Effects of Supplemental Citrulline Malate Ingestion During Repeated Bouts of Lower-Body Exercise in Advanced Weightlifters

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Abstract

Wax, B, Kavazis, AN, Weldon, K, and Sperlak, J. Effects of supplemental citrulline malate ingestion during repeated bouts of lower-body exercise in advanced weightlifters. *J Strength Cond Res* 29(3): 786–792, 2015—The purpose of this investigation was to test the efficacy of citrulline malate supplementation on exercise performance, blood lactate, heart rate, and blood pressure during lower-body dynamic resistance exercise. We hypothesized that citrulline malate ingestion before performing submaximal repeated bouts of multiple lower-body resistance exercises would improve performance. Twelve advanced resistance-trained male subjects participated in a randomized, counterbalanced, double-blind study. Subjects were randomly assigned to placebo (PL) or citrulline malate (8 g) groups and then performed repeated bouts of multiple lower-body resistance exercise. Specifically, subjects performed 5 sequential sets (60% 1 repetition maximum) to failure on the leg press, hack squat, and leg extension machines. Blood lactate, heart rate, systolic blood pressure, and diastolic blood pressure were determined before and after exercise. The exercise protocol resulted in sequential significant ($p \leq 0.05$) decrease in the number of repetitions in all 3 exercises. However, subjects in the citrulline malate group performed significantly ($p \leq 0.05$) higher number of repetitions during all 3 exercises compared with PL group. Blood lactate and heart rate were significantly increased ($p \leq 0.05$) after exercise compared with before exercise but were not significantly different between citrulline malate and PL ($p > 0.05$). No significant ($p > 0.05$) differences were detected for blood pressure measurements. In conclusion, our results suggest that citrulline malate supplementation may be beneficial in improving exercise performance during lower-body multiple-bout resistance exercise in advanced resistance-trained men.

Key Words ergogenic aids, supplement, weight training, fatigue, anaerobic exercise

Introduction

In the competitive arena of sports, athletes are continuously seeking training aids and supplements that may provide them with a competitive edge. Exogenous substances that increase athletic performance (i.e., enhanced muscular power, strength, and endurance) are referred to as ergogenics (37). Recently, studies reported that an over-the-counter supplement named citrulline malate enhanced aerobic energy production (5), augmented muscular force output (27), and mitigated muscle fatigue (5).

In this regard, citrulline malate (brand name Stimol) was originally developed to improve the muscle performance of patients suffering from asthenia and to improve recovery time from physical activity for individuals with acute diseases (11). Citrulline malate is made of L-citrulline and malate. L-citrulline is a nonessential amino acid produced endogenously in the body through 2 key metabolic processes. First, L-citrulline can be synthesized in the intestinal tract from the amino acid glutamine. Also, L-citrulline can be synthesized from the conversion of L-arginine to nitric oxide in a reaction catalyzed by nitric oxide synthase enzymes (31). Importantly, oral L-citrulline, unlike oral L-arginine, bypasses the hepatic metabolism and is not catabolized by arginase enzymes, thus allowing it to be transported to the kidneys where approximately 80% of L-citrulline is converted into plasma arginine by the cells of the proximal tubules (32). Specifically, research has shown that L-citrulline supplementation augments plasma L-arginine concentrations (19), accelerates the clearance of plasma lactate and ammonium through urea cycle, thereby contributing to improved muscle function (8,16,33). Malate is an intermediate of tricarboxylic acid cycle (TCA) and its supplementation may augment energy production (5,34). The beneficial effects of citrulline malate may actually be attributed to the synergistic combination of both L-citrulline and malate at the muscles'

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metabolic level. In particular, increased rates of adenosine triphosphate (ATP) during exercise, followed by an increased rate of phosphocreatine recovery after exercise have been observed (5).

