

Influence of Xpand Nitric Oxide Reactor, L-Arginine Alpha-Ketoglutarate, and Caffeine Supplementation on Calf Muscle Re-Oxygenation During and after Acute Resistance Exercise

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Abstract: Xpand Nitric Oxide Reactor is a 'cocktail' supplement proposed to improve skeletal muscle blood flow via arginine's effect on nitric oxide synthesis and vasodilation. Two other major ingredients, caffeine and creatine, cause vasoconstriction, which could potentially counteract the proposed hemodynamic effects of arginine. The purpose of this study was to examine the influence of Xpand Nitric Oxide Reactor on muscle re-oxygenation after resistance exercise compared to supplementation with constituent ingredients L-arginine alpha-ketoglutarate and caffeine. Nine recreationally active men (21±1y) performed 3 sets of 20 repetitions of seated single-leg calf raise at 60% 1-RM with 3 min rests. The same calf raise exercise was performed following 4 separate supplementation conditions: L-arginine alpha-ketoglutarate (AAKG), caffeine (CAFF), Xpand Nitric Oxide Reactor (XPAND), and placebo (PLAC). Soleus muscle re-oxygenation time was measured before, during, and immediately after exercise using near infrared spectroscopy. Supplementation with XPAND (0.43±0.03), AAKG (0.34±0.02), and CAFF (0.45±0.05) did not significantly affect muscle re-oxygenation half-time (minutes) compared to placebo (0.35±0.04). An arginine containing 'cocktail' supplement did not affect skeletal muscle re-oxygenation after resistance exercise, possibly due to a wash-out effect caused by the multiple ingredients.

Keywords: Ergogenic, blood flow, oxygen delivery, supplements, vasomotor, athletic performance, near infrared spectroscopy.

INTRODUCTION

Nitric Oxide (NO) is an endogenously produced gas that helps to maintain arterial vasodilation and regulate blood flow at rest *via* its actions on vascular smooth muscle [1-3]. During exercise, NO production increases to enhance blood flow and ensure that sufficient oxygen is delivered to working skeletal muscle [4]. Enhanced blood flow during exercise could also increase nutrient delivery to (e.g. amino acids, glucose, creatine, etc.), and metabolic waste removal from skeletal muscle (e.g. CO₂, nitrogen, bicarbonate, etc.). Because NO is synthesized from the semi-essential amino acid L-arginine [5], this potentially ergogenic mechanism has become an important selling point on which arginine-containing nutritional supplements are claimed to increase "muscle pumps" during resistance exercise, and muscle hypertrophy and performance gains with training. As a result, several products containing L-arginine or L-arginine alpha-ketoglutarate have become increasingly popular and continue to amass millions of dollars in sales annually.

Xpand Nitric Oxide Reactor is a 'cocktail' supplement that is intended for athletes and others who wish to increase muscle hypertrophy and enhance resistance exercise performance, and the ergogenic potential of Xpand has been previously investigated [6]. Xpand contains L-arginine alpha-ketoglutarate (AAKG), as well as other ingredients including caffeine and creatine monohydrate. The AAKG is intended to stimulate NO production for vasodilation [5], while caffeine may increase blood pressure, heart rate, and endurance performance [7], and creatine has been shown to increase strength, power, and recovery during short-burst resistance exercise [7-8]. Because creatine and caffeine have been demonstrated to have beneficial effects on skeletal muscle performance, it is logical that supplement companies combine these ingredients with the potential vasodilator arginine in an attempt to exploit the combined activities of these compounds. Thus the strategy of supplement companies is to promote that when taken just prior to exercise, Xpand Nitric Oxide Reactor and other similar products should increase exercise vigor and blood flow, thereby increasing nutrient and creatine delivery to skeletal muscle. The resultant enhanced re-oxygenation and creatine delivery to muscle could also improve recovery

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between intense contractions, which might further increase exercise performance [7, 9-12].

Alone, L-arginine supplementation has resulted in improved gains in strength and anaerobic power compared to placebo following twelve weeks of resistance training in healthy men [13]. A possible explanation for these ergogenic effects could be related to L-arginine's role in NO synthesis, as NO-mediated vasodilation has been shown to partly account for the greater muscle blood flow during exercise after a period of training [1, 14]. To further test this observation, Little *et al.* (2008) compared the effects of ten days of supplementation with Xpand Nitric Oxide Reactor, creatine, or placebo on bench press endurance and Wingate power, in what is currently the only study that has examined the ergogenic potential of Xpand [6]. The results showed that only the Xpand Nitric Oxide Reactor group improved in Wingate peak power, prompting the authors to propose that arginine and creatine may be more beneficial when taken together. Despite the reported benefits of L-arginine as an ergogenic aid, it remains unclear whether supplementation with L-arginine or L-arginine containing products alters hemodynamic properties in skeletal muscle for improved re-oxygenation.

