Effects of the acute arginine aspartate supplement on the muscular fatigue in trained volunteers

Ricardo Pombo Sales[1], Carlos Eduardo César Miné[1], Andréia Dellú Franco[1], Érika Lima Rodrigues[1], Naira Correia Cusma Pelógia[2], Renato de Souza e Silva[3], José Carlos Cogo[1], Rodrigo A.B. Lopes-Martins[1], Rodrigo Lazo Osorio[1] and Wellington Ribeiro[1]

ABSTRACT

The physical activity influences specific mechanisms responsible by a reduction in the power production, and consequently on the fatigue. It has been proposed premises to improve the physical performance, and we observed that some studies have been focused on the reduction of the metabolites that decrease the fatigue on intense physical exercising, using aminoacids known for their properties to induce to metabolic changes, and among these, it is the arginine. The present study had the purpose to study the effects of the acute arginine aspartate supplement in trained healthy individuals submitted to an exhaustion protocol on ergonomic bicycle. Twelve 22.6 ± 3.5 years old trained individuals were used in the research. After taking a single dose of arginine aspartate or a placebo solution, they performed three 90 minute test on an ergonomic bicycle to which load increments were added up to reaching the exhaustion. The blood samples were obtained through biochemical analysis, such as: creatinine, urea, glycosis, and lactate. It was found no statistical differences upon the comparison of the Maximal Heart Rate, Maximal Time and Load, and also comparing to the previous and later results on the urea, creatinine and glycosis tests. The lactate concentrations (mmol/l) presented statistical differences compared to the pre-test values (Control: 2.2 ± 0.14; Arginine: 2.43 ± 0.23; Placebo: 2.26 ± 0.11) to the post-test values (Control 10.35 ± 0.57; Arginine: 12.07 ± 0.88; Placebo: 12.2 ± 0.96), $p < 0.001$. The main results found in this study indicate that the acute administration of the arginine aspartate did not show effective to increase the fatigue tolerance in the individuals evaluated and treated in the incremental test protocol up to the exhaustion. Thus, it can be concluded that the dosage used was not able to increase the muscular fatigue tolerance.

Keywords: Lactate. Aminoacid. Exhaustion.

INTRODUCTION

It is known that during high intensity exercising, the major ways for the ATP supply are the phosphate creatine breakdown, and the degradation of the muscular glycogen to the lactic acid. Thus, the reduction in the phosphate creatine and glycogen contribute to the decrease in the anaerobic production of the energy and in the exercise performance[1-3]. It is clear that the skeletal-muscular performance decreases during an intense physical activity, and such phenomenon is known as fatigue[4,5]. There is a consensus among several researchers that the term *fatigue* is the decrease in the muscular ability in keeping the power generation and the relaxation velocity, induction to changes in the contractile feature and in the electrical properties that generate malfunctions in the human neuromuscular system[5-13]. The fatigue is a quite researched subject, but the precise mechanisms that lead to the changes it causes are still to be clarified[14].

It is clear that the fatigue is followed by several physiological and metabolic changes. Among them, there are indicative factors such as hematological and immunological parameters, glycemia, lipid level, enzymatic activity, blood urea, uric acid, and other factors[15]. The nature of the physical activity performed has influence on specific mechanisms responsible by the reduction in the ability to produce power, and consequently the fatigue[16,17].

Two major mechanisms were described to explain the fatigue in the skeletal muscle solely: (i) decline in the contractile power generation of the muscle through a metabolic effect in the contractile proteins, and (ii) decrease in the Ca^{2+} releasing from the sarcoplasmic reticulum[18]. Also, it is asserted that the point of fatigue during prolonged exercising coincides with lower reserves of the muscular glycogen[19,20].

One practice used in the Exercise Physiology Laboratory is to determine the blood lactate concentration ($[La]_b$)[21,22]. High lactate concentrations can favor the appearance of the fatigue, as they increase the H^+ ions concentration generated by the dissociation of the lactic acid in lactate and H^+, and decrease the pH. The decreased pH can be associated to a reduction in the power produced by the inhibition of the glycolysis through the phosphofructokinase inhibition, and consequently, the interruption of the energetic supply[2,7,13]. The issue related to the lactate accumulation into the muscle and blood in submaximal workloads is attributed to an unbalance between the supply and utilization of the O_2 in the muscular work[21,23].

