

Single Dose of Dietary Supplement Nutrex Lipo-6 Black[®] Limits the Post Exercise Hypotension Induced by Aerobic Exercise in Young Adults

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Abstract: *Objective:* to evaluate the blood pressure (BP) behavior and sympathetic activity in response to an aerobic exercise session after taking a dose of Nutrex Lipo-6 Black[®].

Methods: This randomized, placebo-controlled study utilized seventeen subjects, divided in supplementation (n=10, 26.5±5.3 years) and placebo groups (n=7, 22.4±2.8 years). They ingested a dose of Nutrex Lipo-6 Black[®] (containing synephrine, caffeine, yohimbine and diiodine) or placebo and underwent a session of 40min of aerobic exercise of moderate intensity. Heart rate (HR), BP and cardiac autonomic balance (measured by heart rate variability) (CANA) were monitored at baseline, 30min after supplementation, at the end of the exercise and every 10min during a recovery period of 30min.

Results: After 30min of intake, Nutrex Lipo-6 Black[®] and placebo groups exhibited HR, BP and CANA similar to each other and in relation to the pre-supplementation moment. At the end of the exercise all variables showed a rise in relation to rest, but without statistical difference between groups (p>0,05). Moreover, at 30min of recovery, the Nutrex Lipo-6 Black[®] group presented with diastolic hypertensive response (increase of 4.2 mmHg) and a discrete post-exercise hypotension only to systolic pressure (-0.2 mmHg) relative to the pre-supplementation, while the placebo group showed evident both systolic and diastolic hypotension (-6.3 and -0.5 mmHg, respectively). HR and CANA were similar to pre-supplementation at this time.

Conclusion: single dose of Nutrex Lipo-6 Black[®] is able to limit the benefits of an exercise session in reducing BP, even without affecting the resting conditions of BP and CANA.

Keywords: Dietary Supplements, Sympathetic Nervous System, Exercise, Blood Pressure, Heart Rate, Post-Exercise Hypotension.

INTRODUCTION

Nutritional supplementation is a notorious practice among athletes and practitioners of physical exercise [1, 2]. Studies report prevalence of use that ranges from 60 to 80% in elite young athletes under 20 years [2], 65 to 99% in athletics [3, 4] and 55 to 99% in elite athletes [1], presenting a great variety in the types of products used [4]. In this context, dietary supplements marketed as being capable of promoting weight loss have been widely used, reaching the figure of \$ 50 billion annually only in the United States [5].

Considering the process of lipolysis is initiated by activation of beta adrenergic receptors in adipose tissue by increasing the serum concentration of catecholamines [6] and several substances that can mimic these effects, supplements called thermogenic were marketed with this biochemical argument for its

effectiveness. One of the most potent sympathomimetic substances is extracted from the native plant of Asia of genus Ephedra, which are natural sources of alkaloids, mostly ephedrine [7]. However, severe neurological complications including cardiovascular and cerebrovascular accident, seizures, myocardial infarction and sudden death were associated with supplements containing ephedra and ephedrine alkaloids [8, 9]. Shekelle *et al.* [10] found 16,000 adverse events associated with the use of ephedrine contained in dietary supplements. Consequently, the U.S. Food and Drug Administration (FDA) has determined to ban the marketing of these products [8].

With this ban, new formulations appeared on the market that does not use ephedrine, but other substances with sympathomimetic similar actions. A commercial product free of ephedrine that has been widely marketed is called Nutrex Lipo-6 Black[®] (Nutrex Research, Inc., Oviedo, Fla.), voted "Fat-loss Product of the Year" between 2005-2008 by the specialized website bodybuilding.com. It consists of replacing the ephedrine for synephrine, and in its formula still

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contains caffeine, yohimbine and diiodine that act synergistically with synephrine.