Contrary to the product claims, the main ingredients of 'cocktail' supplements like Xpand could have conflicting effects on arterial and capillary vasomotor control. AAKG is believed to increase NO production and vasodilation [15], yet two other ingredients creatine and caffeine may decrease vasodilation [8, 16]. Theoretically, the cumulative effect of these three ingredients could be decreased or unaltered vasodilation and blood flow. In fact, Bloomer *et al.* (2010) reported no difference in skeletal muscle oxygen saturation following pre-exercise supplementation with three different L-arginine containing 'cocktail' supplements compared to placebo [17]. To date, however, no study in humans has directly examined the effects of an L-arginine containing 'cocktail' supplement compared to its constituent ingredients on skeletal muscle re-oxygenation following intense resistance exercise. Thus the purpose of this study was to compare muscle re-oxygenation during and after acute resistance exercise among Xpand Nitric Oxide Reactor (XPAND), caffeine (CAFF), L-arginine alpha-ketoglutarate (AAKG), and placebo (PLAC) supplemented conditions. We hypothesized that the time to re-oxygenate skeletal muscle would decrease following AAKG, increase following CAFF, and would

not change following XPAND supplementation when compared to PLAC.

METHODS

Subject Participation

Ten resistance trained men (21 ± 1 y) from the Salisbury University community volunteered to complete the requirements of this study, but one subject withdrew due to circumstances unrelated to the study leaving a final n-size equal to nine. Each participant had a minimum of two years resistance training experience. Participants were non-smoking, free from any cardiovascular or metabolic diseases, and cleared to complete the study and consume the supplements by the study physician. Medical history questionnaires were completed by the subjects and reviewed by the physician to determine possible contraindications for supplementation. Subjects were asked to refrain from nutritional supplements and resistance exercise during the entirety of the study, as well as stimulants (e.g., caffeine) and alcohol for 72 hours prior to each protocol. Subjects were asked to not ingest anything 3 hours prior to their trial. Subjects were excluded from the study if they were currently using supplements or had discontinued supplement use in the previous 3 months. The Salisbury University Committee on Human Research approved this study, and all participants provided verbal and written consent.

Study Design

This was a randomized, placebo controlled, double blind study. The subjects' height, weight, and body composition (7-site skinfold method) were measured during the first visit prior to 1-repetition maximum (1-RM) testing. Each subject's dominant leg 1-RM was determined on a seated calf-raise machine (Body Masters Sports Industries, Rayne, LA) following NSCA guidelines for 1-RM testing [18]. Following 1-RM testing, subjects were further familiarized with single leg calf raises with the near infrared spectrometer (RunMan, NIM Inc., Philadelphia, PA). Exactly one week after 1-RM testing, subjects began experimental protocols (see Exercise Protocols below).

Supplementation

Participants orally ingested one of four supplements in solution with similar coloration: L-arginine alpha-ketoglutarate powder ($0.075 \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) (Olympian Labs Inc., Phoenix, AZ), pulverized Jet Alert caffeine

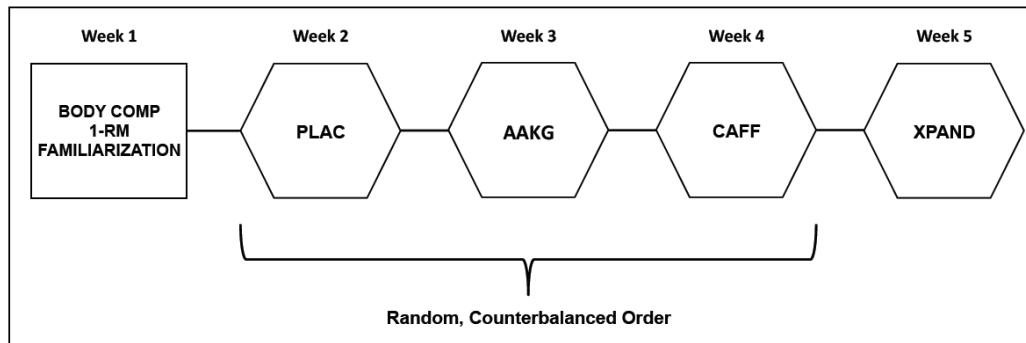


Figure 1: Study design timeline. Body Comp = body composition, 1-RM = 1-repetition maximum, PLAC = placebo, AAKG = L-arginine alpha-ketoglutarate, CAFF = caffeine, XPAND = Xpand Nitric Oxide Reactor.