Another factor considered is the sarcoplasmic reticulum that actuates as a storage spot to the Ca^{2+}, and it still controls the cytoplasmatic concentrations of the Ca^{2+} that regulates the muscular contractions. If the function of the sarcoplasmic reticulum is decreased, it can be started a critical role: the appearance of the fatigue. Especially, the decreasing utilization of the Ca^{2+} can be responsible by the difficulty in the relaxation, as well as by a power reduction during the fatigue[14,24-26].

By its turn, the lactate significantly inhibits the Ca^{2+} channels activation. So, the contraction-excitatory coupling process, and the Ca^{2+} releasing inhibition in the sarcoplasmic reticulum can be the only responsible factor by the decreasing performance, but such disturbance in the Ca^{2+} transition contributes to the muscular fatigue[18,27].

Recent studies indicate that there is an increase in the blood flowing whenever there is a reduction in the blood pH[28]. Such metabolic vasodilation increases the Oxygen and nutrients supply as a response to the tissular demand[12,29].

1. Vale do Paraíba University – IP&D – Laboratory of Physiology and Pharmacodynamics – São José dos Campos – São Paulo, Brazil.
2. Taubaté University – Institute of Biosciences – Taubaté – Brazil.
3. Taubaté University – Department of Physical Education – Taubaté – Brazil.

Received in 14/2/05. Final version received in 2/8/05. Approved in 5/9/05.

Correspondence to: Ricardo Pombo Sales, Rua Irmã Maria Rita de Moura, 230, Independência – 12031-140 – Taubaté, SP. Phone: (12) 3681-4430. E-mail: ricardofisiologia@hotmail.com

Thus, the concern on the improvement in the physical performance using several resources has been proposed in the last few years[30,31]. This way, we observed that studies are more focused in the reduction of the metabolite accumulations that decrease and/or induce the fatigue during physical exercising using aminoacid supplements known for their property to induce to beneficial metabolic changes[31-35]. Among these aminoacids, the L-arginine, which is essential to the child's growth and a substrate for different and important enzymes, such as the arginase, the NO synthase (NOS), decarboxylase arginine, etc. The arginase is a classical catabolizing enzyme of the arginine in the Urea Cycle, and the decarboxylase arginine catalyzes the change of the L-arginine to the agmatine, an endogenous agonist of the α_2-adrenoceptors that can have a role in the antihypertensive effect of the L-arginine. In healthy humans and in some animals, the L-arginine has been elucidated by being able to induce hypotension caused by the stimulation of the nitric oxide (NO) through the L-arginine-NO way[13,36-42]. The arginine's biochemistry is complex, and it involves several metabolic ways and organic systems. Arginine has an important role in the urea, protein, high energy compounds (creatine and phosphate creatine), polyamine, and nitric oxide synthesis[42-48].

The vasodilation of the muscle-skeletal arteriole as a response to the exercising increases the nutrient and oxygen supply to the muscles that are requested during the movement. Studies conducted with mouse and the action of the L-arginine supplement as determinant of the ability to perform a specific physical activity have showed an improvement in the ability to perform the activity due to the systemic increase in the production of the nitric oxide derived from the endothelium[49]. Some studies have already pointed out that the arginine supplements helped to reduce the physiological fatigue through the reduction of the ammonia a few time after the oral ingestion[50].

The present study had the purpose to study the effects of the acute arginine aspartate supplement in trained healthy individuals submitted to an exhaustion protocol on an ergometric bicycle.

METHODOLOGY

The sequence of the arginine aspartate administration for each volunteer was based on a randomized schedule previously approved by the Committee of Ethics in Human Researches under the number A020/2003/CEP.

To perform this study it was used tablets containing 1,5 g of arginine aspartate, commercially known as TARGIFOR® produces by the company Aventispharma, batch number 300971, and expiration date 02/2006. Volunteers received orally 4,5 g (3 tablets) of arginine aspartate in a sole dose diluted in mineral water (250 ml) containing a non-energetic dye. The placebo group received only dyed mineral water (250 ml).

It was used twelve healthy male individuals with ages from 22.6 ± 3.5 years.

Volunteers were submitted to a fatigue-inducing protocol organized as follows: all volunteers were evaluated, in order to obtain the controlling values. Later, they passed through the below described two experimental phases (FI and FII):

FI: 4,5 g administration of the arginine aspartate to volunteers I, II, IV, VII, IX, and XII.