To date, only 1 published study investigated the potential ergogenic benefit of citrulline malate on resistance exercise performance. Perez-Guisado and Jakeman (27) investigated the effects of a single dose of citrulline malate (8 g) on repeated bouts of upper-body resistance exercise performance. The authors also measured muscle soreness 24 and 48 hours after the high-intensity session. The authors reported that citrulline malate supplementation increased the work performed (repetitions) during an upper-body resistance exercise protocol and mitigated muscle soreness at 24 and 48 hours after exercise in comparison with the placebo (PL) treatment.

Importantly, the aforementioned study only used upper-body resistance exercises. To the best of authors' knowledge, no previous study has investigated the effects of citrulline malate supplementation on resistance exercise performance using the lower extremities, which entails a greater utilization of muscle mass; thereby, placing a greater demand on the body's metabolic systems. Therefore, the aim of this study was to investigate the effects of citrulline malate supplementation on lower-body resistance exercise performance, blood lactate, heart rate, and blood pressure. Based on citrulline malate's chemical composition and a review of the current literature (8,16,27,33), we hypothesized that citrulline malate supplementation would mitigate fatigue occurring to the working muscle; therefore, augmenting resistance training performance.

Methods

Experimental Approach to the Problem

This study was designed as a randomized, counterbalanced, and double-blind experiment. Subjects reported to the laboratory 3 times (i.e., session 1, session 2, and session 3) at the same time of day. Session 1 was used to obtain anthropometric data and obtain the 1 repetition maximum (1RM) for each subject in each of the 3 exercises (i.e., leg press, hack squat, and leg extension). During session 2, half of the subjects chosen at random ingested a citrulline malate solution (described below) and the other half consumed a PL solution 60 minutes before the exercise protocol (described below). On session 3, subjects were crossed over and consumed the other supplement and then performed the same exercise protocol. There was a 7-day period between sessions 1 and 2 and between sessions 2 and 3.

Subjects

All experimental procedures were reviewed and approved by the institutional review board before the initiation of the study. Fourteen advanced resistance-trained males enrolled at the university where the investigation was performed volunteered for the study; however, because of injuries to 2 of the subjects, only 12 were included in the final results. The 2 subjects incurred the injuries outside the purview of this study. Before the investigation, subjects completed a health history questionnaire and signed a statement of informed consent. To qualify for this study (i.e., inclusion criteria), the males were classified as low-risk individuals as categorized by the American College of Sports Medicine (1) risk stratification and have currently been resistance training for no less than 1 year (3). Also, subjects indicated that they had completed a minimum of 3–4 sessions per week at a perceived high training stress level. The exclusion criteria of the study included the following: (a) musculoskeletal problems, (b) metabolic disorders, (c) cardiorespiratory ailments, (d) blood disorders, (e) history of psychological disorders, (f) use of tobacco products, (g) consuming more than 10 alcoholic beverages per week, (h) taking medication, (i) less than 12 months of continuous resistance training, (j) use of over-the-counter supplements in the past 6 months, and (k) any previous or current use of anabolic steroids. Descriptive characteristics for the subjects are presented in Table 1.

Procedures

Supplementation. Subjects in the citrulline malate group ingested 8 g of over-the-counter pharmaceutical grade citrulline malate (99% pure with no fillers, excipients, flavors, sweeteners; NutraBio Inc., Middlesex, NJ, USA). Subjects in the PL group ingested a PL that contained maltodextrin and aspartame (Merisant US, Inc., Chicago, IL, USA). Both substances were mixed with 300 ml of Crystal Light lemonade (Kraft Foods Global Inc., Northfield, IL, USA) and provided to subjects 60 minutes before performing the exercise protocol. The dosage of citrulline malate and timing was selected based on a previous study that reported positive effects of oral citrulline malate in multiple bouts of upper-body weight training (27). The PL beverage was similar in color, smell, taste, and volume to the supplement. Additionally, subjects wore a nose clip during ingestion of the treatments (citrulline malate and PL) to mitigate their sense of smell and taste. No subject reported any discomfort after citrulline malate ingestion.

Table 1. Anthropometric characteristics of the subjects used in the study.*

Age (y)	Height (m)	Body mass (kg)	Body fat (%)
22.1 ± 1.4	1.79 ± 0.10	84.8 ± 10.9	11.9 ± 4.3

*Data are presented as mean ± *SD*.