pill (100mg) (Bell Pharmaceuticals, Minneapolis, MN), Xpand Nitric Oxide Reactor powder (0.35g/kg) (Dymatize Nutrition, Farmers Branch, TX), and placebo ($1\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ sugar free fruit punch powder) (Wal-Mart Stores Inc., Bentonville, AR). These amounts were selected because they reflect the specific ingredient amounts in one serving of XPAND, and have been used in previous research [6]. The PLAC was similar in caloric content to the XPAND, and the placebo fruit punch powder was added to CAFF and AAKG to match caloric content and color. AAKG, CAFF, and PLAC were taken in a randomized, counterbalanced order. Because creatine requires a wash-out period after use, XPAND was consumed during the last testing session for all subjects, and this was also the reason for not including a creatine only protocol. Subjects were instructed that the order of all trials would be randomized, and were not aware that XPAND would be last (Figure 1).

Exercise Protocol

All testing protocols were identical and performed at the same time of day (1600hr) exactly one week apart for each subject. Consistent with supplement instructions and previous research [6], testing consisted of consuming the assigned supplement 45 minutes prior to exercise (Figure 2). Subjects were then fitted with the near-infrared apparatus secured by an

elastic bandage on the lateral lower limb over the soleus muscle and subsequently completed three sets of twenty repetitions of single leg calf raises with three minutes of rest between sets. All calf-raise repetitions were completed with 60% of 1-RM as determined from 1-RM testing and familiarization. Subjects lowered the loads in 2s and raised the loads in 2s guided by the cadence of a metronome.

Near Infrared Spectroscopy

The near infrared spectrometer is a non-invasive device that monitors the relative de-oxygenation of hemoglobin and blood volume used to determine the oxygen delivery to the subject tissue. It emits a white light into skeletal muscle that is read on the near-infrared spectrum. The spectrometer shows an optical density, which decreases when the muscle is de-oxygenated. Near infrared spectrometry has been previously validated [19-23]. In addition, intra-subject muscle re-oxygenation coefficients of variation (CV) were calculated during the familiarization session to ensure its reliability (CV = 3.7%).

Statistical Analysis

A repeated-measures two-way analysis of variance was used to compare amongst supplement groups with all sets combined. A separate ANOVA was used for

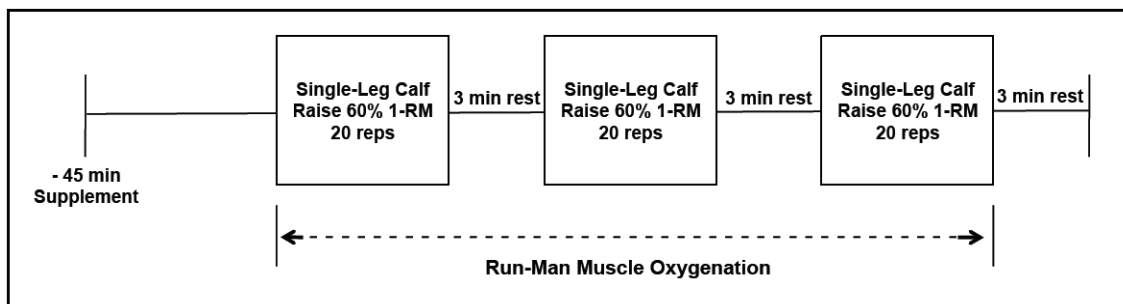


Figure 2: Single-leg calf raise exercise protocol.

between sets and relative percent change. A paired student's t-test was used to compare pre- and post-exercise optical density values. Data are reported as means ± standard error (MEANS±SEM). Statistical power ranged from 0.80 to 0.97 at a P-value equal to 0.05. Significance for this study was set at P≤0.05.

RESULTS

Subject Characteristics and Reported Side Effects

Subjects were weight stable throughout the course of the study. Moreover, there were no significant differences between subjects for each of these measures (Table 1). In addition, three subjects reported side effects such as itchy skin, nausea, tachycardia, and flushed face, which has also been previously reported [24]. Subjects reported that these symptoms distracted them mostly during the 45 minute pre-exercise period (since they were required to sit still), and that they were hardly noticeable during the exercise and did not adversely affect their exercise performances.