FII: 4,5 g administration of the arginine aspartate to volunteers III, V, VI, VIII, X, and XI.

The fatigue-inducing protocol was performed 90 minutes after the administration of the arginine aspartate or the placebo solution, when volunteers were oriented to be positioned in one ergonomic bicycle (LifeFitness).

Pedaling at a 60 rpm frequency and after a two minute period at 38 watt it increased approximately 25 watts every two minutes except in the sixth minute (50 Watts) up to reaching the fatigue using a frequency meter to record the heart rate.

Each volunteer performed four times the same fatigue-inducing protocol (adaptation, control, arginine, and placebo) always using the same criteria[adapted 13].

Biochemical Analysis: blood collection: 5 ml before and 5 ml after the protocol, in order to perform the biochemical analysis such as: creatinine, urea, glycemia, and lactate. All biochemical analysis were made using Laborlab® diagnostic kits (Guarulhos/São Paulo, Brazil) through the non-kinetic methodology at 37ºC in a Shimadzu UV-1650 PC spectrophotometer. The plasmatic lactate was analyzed before and after the fatigue-inducing protocol using an Accusport® equipment, and stripes for the BM-Lactate analysis (Roche Diagnostics, Manheim, Germany).

Statistical Analysis: It was used the variance analysis (ANOVA) followed by the Tukey test for independent sampling. The significance level lower than 5% ($p < 0.05$) was adopted.

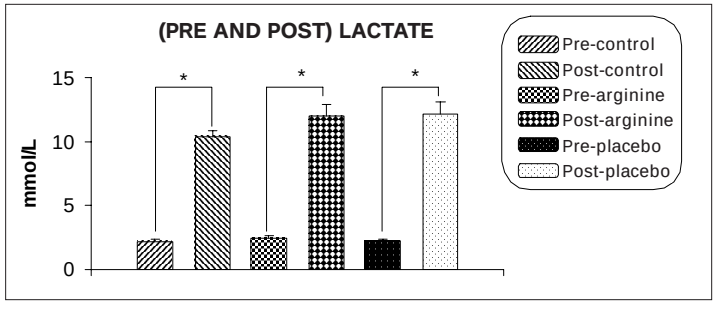
RESULTS

The data below presented are the Mean ± Standard Error of the Mean (SEM). The Maximal Heart Rate (HR_{max}) was recorded in beatings/minute (bpm) immediately after performing the fatigue-inducing protocol, and compared to the three groups, and it was found no statistically significant difference: Control (185 ± 4) vs. Arginine (184 ± 3), and Placebo (185 ± 4).

The Maximal Time (T_{max}) obtained in the fatigue-inducing protocol for different groups did not present statistical significance where it was verified the Control (17.86 ± 0.78) vs. Arginine (18.87 ± 0.71), and Placebo (18.31 ± 0.72).

No statistical difference could be observed in response to the Maximal Load ($Load_{max}$) obtained in Watts (W) after performing the fatigue-inducing protocol, with the following results: Control (266.08 ± 9.20) vs. Arginine (285.36 ± 8.23), and Placebo (276.67 ± 7.94).

The Lactate concentration (mmol/L) in trained volunteers was previously determined just after the conclusion of the fatigue-inducing protocol. Graphic 1 shows the plasmatic concentration of the pre-protocol Lactate, where it can be observed no difference between the experimental groups: Pre-Control (2.2 ± 0.14) vs. Pre-Arginine (2.43 ± 0.23), and Pre-Placebo (2.26 ± 0.11). The post-protocol plasmatic concentration, Post-Control (10.35 ± 0.57) vs. Post-Arginine (12.07 ± 0.88), and Post-Placebo (12.2 ± 0.96) did not present any statistical difference. Upon the comparison of the post-protocol concentration ($[La]_b$) before and after the fatigue-inducing protocol in the different phases, it was observed statistical differences. The Pre-Control (2.2 ± 0.14) vs. Post-Control (10.35 ± 0.57); Pre-Arginine (2.43 ± 0.23) vs. Post-Arginine (12.07 ± 0.88); Pre-Placebo (2.26 ± 0.11) vs. Post-Placebo (12.2 ± 0.96), $p < 0.001$.