Session 1. This session was used to determine subjects' anthropometric data. Subjects were instructed to refrain from strenuous lower-body (72 hours) and upper-body (48 hours) exercise before each trial. Also, the subjects were asked to refrain from caffeine and alcohol intake 48 hours before the following 2 sessions. Furthermore, subjects were asked to maintain a log of their dietary intake 24 hours before session 2 and were instructed to duplicate the nutritional intake before session 3. In addition, subjects performed 1RM test for the leg press (Precore Inc., Woodinville, WA, USA), hack squat (Precore Inc.), and leg extension (Life Fitness, Brunswick Corporation, Lake Forest, IL, USA) machines. One repetition maximum was determined according to the methods of Baechle and Earle and the National Strength and Conditioning Association (3). Three of the individuals collecting data were certified strength and conditioning specialists, thus ensuring proper technique of all exercise movements. The 1RM was obtained in 3–6 sets for all subjects.

Sessions 2 and 3. Subjects reported to the laboratory at their prescheduled time and prepared for testing. Upon arrival, subjects were questioned about their compliance in regards to their activity level. If a subject failed to meet the pretesting guidelines required for participation in that day's protocol, the session was rescheduled. All subjects except 2 completed their scheduled sessions. These 2 subjects were eliminated from the investigation. After the evaluator's review and approval of the compliance guidelines, subjects ingested either the citrulline malate or the PL beverage and then rested quietly for 60 minutes. Next, subjects warmed up on an upright stationary bike (Life Fitness, Brunswick Corporation) for 5 minutes, at 60–70 revolutions per minute with a mass of 3–5 kg. After this warm-up, subjects performed 2 warm-up sets (10 repetitions at 90.9 kg and 8 repetitions at 136.4 kg) on the leg press machine. Subjects rested 3 minutes between sets during the warm-up and trial sets. Next, 60% of each subject's predetermined 1RM was loaded on the leg press machine and the subject completed as many repetitions as possible until failure occurred. This process was completed for 4 additional sets for a total of 5 sets on the leg press. Next, the subjects performed 1 warm-up set (10 repetitions) on the hack squat machine at a mass of 40.9 kg. This warm-up set was followed by 5 sets of 60% of their predetermined 1RM to failure. Finally, after 1 warm-up set (10 repetitions at 36.4 kg) on the leg extension, subjects completed 5 sets of 60% of their 1RM to failure. Failure was defined as the inability to complete a full repetition without assistance. The rest periods (recovery periods between sets of exercise), exercise order, and number of sets performed were the same for all subjects in this investigation for sessions 2 and 3.

Heart Rate, Blood Pressure, and Blood Lactate

A single-use lancet device was used to puncture the skin just off the center of the finger pad. The first flow of blood was wiped away, and then approximately 5 μl (2 mm) of blood was loaded on the lactate strip and immediately analyzed using the Lactate Pro Analyzer (ARKRAY Inc., Shiga, Japan). Blood lactate concentrations were determined at rest (baseline) and immediately after failure of the fifth set of leg extension exercise (postexercise). Heart rate and blood pressure were measured at rest (baseline), 5 minutes after exercise, and 10 minutes after exercise by using an automated instrument (SunTech Medical, Morrisville, NC, USA). Heart rate was measured to indicate the effects of exercise intensity on the cardiovascular system during citrulline malate and PL supplementation, whereas blood pressure was ascertained to observe possible treatment effects.