Table 1: Subject Characteristics Measured at Baseline (Mean ± SEM)

Baseline Measurements	n = 9 Males
Age (yrs)	21.00 ± 0.37
Height (cm)	178.1 ± 2.99
Weight (kg)	91.05 ± 3.87
BMI	27.44 ± 1.86
Body Fat (%)	14.06 ± 2.74
1-RM (kg)	76.22 ± 3.75
60% 1-RM (kg)	42.78 ± 3.32

Note: BMI, body mass index; 1-RM, one repetition maximum.

De-Oxygenation of the Soleus Muscle During the Exercise Protocol

We validated our experimental protocol to de-oxygenate the soleus muscle and to return to baseline after rest (Figure 3). Figure 3 is representative data for each of the subject's optical densities measured by near infrared spectrometry throughout the experimental protocol. The exercise optical density was significantly decreased compared to pre- and post-exercise values (P = 0.000002).

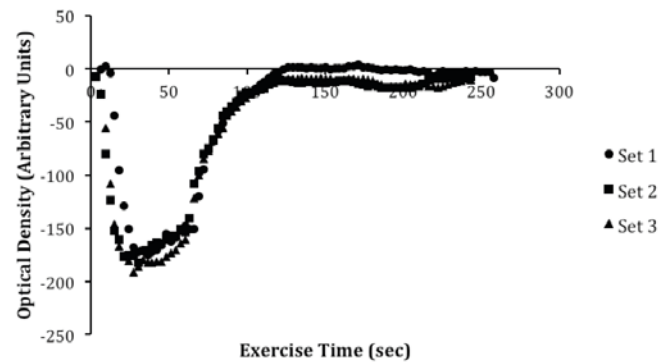


Figure 3: Blood oxygenation (optical density) during each set of seated-calf raise exercise.

Re-Oxygenation Half-Time (t_{1/2})

Skeletal muscle blood flow was significantly (P < 0.05) decreased during exercise compared to resting and recovery values. Despite a trend, there were no significant differences in subjects' half-times among the supplement groups (P = 0.07) (Figure 4). There were also no significant differences in half-times for each set among the supplement groups (P = 0.07) (Figure 5). Interestingly, AAKG supplementation consistently had the shortest half-time and CAFF supplementation consistently led to the longest half-time during all three sets and with all sets combined (Figures 4 and 5). This is also depicted in the percent changes of the half-times when relative to placebo (Figure 6). Again, there were no significant differences in the percent changes among the supplement groups (P = 0.1). Overall, supplementation of CAFF, AAKG, and XPAND did not affect re-oxygenation of the soleus muscle after exercise.

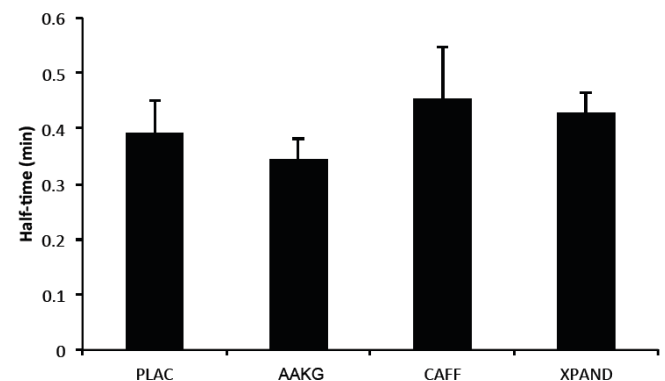


Figure 4: Blood re-oxygenation half-times (min) for all sets combined for each supplement.

DISCUSSION

To compare the effects of an L-arginine containing 'cocktail' supplement versus its constituent ingredients, we tested three different supplementation conditions

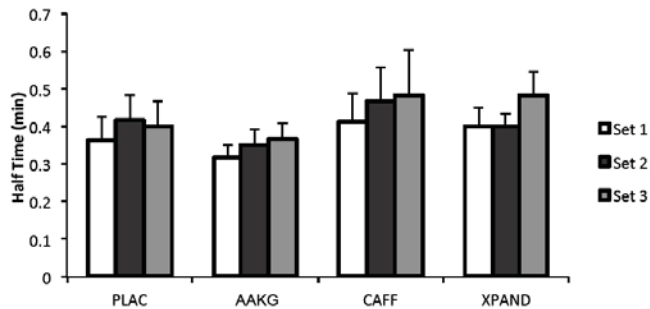


Figure 5: Blood re-oxygenation half times (min) for each set of seated calf-raise exercise for each supplement.

