no difference between conditions for HR, VCO₂ (L·min⁻¹), VE (L·min⁻¹), respiratory rate (RR), VE/VCO₂, VE/VO₂, RER (VCO₂/VO₂), and CHO oxidation. Fat oxidation was significantly lower in the ARG condition at the start of exercise. There was a significant time main effect (\(p < .001\)) for RPE, indicating an increase throughout the exercise, while no difference between conditions was observed.

**Discussion**

This study examined the hypothesis that L-arginine may alter the hormonal and metabolic milieu during prolonged submaximal exercise for endurance-trained males. This rationale was based on research indicating that L-arginine administered intravenously (30 g) increased GH (Widman et al., 2000), which is known to increase lipolysis and NEFA release and enhance fat oxidation (Hansen et
In addition, L-arginine may increase NO production (Bailey et al., 2010), which has been shown to enhance vasodilation thereby increasing blood flow (Ohta et al., 2007), nutrient delivery (McCormell et al., 2006), and waste-product removal (Schaefer et al., 2002). This is the first study to examine the effects of L-arginine ingested orally before a bout of submaximal aerobic exercise on GH and the subsequent metabolic responses in trained cyclists. The findings of the current study demonstrated that circulating concentrations of L-arginine was increased by 146% in plasma and lead to an increased glycerol concentration at the 45-min time point, which partially supports one of our hypotheses. However, there were no difference between conditions for GH, NEFA, glucose, lactate, and CHO oxidation. A small but significant reduction in fat oxidation was observed at the start of the exercise bout that was contrary to our hypothesis. Furthermore, the current study found no change in NOx between the two conditions.

Intravenous infusion and orally ingested L-arginine at rest have both been shown to increase GH in men (Wideman et al., 2000; Collier et al., 2005, 2006) despite some research showing little change with oral ingestion (Forbes and Bell, 2011; Abel et al., 2005). Enhancing GH is known to increase lipolysis and fat oxidation (Gravhølt et al., 1999; Hansen et al., 2005; Lange et al., 2002) which may spare muscle and liver glycogen (Bescós et al., 2012a; Phillips et al., 2011). Wideman et al. (2000) found an enhanced effect of L-arginine administered intravenously before a bout of aerobic exercise on plasma GH compared exercise alone. The present study found no effect on growth hormone when L-arginine was consumed orally before a submaximal exercise bout compared with exercise alone in trained subjects. These differences are most likely due to the method of administration; intravenous compared with oral ingestion (Böger et al., 2001). Previous research has shown that a substantial amount of orally administered L-arginine does not enter the systemic circulation because approximately 40% of orally administered dietary L-arginine was degraded by the small intestine (Wu et al., 1998). High doses of L-arginine can cause GI distress due to the osmotic movement of water into the stomach and intestine (Brinson et al., 1988; Collier et al., 2005; Forbes et al., 2011) potentially leading to an increase in the excretion of L-arginine (Collier et al., 2005; Brinson et al., 1988).

The present study showed a significant increase in plasma L-arginine and our laboratory has previously shown no difference in L-arginine plasma concentrations when consuming 0.075 g·kg−1 compared with 0.150 g·kg−1 of body mass of L-arginine, suggesting that the dose used in the present investigation was appropriate and represented a high oral dose while limiting negative side effects.

Although there was no statistical difference in GH between conditions, there was a 26% lower GH in the ARG condition, which is similar to previous research examining L-arginine consumed orally before a bout of resistance exercise (Collier et al., 2006). Two possibilities for the attenuated GH response include a down regulation of growth hormone releasing hormone (GHRH) induced GH release, which appeared to be similar to research that has shown a reduction of plasma GH after repeated intravenous injection of GHRH at rest (Ghigo et al., 1991). Secondly an auto-negative feedback following the stimulation of IGF-1 before the exercise bout may suppress subsequent stimulation of GH release (Collier et al., 2006; Jaffe et al. 1998). Although, these results are contrary to others who have shown an enhanced GH response following L-arginine infusion combined with aerobic exercise (Wideman et al., 2000). These differences may be associated with the administration of L-arginine (i.e., oral versus intravenous), the timing of administration, or training status. In addition, the current study found a significantly lower fat oxidation at the start of exercise in the ARG condition. Since this occurred with no changes in plasma NEFA concentration, it is possible that L-arginine ingestion may have led to a reduction in intramyocellular lipid oxidation (IMCL). However, this is speculative and further research would be necessary to determine the influence of the L-arginine on IMCL.