Statistical Analyses

All statistical analyses were performed using the GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA) by using data from all 12 subjects that completed the study for both PL and citrulline malate groups. Data for leg press, hack squat, and leg extension repetitions were analyzed by using a 2 (condition: citrulline malate and PL) $\times$ 5 (sets: 1, 2, 3, 4, and 5) repeated-measures analysis of variance. When an interaction was observed, a comparison of simple effects was performed, and when no interaction was present, the individual main effects were analyzed using adjustments for multiple comparisons. Data for heart rate, systolic blood pressure, and diastolic blood pressure were analyzed by using a 2 (condition: citrulline malate and PL) $\times$ 3 (time: baseline, 5 minutes after exercise and 10 minutes after exercise) repeated-measures analysis of variance. When an interaction was observed, a comparison of simple effects was performed, and when no interaction was present, the individual main effects were analyzed using adjustments for multiple comparisons. Data for blood lactate were analyzed by using a 2 (condition: citrulline malate and PL) $\times$ 2 (time: baseline and after exercise) repeated-measures analysis of variance. When an interaction was observed, a comparison of simple effects was performed, and when no interaction was present, the individual main effects were analyzed using adjustments for multiple comparisons. Statistical significance difference was established at $p \leq 0.05$. Data are reported as mean $\pm$ *SD*.

Results

Performance measures for muscular endurance were determined on the leg press, hack squat, and leg extension exercises. Importantly, resistance to fatigue for the lower body was determined by using 60% of their predetermined 1RM to failure for each set and all exercises performed. Specifically, the leg press exercise protocol indicated citrulline malate mitigated fatigue ($p \leq 0.05$) occurring in set 5 compared with set 2 in the same treatment (Figure 1). Additionally, repeated sets of the leg press revealed a significant decrease in the number of repetitions performed compared with set 1 in both treatment groups for sets 2, 3, 4, and 5. Also, the hack squat exercise protocol indicated that

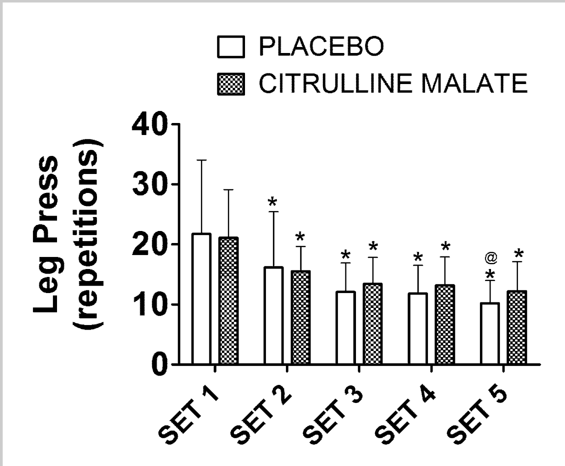

Figure 1. Number of repetitions performed in the 5 sets of leg press. *$p \leq 0.05$ from set 1 in same treatment. @$p \leq 0.05$ from set 2 in same treatment.

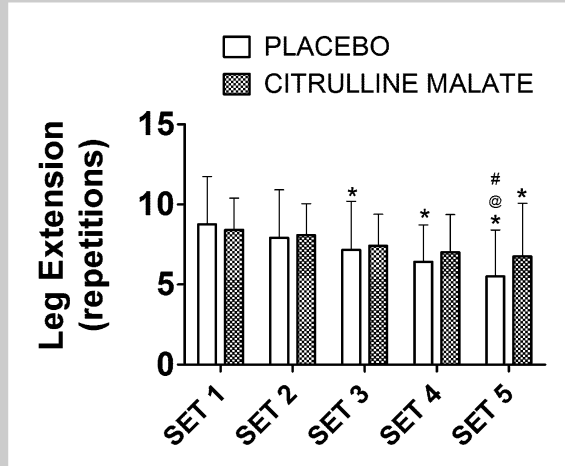

Figure 3. Number of repetitions performed in the 5 sets of leg extension. *$p \leq 0.05$ from set 1 in same treatment. @$p \leq 0.05$ from set 2 in same treatment. #$p \leq 0.05$ from set 3 in same treatment.

citrulline malate mitigated fatigue ($p \leq 0.05$) occurring in sets 4 and 5 compared with sets 2 and 3 in the same treatment (Figure 2). Finally, the leg extension exercise protocol indicated that citrulline malate mitigated fatigue ($p \leq 0.05$) occurring in set 5 compared with sets 2 and 3 in the same treatment (Figure 3).