As Nutrex Lipo-6 Black[®] brings in his formula sympathomimetic substances, adverse events related to ephedrine could also be expressed in this supplement. However, few studies so far have sought to clarify the effects of this supplement, despite having already been reported by Thomas *et al.* [11] a case of myocardial infarction in a young man with no previous risk factors that was in continuous use (3 weeks) of Nutrex Lipo-6 Black[®]. Whereas there is evidence that a single dose of sympathomimetic substances can promote cardiovascular repercussions in sympathetic nerve activity, heart rate, blood pressure [8, 11, 12], and studies reporting that only caffeine is capable of abolishing the post-exercise hypotension (a decrease in blood pressure in the minutes following the completion of exercise) [13, 14], there is the possibility that Nutrex Lipo-6 Black[®] users may already be suffering adverse effects regardless of the outcome reached with infarctions or strokes.

Therefore, this study was conducted to test the safety of a single dose of the supplement Nutrex Lipo-6 Black[®] on hemodynamic and cardiac autonomic responses associated with an acute bout of aerobic exercise.

MATERIALS AND METHODS

Subjects

This double-blind study was conducted with 17 subjects practicing regular physical activity of various forms of gymnastics academy, divided into two groups, one using Nutrex Lipo-6 Black[®] (n = 10, 26.5 ± 5.3 years) and the other placebo (n = 7, 22.4 ± 2.8 years). They should have at least three months of physical activity, with minimum frequency of three days per week. The study excluded those with more than three absences per month in exercise programs, as well as heart disease, pregnant women and people with thyroid gland dysfunction and smokers. All wore nutritional supplements, but none made use of thermogenic or any other product with the promise of weight loss for at least three months. The study was approved by the research ethics committee of the Centre for Health Sciences, Federal University of Paraíba - UFPB being approved under the protocol number 300/10. All subjects in the study signed an informed consent in accordance with resolution 196/96 of the National Health Council

Study Design

After resting for 10 min., measures of blood pressure (BP), heart rate (HR) and cardiac autonomic nervous activity (CANA) were taken. Soon after, the two groups ingested capsules of Nutrex Lipo-6 Black[®] or placebo and remained seated for 30 minutes, being registered BP, HR and CANA. Then held a session of aerobic exercise on a cycle ergometer with duration of 40 minutes and intensity between 60% and 70% of maximum heart rate, which is capable to promote PEH in accordance to ACSM [15]. New measures of BP, HR and CANA were performed during exercise and every 10 minutes of a recovery period of 30 minutes that followed the exercise.

Preparation and Ingestion of Nutrex Lipo-6 Black[®] and Placebo

All subjects performed a washout of 48 hours for coffee, soft drinks as well as any nutritional supplement and other products containing caffeine known from a list prepared by a nutritionist. The supplement Nutrex Lipo-6 Black[®] is composed mainly for synephrine, yohimbe, caffeine, phenylethylamine, diiodo-thyronine and other substances. The chemical composition of this product is shown in Table 1. It was adopted as a criterion for the determination of the Nutrex Lipo-6 Black[®] dosage the recommendation provided by the manufacturer. Thus, the subjects ingested two capsules of the product 30 minutes before starting the exercise protocol. This protocol was intended to enable the investigation of physiological effects in similar manner of real life settings.

Table 1: Supplement's Composition (2 Capsules)

Ingredients	Amount
33 Diiodine – L – thyronine 35 Diiodine – L – thyronine	100 mcg
Yohimbine HCL 11 – Hidroxi – yohimbine Alfa – Yohimbine	4 mg
Synephrine HCL Metilsynephrine	20 mg
B – phenylethylamine HCL R – Beta – Metilphenylethylamine HCL N – Metil – B – phenylethylamine HCL	120 mg
Caffeine Anhydrous 1 – Metilcaffeine	200 mg

Placebo capsules were obtained from a manipulation pharmacy. Were made with similar

external appearance to supplement capsules, but being composed of starch and placed in a container similar to Nutrex Lipo-6 Black®.