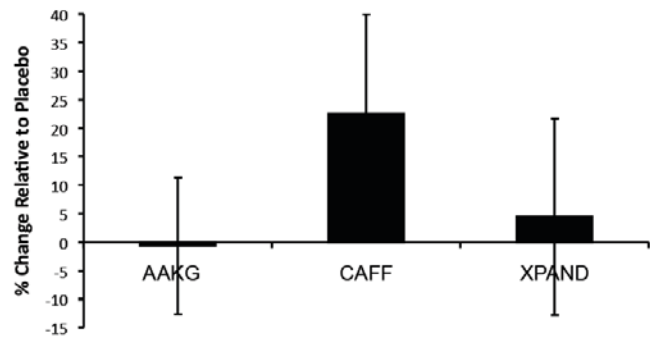


Figure 6: The percent change in blood re-oxygenation half-times relative to the placebo supplement.

(AAKG, CAFF, and XPAND) on soleus muscle re-oxygenation during and after resistance exercise in men. We predicted that AAKG would decrease and CAFF would increase re-oxygenation time, and that the combination of ingredients in XPAND would elicit no effect. As expected, XPAND supplementation had no effect on calf muscle re-oxygenation. However, contrary to our hypotheses, the individual responses of AAKG and CAFF were also not significant.

This was the first study to compare calf muscle re-oxygenation time after resistance exercise in men who performed the same protocol on three different occasions with a 'cocktail' supplement compared to two constituent ingredients. This study design allowed us to examine the effects of arginine and caffeine individually, and as combined ingredients of Xpand Nitric Oxide Reactor versus a control condition. We found that Xpand Nitric Oxide Reactor did not change re-oxygenation half-time compared to placebo. Our study is unique, because most studies that have examined supplementation with L-arginine 'cocktail' supplements have assessed performance variables such as muscle power, time to fatigue, muscle fatigue recovery, anaerobic power, and muscle strength [25]. One study by Bloomer *et al.* (2010) examined the effect of 'cocktail' supplements on muscle hemodynamics,

and similar to our findings, reported no effect on muscle oxygen saturation [17].

Our study was also the first to examine the effects of constituent ingredients compared to the 'cocktail' supplement. L-arginine alpha-ketoglutarate is the major ingredient in Xpand Nitric Oxide Reactor, and it is converted to L-arginine *in vivo*. Furthermore, supplementation with L-arginine alpha-ketoglutarate has been shown to increase plasma levels of L-arginine [26], and L-arginine is a precursor for nitric oxide synthesis [27]. But similar to recent studies by Tang *et al.* (2011) and Willoughby *et al.* (2011), we found no effect of AAKG supplementation on hemodynamics. Tang *et al.* (2011) found no increase in lower-body muscle blood flow at rest or after resistance exercise following bolus arginine supplementation compared to placebo [28], and Willoughby *et al.* (2011) reported no change in upper-body muscle blood flow following 7 days of L-arginine alpha-ketoglutarate supplementation with resistance exercise [26]. It is still possible, however, that the L-arginine alpha-ketoglutarate supplementation in our study was not sufficient enough to increase NO, thus potentially explaining the lack of change in hemodynamic characteristics in the muscle. Increased vasodilation in humans has been demonstrated with supraphysiological doses of arginine (30g) that were administered intravenously [29]. But we used doses consistent with Xpand Nitric Oxide Reactor for all supplement treatments (ranging from ~4 to 8g).

Caffeine, the other major ingredient in Xpand Nitric Oxide Reactor, also did not significantly affect soleus muscle re-oxygenation half-time after exercise. Flow mediated dilatation has been shown to be impaired up to 60 minutes after caffeine ingestion [7]. In our study, caffeine was ingested 45 minutes prior to exercise, and perhaps not enough time was permitted for impairment of endothelial function. However, our recorded caffeine supplementation half-times were consistently the longest amongst all subjects, and our results were trending towards significance.

SUMMARY

In summary, we examined the effects of pre-exercise supplementation with an L-arginine containing 'cocktail' supplement compared to two main ingredients, caffeine and L-arginine alpha-ketoglutarate, on calf muscle re-oxygenation during and after 3 sets of intense resistance exercise. Our study is the first to examine L-arginine alpha-

ketoglutarate supplementation on hemodynamics in the soleus muscle of the leg, and our results are in agreement with previous findings. Even though arginine-containing 'cocktail' supplements may improve physical performances, there is growing evidence that these supplements have little to no effect on muscle hemodynamics. Thus, any ergogenic effects of these supplements are likely to not be related to improvements in blood flow nor re-oxygenation, instead creatine monohydrate or caffeine may have been responsible for previous reports of increased performance with arginine-containing 'cocktail' supplements. It seems possible that by combining ingredients for the purpose of optimizing physical performance may actually cause a wash-out of the intended physiological benefit of increased muscle blood flow because of interference between ingredients.

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