Blood lactate was measured to provide an indirect measure of lactic acid being formed and dissociated in the working muscle. At rest (baseline), there were no differences ($p > 0.05$) between citrulline malate (1.22 ± 0.34 $mmol \cdot L^{-1}$) and PL (1.33 ± 0.28 $mmol \cdot L^{-1}$). After the lower-body protocol, blood lactate increased significantly in both treatments (citrulline malate = 10.65 ± 1.41 $mmol \cdot L^{-1}$; PL = 10.74 ± 1.97 $mmol \cdot L^{-1}$; $p \leq 0.05$ compared with baseline), but it was not different ($p > 0.05$) between groups (Figure 4).

At rest (baseline), there were no differences for heart rate between citrulline malate (70.9 ± 11.0 $b \cdot min^{-1}$) and (PL 72.9 ± 14.0 $b \cdot min^{-1}$) ($p > 0.05$). After the exercise protocol, heart rate remained significantly increased in both groups at 5 minutes after exercise (citrulline malate = 103.7 ± 15.0 $b \cdot min^{-1}$; PL = 103.5 ± 8.6 $b \cdot min^{-1}$; $p \leq 0.05$ compared with baseline) and at 10 minutes after exercise (citrulline

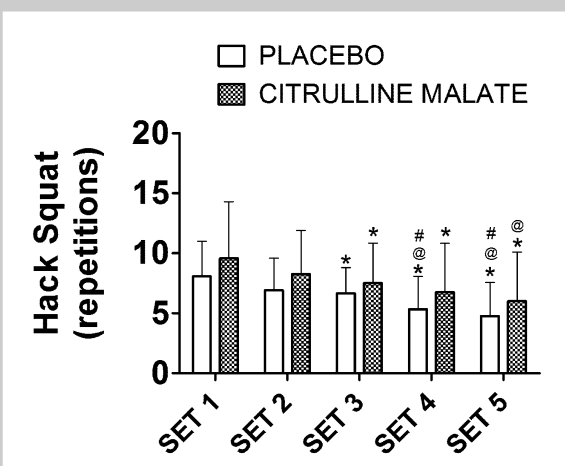

Figure 2. Number of repetitions performed in the 5 sets of hack squat. *$p \leq 0.05$ from set 1 in same treatment. @$p \leq 0.05$ from set 2 in same treatment. #$p \leq 0.05$ from set 3 in same treatment.

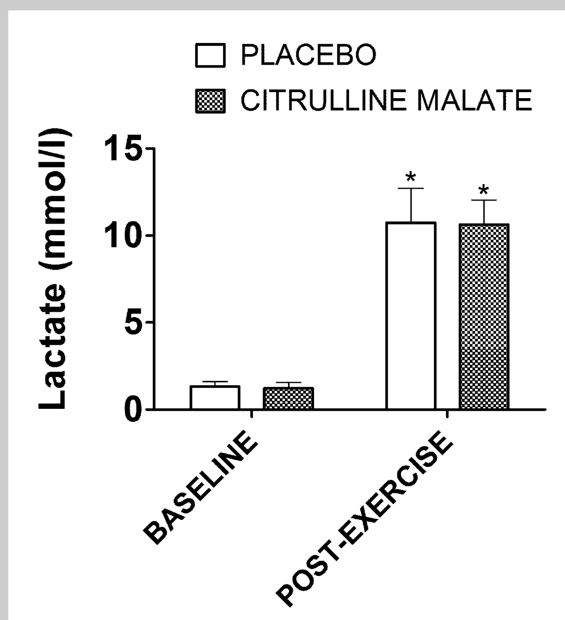

Figure 4. Blood lactate. *$p \leq 0.05$ from baseline in same treatment.