Blood Pressure Measurement

All procedures were performed in the same manner. Upon arrival at the laboratory, subjects were asked to remain at rest 10 minutes, being performed at the end of this period the resting BP. New measures were taken immediately at the end of the exercise and every 10 minutes during recovery of 30 minutes. The BP measurements were performed by auscultation following the VI Brazilian Guidelines on Hypertension [16].

Registration on Cardiac Autonomic Nervous Activity

Autonomic activity was determined by recording the RR interval variability of heart rate *via* a Polar Heart Rate Monitor RS800CX (*Polar Electro Oy, Kempele, Finland*). This handset has been validated before registration of ECG at rest and during exercise. Records were made at rest, five minutes before performing the exercise (25 minutes after supplementation), immediately after exercise and every 10 minutes of the recovery period. Each record lasted five minutes. The data were presented according to the criteria of mean differences of two consecutive RR intervals, standard deviation of the difference between the sum of intervals and differences between the RR intervals in the zone of low frequency and high frequency.

Exercise Protocol

The exercise lasted 40 minutes and had moderate intensity (between 60 and 70% of maximum heart rate),

as proposed by Karvonen [17]. The intensity was monitored throughout the exercise through heart rate by using a heart rate monitor from Polar brand, model RS800CX (*Polar Electro Oy, Kempele, Finland*).

Statistical Analysis

Data are presented as mean and standard deviation. Tests of Levine and Barlett were performed to verify data normality and differences between the standard-deviation of the variables, respectively. The independent t test was performed to compare the characteristics of the subjects in both groups, while ANOVA for repeated measures was adopted to compare differences between groups for the dependent variables of the study. When appropriate, the Bonferroni post hoc was performed. It was adopted confidence level of 5% for the tests ($p < 0.05$). All procedures were performed using the InStat software 3.0.1 (*Calli Graph Pad, San Diego, CA, USA*).

RESULTS

All 17 subjects completed the study without any adverse complications. The anthropometric and hemodynamic characteristics are described in Table 2. The subjects were normal, blood pressure and cardiac autonomic balance were within normal values. There were no statistical differences between groups for any of these variables.

During the 30 minute-period following the supplement or placebo intake, heart rate was similar for both groups, with no significant changes being observed. The chronotropic response to exercise was similar between the two groups, as well as a post-exercise recovery. These data are shown in Figure 1.

Table 2: Anthropometric and Hemodynamic Characteristics of Subjects

Variable	Nutrex Lipo-6 Black®	Control Group	p
N	10	7	
Age (years)	26,5±5,3	22,4±2,8	0.06
Height (m)	1,66±0,0	1,70±0,1	0.67
Body mass (kg)	65,7±10,1	67,5±16,7	0.80
BMI (kg/m ²)	23,6±1,9	23,7±4,2	0.95
Resting HR	69,7±6,4	80,4±16,2	0.14
Resting SBP	106,2±13,7	111,7±6,4	0.28
Resting DBP	66,8±5,9	65,4±5,3	0.62
Resting CANA	2,3±1,3	2,9±1,4	0.32

Data presented as mean and standard deviation. BMI: Body Mass Index. HR: Heart Rate. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. CANA: Cardiac Autonomic Nervous Activity.

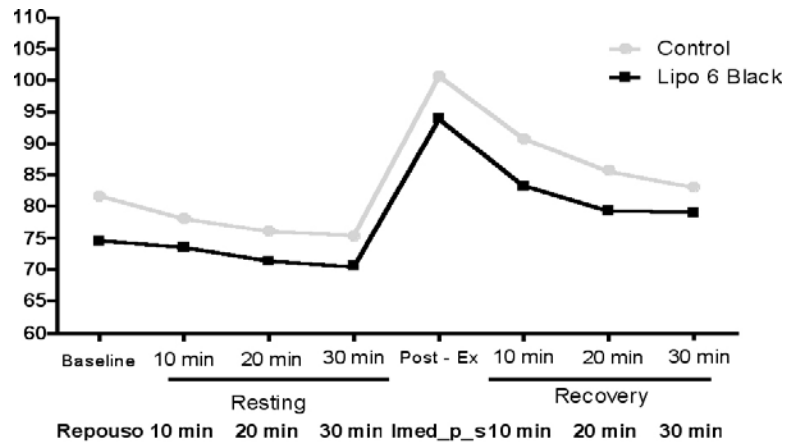


Figure 1: HR response to ingestion of Nutrex Lipo-6 Black® and placebo before, immediately after and during recovery from exercise.