Figure 1 — Mean ± SEM. Plasma L-arginine concentrations over time after ingesting L-arginine or a placebo and completing an aerobic exercise bout. n = 9. * = indicates a significant difference between the L-arginine condition and the placebo condition. a = significant difference from all other time points except the 180-min time point. b = significant difference from 120, 135, and 180 min. c = significant difference from 150- and 180-min time point. d = significant difference from 180-min time point.
Figure 2 — Mean ± SEM. Plasma (A) growth hormone (B) NEFA (C) Lactate (D) Glycerol over time after ingesting L-arginine or a placebo and completing an aerobic exercise session. * = significant difference between the arginine and placebo condition. a = significant difference from the 0- and 60-min time points. b = significant difference from the 135-, 150-, and 180-min time points. c = significant difference from the 150- and 180-min time points. d = significant difference from the 0-, 60-, 75-, 90-, and 105-min time points. e = significantly different from all other time points.
metabolism during exercise. McConell et al. (2006) and Linden et al. (2011) infused 30 g of L-arginine during a bout of aerobic exercise and found significant elevations in skeletal muscle glucose clearance. McConell et al. (2006) postulated that the elevated glucose clearance may be associated with a greater NO production since plasma insulin concentration was unaffected; however, they did not measure any markers of NO. Linden et al. (2011) found no effect on markers of NOS, however, a higher insulin concentration was found following L-arginine administration. The present study corroborates these findings showing no effect on NOx. In addition, although no significant difference was found, carbohydrate oxidation during the L-arginine trial was on average 152.6 g compared with only 145.4 g during the placebo condition. McConell et al. (2006) and Linden et al. (2011) combined glucose tracers and respiratory analysis to assess substrate oxidation. A limitation of the current study is substrate oxidation was measured through indirect calorimetry (Schutz, 1997). In addition, the current study found no effect on markers of NO production. Interestingly, in the current study, there was a significant increase in glycerol after 45 min of exercise, which occurred without a change in GH and NEFA. Linden et al. (2011) found no effect of L-arginine infused during aerobic exercise on plasma glycerol and NEFA.

Secondly, L-arginine is thought to enhance endurance performance as a precursor for NO. Nitric oxide is a signaling molecule produced by the NOS enzymes, which catalyze the oxidation of L-arginine (Moncada et al., 1989). NO production can elevate cyclic guanosine monophosphate, resulting in the relaxation of smooth muscle and vasodilation (Lau et al., 2000), and there is evidence that interventions (e.g., nitrate or beetroot supplementation) that influence NO bioavailability, through oxygen independent mechanism which may be facilitated by acidosis, can also alter the O2 cost of exercise in humans (Bailey et al., 2009, 2010) and improve cycling performance (Cermak et al., 2012). However, other recent studies have shown that the effect of nitrate supplementation did not improve cycling performance in well-trained athletes (Wilkerson et al., 2012; Bescós et al., 2012a; Christensen et al., 2012). Exogenous L-arginine administration has been reported to increase urinary (nitrate; Maxwell et al., 2001) and plasma [nitrite]+[nitrate] (NOx; Xiao et al., 2003) in mice. However, in healthy humans markers of NO bioavailability were not increased in most studies (Koppo et al., 2009; Bescós et al., 2009; Linden et al., 2011; Liu et al., 2009) which support our findings. Linden et al. (2011) measured total skeletal muscle NOS (nNOS and eNOS) activity in tissue extracts during aerobic exercise and found a significant rise during exercise but no significant difference between the L-arginine and placebo conditions. The present study found no effect of exercise or L-arginine on markers of NOx, however, there may have been an increase in NOx production since previous research has shown an increase in skeletal muscle NOx uptake during exercise (Kingwell et al., 2002). Recently, Bailey et al. (2010) found an increased plasma nitrite concentration following a nutritional supplement which contained 6 g of L-arginine. A potential difference

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Table 1  Cardio-Respiratory Responses Between the L-arginine and Placebo Condition During the Submaximal Exercise at the Start (0–6 Min), Middle (27–33 Min), and End (54–60 Min)