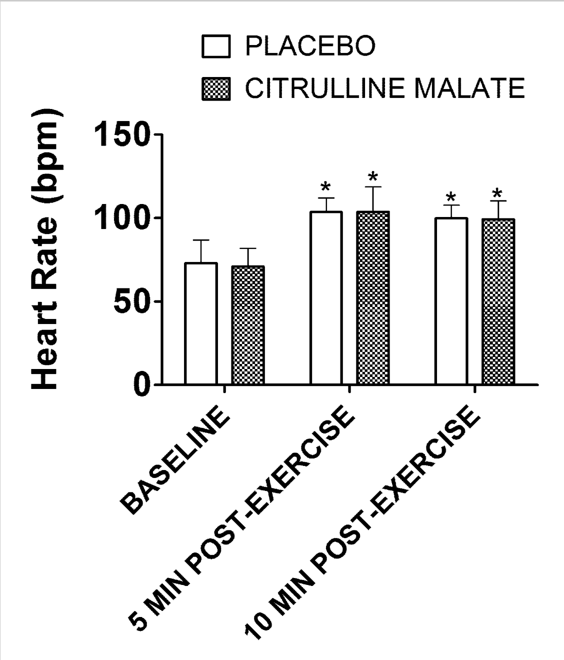

Figure 5. Heart rate in beats per minute. *$p \leq 0.05$ from baseline in same treatment.

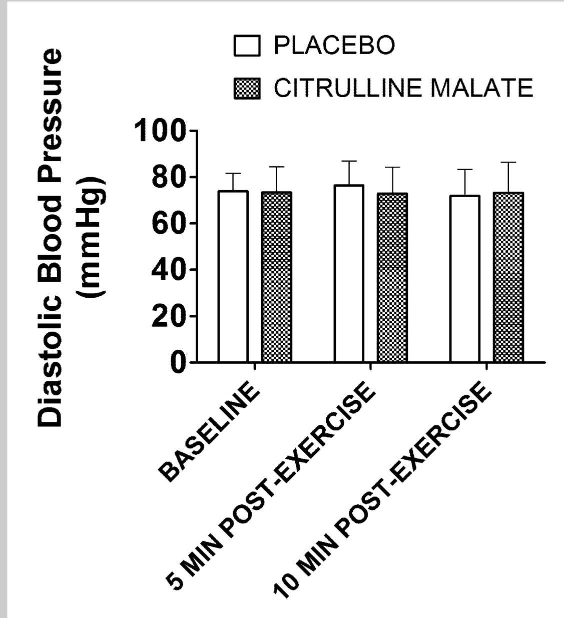

Figure 7. Diastolic blood pressure. No significant differences existed.

malate = 99.3 ± 11.0 $b \cdot min^{-1}$; PL = 99.8 ± 7.9 $b \cdot min^{-1}$; $p \leq 0.05$ compared with baseline); however, no differences were observed at each time point between the 2 treatments ($p > 0.05$) (Figure 5).

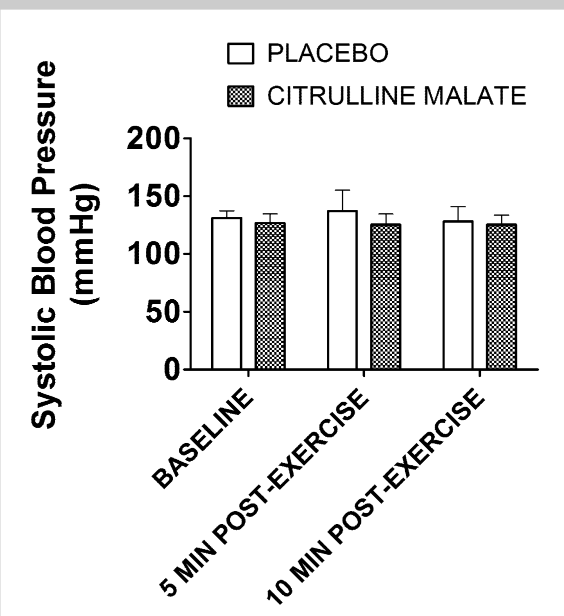

Figure 6. Systolic blood pressure. No significant differences existed.

Repeated-measure analysis of systolic blood pressures (Figure 6) and diastolic blood pressures (Figure 7) revealed no significant differences ($p > 0.05$).