Despite the Nutrex Lipo-6 Black® didn't affect neither the resting blood pressure nor the responses to exercise, it was shown that the supplement has limited post-exercise hypotension, since, while the control group showed a pressure reduction of - 6.3 and -0.5 mmHg at 30 minutes post-exercise compared to pre-supplementation, for systolic and diastolic BP, respectively, the group Nutrex Lipo-6 Black® presented a hypertensive response for the diastolic component of blood pressure (increase of 4.2 mmHg compared to the pre-supplementation), and a nearly complete abolition of systolic hypotension (decrease of only 0.2 mmHg).

reduction of sympathetic-vagal balance to values similar to those obtained at baseline, but without differences between groups.

DISCUSSION

The main finding of this manuscript corresponds to the fact that a single dose of Nutrex Lipo-6 Black® did not affect the hemodynamic behavior in young adults subjects previously involved in physical exercise. However, the acute use of this supplement was able to limit a classic benefit of exercise, called post-exercise hypotension (PEH), a reduction in blood pressure observed in the first minutes of recovery compared to pre-exercise values.

Cardiac autonomic modulation data are shown in Table 3 through the component of heart rate variability. It is observed that the supplement or placebo intake did not affect the sympathetic-parasympathetic balance in the 30 until the exercise was initiated. At end of exercise the sympathetic vagal balance was increased in both groups compared to their respective pre-exercise values, but without differences between them. The recovery period was characterized by a gradual

To our knowledge, there is only one report on the effects of ingesting Nutrex Lipo-6 Black® in literature, but it was a case study of the occurrence of myocardial infarction in a workout after the consumption of this product [11]. Nevertheless, there was concomitant use of caffeine-rich products prior to exercise by the subject.

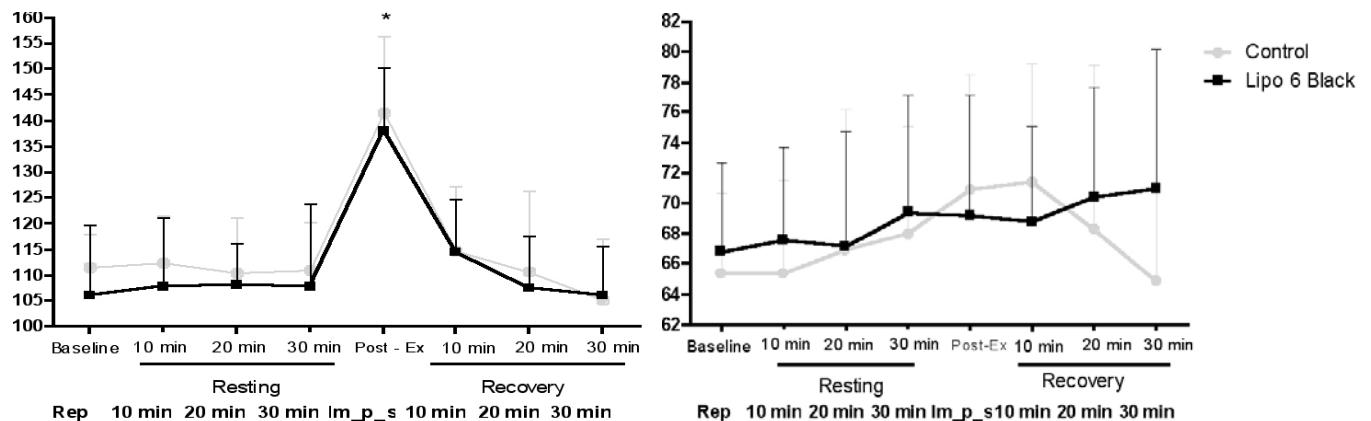


Figure 2: SBP and DBP response after intake of Nutrex Lipo-6 Black® and placebo before, immediately after and during recovery from exercise. *Denotes significant difference at rest (p <0.05).