<table>
<thead>
<tr>
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<th>L-arginine</th>
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<th>Placebo</th>
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<tr>
<td></td>
<td>Start</td>
<td>Middle</td>
<td>End</td>
<td>Start</td>
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<tr>
<td>VO2 (ml·kg⁻¹·min⁻¹)</td>
<td>35.2 ± 6.5</td>
<td>36.9 ± 6.8</td>
<td>37.0 ± 6.1</td>
<td>34.9 ± 6.2</td>
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<tr>
<td>VO2 (L·min⁻¹)</td>
<td>2.71 ± 0.54</td>
<td>2.85 ± 0.55</td>
<td>2.86 ± 0.52</td>
<td>2.70 ± 0.52</td>
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<tr>
<td>VCO2 (L·min⁻¹)</td>
<td>2.49 ± 0.46</td>
<td>2.55 ± 0.45</td>
<td>2.55 ± 0.44</td>
<td>2.44 ± 0.44</td>
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<tr>
<td>RER (VCO2/VO2)</td>
<td>0.92 ± 0.05</td>
<td>0.90 ± 0.04</td>
<td>0.89 ± 0.04</td>
<td>0.91 ± 0.4</td>
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<td>VE (L·min⁻¹)</td>
<td>64.3 ± 11.5</td>
<td>69.7 ± 12.2</td>
<td>72.3 ± 12.4</td>
<td>62.2 ± 10.6</td>
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<tr>
<td>VE/VO2</td>
<td>24.2 ± 2.2</td>
<td>25.1 ± 2.5</td>
<td>26.0 ± 2.4</td>
<td>23.5 ± 2.0</td>
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<tr>
<td>VE/VCO2</td>
<td>25.5 ± 1.8</td>
<td>27.0 ± 2.2</td>
<td>27.9 ± 2.2</td>
<td>25.3 ± 2.1</td>
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<tr>
<td>RR (b·min⁻¹)</td>
<td>24.7 ± 4.3</td>
<td>27.6 ± 5.0</td>
<td>29.6 ± 5.0</td>
<td>23.7 ± 3.7</td>
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<tr>
<td>HR (b·min⁻¹)</td>
<td>137 ± 12</td>
<td>141 ± 13</td>
<td>145 ± 14</td>
<td>137 ± 13</td>
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<tr>
<td>CHO oxidation (g·min⁻¹)</td>
<td>2.68 ± 0.58</td>
<td>2.49 ± 0.58</td>
<td>2.46 ± 0.58</td>
<td>2.49 ± 0.53</td>
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<tr>
<td>Fat oxidation (g·min⁻¹)</td>
<td>0.36 ± 0.25*</td>
<td>0.49 ± 0.27</td>
<td>0.51 ± 0.25</td>
<td>0.42 ± 0.23</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>79 ± 5</td>
<td>74 ± 8</td>
<td>72 ± 11</td>
<td>79 ± 8</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>125 ± 7</td>
<td>163 ± 13</td>
<td>161 ± 13</td>
<td>125 ± 7.5</td>
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*Significant difference between the L-arginine and Placebo conditions (p < 0.05).

Note: Mean ± SD. VO2 = oxygen consumption; VCO2 = carbon dioxide production; RER = respiratory exchange ratio; VE = minute ventilation; RR = respiratory rate; HR = heart rate; CHO = carbohydrate; BP = blood pressure.
is the marker used for NO bioavailability. Thus, a limitation of our study and recent studies (Bescós et al., 2009; Liu et al., 2009; Olek et al., 2010; Tsai et al., 2009) may be that nitrate + nitrite, which is conventionally used to assess nitric oxide synthase activity might not be as sensitive as nitrite alone (Lauer et al., 2001). Another difference may be the combined effects of other ingredients (vitamins E, C, Ba, B12; L-glutamine, L-leucine, L-valine, L-carnitine, L-citrulline, L-cysteine, and L-isoleucine, and fructose) provided in the Bailey study. Combining multiple ingredients makes it difficult to interpret direct cause and effect of L-arginine alone. A strength of the current study was only pure L-arginine was used. Furthermore, a potential difference in the literature may be associated with method of delivery and dose. Bode-Böger et al. (1994) demonstrated that intravenous infusion of 30 g of L-arginine significantly increased arterial blood flow in the femoral artery of healthy subjects by a mean of 44%. However, in a subsequent study, a lower dose of L-arginine (6 g), administered either intravenously or orally, failed to produce acute vasodilation. Furthermore, Schellong et al. (1997) found that a single systemic infusion of 30 g of L-arginine increased muscle blood flow by a mean 43%, whereas a lower dose of 8 g of L-arginine had no significant effect. This latter research suggests that to achieve a metabolic effect in healthy young humans it seems that a high dose, beyond which can be consumed orally may be necessary (Collier et al., 2005; Forbes et al., 2011). This might also explain why the current study found no difference in any cardio-respiratory parameters—such as VO2, HR, VE, and systolic or diastolic blood pressure—suggesting that L-arginine has little effect in endurance-trained males.

**Conclusion**

L-arginine ingested at an oral dose of 0.075 g·kg\(^{-1}\) before a bout of submaximal aerobic exercise significantly elevates plasma L-arginine concentration in endurance-trained cyclists. Despite this latter elevation, there were no changes in any hormone, metabolite, or cardio-respiratory parameter measured, except for a small but significant increase in glycerol at the 45-min time point and a reduction in fat oxidation at the start of exercise.

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**References**