Discussion

In this study, it was hypothesized that citrulline malate supplementation before repeated bouts of lower-body resistance exercise would mitigate fatigue occurring to the working muscle, thus allowing subjects to perform more repetitions. Our results indicated that subjects who consumed citrulline malate experienced less fatigue to the working muscles compared with the PL group, allowing them to perform more repetitions. Furthermore, the data showed that blood lactate, heart rate, and blood pressure were not altered in this study after either citrulline malate or PL supplementation.

The precise mechanism by which citrulline malate enhances exercise performance remains elusive; however, several have been proposed: (a) malate is an intermediate of the TCA and increased levels through supplementation may augment energy production (5,34) by allowing malate to act as a shuttle between the sarcoplasma and mitochondria, thus mitigating the formation of lactic acid, increasing pyruvate genesis, and enabling the glycolytic process, (b) increased production of nitric oxide, which regulates functions of the mammalian muscle, including contractile functions, nutrient delivery, and muscle fiber repair, through satellite cell activation and myotrophic factors (28), and (c) alterations in acid base balance (6,10,15,25,35).

In this regard, lactate is constantly produced in humans at both rest and during exercise (9,12,18). At rest, blood lactate concentration varies from minimal to about 2 mmol$\cdot$L^{-1} but can rise to over 20 mmol$\cdot$L^{-1} during intense exertion (20,21). In our study, blood lactate concentration increased after our lower-body training protocol; however, we did not detect any significant differences in blood lactate concentration between the citrulline malate and PL trials. Thus, based on our current findings, we can deduce that citrulline malate does not exert its ergogenic benefits by acting as a buffer (e.g., alters acid base balance).

In this study, a lower-body exercise protocol was used to investigate the potential ergogenic benefits of citrulline malate supplementation during resistance exercise. Our results are in agreement with an earlier study that reported a single oral dose of citrulline malate (8 g) increased work capacity (number of repetitions) by an average of 19% on subjects performing repeated bouts of flat barbell bench press until exhaustion occurred (27). Although our findings indicated that acute supplementation of citrulline malate improved performance by an average of 9%, supplementation did not affect blood lactate, blood pressure, or heart rate responses. Specifically, the aforementioned study used upper-body resistance exercise with 1 minute rest periods between sets and 2 minutes rest periods between exercise, whereas our investigation incorporated 3-minute recovery periods between all sets and exercises. Therefore, the increased recovery time may have allowed for sufficient metabolic recovery (i.e., ATP resynthesis) while mitigating acidosis, lactate, and ammonium accumulation occurring in the working muscle.

Heart rate increases in direct proportion to increasing exercise intensity (23,24,29); hence, heart rate can be used as an indicator of the effort that subjects exert during an exercise protocol. Specifically, exercise intensity can be reflected based on a participant's percentage of heart rate maximum achieved (22,30). Importantly, since resting and exercise heart rates did not show any significant differences after citrulline malate compared with PL ingestion, it can be assumed that citrulline malate does not induce a stimulant like response such as caffeine, which has been shown to increase resting and after exercising heart rates (2,4,17) while augmenting resistance performance (13,14). Furthermore, data obtained from our investigation confirm earlier studies, which reported that nitric oxide–inducing supplements have no effect on the resting (7,38) and exercising heart rates (36). Finally, despite citrulline malate positive effects on lowering blood pressure in patients with heart failure (26), our data revealed no significant changes in systolic or diastolic blood pressure either pre- or post-exercise following our exercise protocol in normal healthy male subjects.

Practical Applications

Although citrulline malate supplements are marketed to improve muscle performance through a reduction in lactic acid and ammonia production, this study does not fully support this assertion. Although our investigation did note improved muscle performance occurring during the strength protocol, blood lactate remained indifferent comparing the citrulline malate treatment to the PL treatment. The known capacity of citrulline malate to increase plasma L-arginine (19) and act as a buffer to lactate and hyperammonemia (8,16,33) remains valid; however, further research is necessary to determine which mechanism may be directly attributed ergogenic effects occurring during resistance training protocols. Finally, specific investigations using training protocols designed to test muscular strength and anaerobic power are warranted.

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