Table 3: Heart Rate Variability in the Baseline, Post-Intake Supplement or Placebo, During and after Exercise at the Criterion of the Sum of Differences between RR Intervals in the Zone of Low Frequency (LF), High Frequency (HF) and Sympathetic-Parasympathetic Balance (LF / HF)

		LF (ms)	HF (ms)	LF/HF (ms)	p
Baseline	Lipo 6	1387,5±825,6	854,6± 977,1	2,3±1,3	0.32
	Placebo	1861,0±1636,7	846,7±888,2	2,9±1,4	
10min post	Lipo 6	1706,6±831,5	848,3±842,6	2,7±1,3	0.73
	Placebo	1791,7±898,3	893,1±961,5	2,9±1,2	
20min post	Lipo 6	2311,9±994,5	939,0±768,3	3,2±1,7	0.21
	Placebo	1955,2±1100,7	1072,9±983,1	2,4±1,0	
30min post	Lipo 6	2383,5±977,8	1150,2±971,3	2,7±1,4	0.31
	Placebo	2597,5±1311,3	1134,4±1218,7	3,7±2,0	
Exercise	Lipo 6	32,0±25,1	8,2±8,9	5,6±3,2 *	0.36
	Placebo	61,7±113,4	19,5±37,9	7,4±4,3 *	
10min rec	Lipo 6	1510,9±710,3	477,0±344,1	4,0±1,8	0.74
	Placebo	1151,2±359,8	290,7±155,2	4,5±1,4	
20min rec	Lipo 6	1762,4±911,0	592,9±292,9	3,2±1,5	0.60
	Placebo	1337,8±413,2	395,9±141,3	3,6±1,1	
30min rec	Lipo 6	1894,9±710,2	703,8±365,0	3,2±1,5	0.88
	Placebo	1896,9±726,9	609,0±268,6	3,3±1,3	

Data presented as mean and standard deviation. rec: recovery period after exercise. *Denotes significant difference at rest ($p < 0.05$).

Although thermogenic products of the category of Nutrex Lipo-6 Black® has not been evaluated in terms of hemodynamic responses, its high levels of caffeine open the possibility of adverse effects on blood pressure. In fact, Cazé *et al.* [13] and Notarius *et al.* [18] found that oral consumption or intravenous infusion of caffeine not only abolish the effect of a physical exercise session on the PEH, but also promoted a hypertensive response at least in the first hour post-exercise recovery.

The fact that the PEH occurs in the first minutes after exercise and can last for up to 24 hours, makes exercise an important tool in the prevention and treatment of hypertension [19]. Due Nutrex Lipo-6 Black® is rich in caffeine and other stimulants compounds of Central Nervous System (CNS), it was reasonable to hypothesize that a high concentration of these stimulants could also generate abolishment of this phenomenon. In fact, the subjects of our study had a diastolic PEH replaced by a hypertensive response when ingested Nutrex Lipo-6 Black®, corroborating data of Cazé *et al.* [13] and Notarius *et al.* [18], but only partially, since these authors found abolishment for both systolic and diastolic blood pressure. On the other hand, when 304mg of caffeine plus 21 mg of synephrine of the commercial supplement Ripped Fuel

Extreme Cut® was used, the subjects showed significant higher diastolic blood pressure compared to placebo group, but not systolic blood pressure [20]. These results are similar to present study. McBride *et al.* [21] using other commercial supplement, Metabolife 356® (12mg alkaloids efedra, 40 mg of caffeine and 16 other ingredients), reported that acute consumption increased systolic BP (unlike the present study, where the change was seen in the diastolic component) and the mean QTc interval of the electrocardiogram, indicating another variable negatively affected acutely by thermogenic substance use.

Some points should be considered to understand the different responses between this study and studies of Notarius *et al.* [18] and Cazé *et al.* [13] with respect to PEH. Although in these studies caffeine (4mg/kg) was the only CNS stimulant substance used, it proved sufficient to completely abolish the PEH. Theoretically, for further contain ephedrine and synephrine alkaloids (20mg), yohimbe (4mg) and thyronine (100mcg), the Nutrex Lipo-6 Black® group of this study should undergo this same effect. Interestingly, only a limitation on the PEH diastolic component was verified. This fact occurred possibly due to differences between the sample populations studies, since this study was used in normotensive young adults while previous were

conducted with middle-aged hypertensive subjects. If hypertensive subjects with predisposing factors for increases in blood pressure would suffer worse hemodynamic effects is something that neither this study nor the previous literature are able to inform.

When previous studies have evaluated the cardiovascular effects of thermogenic supplements, basically evaluated HR, BP and electrocardiographic behavior. Our study presents the differential that has also investigated the cardiac autonomic nervous activity. This is an important variable in clinical practice because it represents one of the most implicated mechanisms in hypertension, since changes in autonomic nervous activity preceded the increase in BP [21]. The fact that our data indicate no change in this variable apparently rules out the involvement in autonomic nervous effects of the supplement, but it should be very clear that our protocol involved a single dose of the product. Therefore, do not endorse the safety of this product for continued use for autonomic nervous activity.

Previous data indeed show deleterious cardiovascular effects resulting from chronic use of ephedrine [8, 22]. With the prohibition of products containing ephedrine by the FDA in 2004 [23], the advent of other substances similar to ephedrine, as p-synephrine and octopamine, increased for commercial use. However, the adverse effects of these alternatives to ephedrine appear not to be discarded, since Stephensen *et al.* [24] and Bui *et al.* [12] reported changes in BP and HR with the use of these substances. Meanwhile, Seifert *et al.* [25] found that the use of a supplement called Acceleron[®] at doses of 52 mg of p-synephrine and 704 mg of caffeine over a period of 24 hours, showed no adverse effect on BP and HR.

Interesting explanation about the conflict in this matter may be brought by Seifert *et al.* [25]. For these authors, confusion about the interpretation of the results of the cardiovascular effects of products containing synephrine may be derived at least in part from a lack of understanding of the pharmacokinetic and pharmacodynamic differences between different isomers (-m and -p) of that substance. These differences are related to the ability to bind to different adrenergic receptors. Evidence demonstrates that p-isomer binds to receptors β_3 - adrenergic receptors (associated with lipolysis and thermogenesis, without adverse cardiovascular effects) [26], while the m-isomer is known for its cardiovascular effects [27].

Unfortunately, this study was unable to draw associations of the results obtained, since the product contains substances as HCL form, which is an economically more feasible to provide product stability, but without isolating its isoforms.

Taking the data from our study and comparing with the prior information from the literature, we can say our work contributes to this line of research to bring two new elements: the effect of a single dose of a commercial supplement that has been used in several countries in post exercise hypotension; and we evaluate the cardiac autonomic responses, a more sensitive parameter regarding cardiac events. Strength of our work was that we show only one dose of the product was able to limit a classic benefit of exercise: the post exercise hypotension (even in young and health subjects).

The set of our data indicates an abolishment of diastolic PEH at an acute and unique Nutrex Lipo-6 Black[®] thermogenic supplement dose. However, the response of the systolic component, as well as cardiac autonomic nervous activity, were not affected. Assessment of response to chronic use in resting blood pressure seems to be a need to better clarify the hemodynamic effects of this nutritional supplement.

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Received on 14-12-2012

Accepted on 11-04-2013

Published on 30-04-2013

DOI: <http://dx.doi.org/10.6000/1927-5951.2013.03.02.3>© 2013 Magalhães *et al.*; Licensee Lifescience Global.

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