Graphic 1 *– Mean Plasmatic Concentration of the Lactate obtained in 12 trained volunteers before and after performing the fatigue-inducing protocol in the different experimental groups. Data represent the mean ± S.E.M., n = 12. * P < 0.001.*

It was observed no statistical difference related to the Urea, Creatinine, and Glycosis concentrations, and the results were: Urea: Pre-control (41.67 ± 3.4), Pre-Arginine (42.56 ± 2.58), and Pre-Placebo (42.54 ± 3.25); Post-Control (45.06 ± 3.58), Post-Arginine

(44.44 ± 2.59), and Post-Placebo (43.08 ± 2.94). Creatinine: Pre-Control (1.68 ± 0.29), Pre-Arginine (2.19 ± 0.31), and Pre-Placebo (2.49 ± 0.40); Post-Control (2.38 ± 0.33) Post-Arginine (2.55 ± 0.30), and Post-Placebo (2.82 ± 0.29), and Glycosis: Pre-control (74.48 ± 4.19), Pre-Arginine (78.70 ± 3.91), and Pre-Placebo (73.60 ± 4.31); Post-Control (85.53 ± 5.04), Post-Arginine (79.28 ± 3.95), and Post-Placebo (70.83 ± 4.63).

DISCUSSION

It have been performed a great number of researches with the purpose to identify more effective ergogenic substances to improve the athletic performance, always focusing the demanded energy in all sports range, and in the control of the dietetic consumption[31]. The oral L-arginine supplement has shown both positive and negative results. The discrepancies between the clinic observations that in some cases, the L-arginine can increase the nitric oxide formation, added to the expectation that this could be the basis for the L-arginine's kinetics to the NO reaction is called "the arginine paradox". Theories related to the arginine paradox have focused the possibility that high doses of the L-arginine would provide the required effects[42], since if there will be an increase in the blood flowing, this would allow a higher lactate and ion releasing of the muscle, thus promoting a higher removal in the circulation due to the blood distribution[51].

The Maximal Heart Rate (HR_{max}) obtained in the tests during the phases clarifies the high intensity developed by volunteers, observing that the arginine aspartate supplement did not change the heart rate (bpm) of individuals along the test after the administration.

Another characteristic where it was obtained no changes was the Maximal Time (T_{max}) of the performance in different phases of the fatigue-inducing protocol, showing that the final performance was not changed by the administration of the 4,5 g of the arginine aspartate.

Upon the evaluation of the Maximal Load produced on the ergonomic bicycle when it was performed the fatigue-inducing protocol in the different phases of the administration, it was kept without any change, and this is certainly in conformity that the supplement used does not exert any effect on the obtainment of heavier workloads when using such fatigue-inducing protocol.

The measurement of the blood lactate concentration is a standard procedure to set the physical exercise intensity. The absolute value of the lactate concentration is used in certain groups of individuals, in order to make an objective estimate of the exercise or as a maximal exhaustion criterion[52]. In this study, these concepts were used to determine the exercise intensity, and when the values found in the post-protocol were checked, it was determined that volunteers attained their maximal exhaustion, that was considered the point of fatigue. The lactate accumulation during the execution of a high intensity exercise protocol means that the lactate production exceeds the amount it is removed. The lactate accumulation is an indicative of the glycogen depletion, and this gives sense to the finding of the high lactate concentrations at point of fatigue, in conformity with the reports made by other authors[18-20,51].

Thus, we observed the significant amount of the ($[La]_b$) when comparing the pre- and the post-protocol. So, it can be asserted that the rising in the plasmatic concentration of the lactate existed in face of the high intensity of the exercises proposed, and there is no differentiation due to the presence of the arginine aspartate supplement.

It is known that the surplus of the aminoacids is metabolized within the cycle of the urea, and it is excreted into the urine. The supplement surplus can lead to renal damage. So, analyzing the urea and creatinine concentrations, it is observed the effects on the renal function[35]. In a study accomplished in 1994, it was verified that the acute oral administration of 20 g arginine induced an increased ureagenesis and cellular ATP concentration[50]. But as to the urea concentrations, our results did not change after the acute oral administration of 4,5 g of arginine aspartate, reassuring that the oral dose suggested in studies was not sufficient to induce the increase in the ureagenegis[13].

The creatinine alone has been used to determine the renal ability and/or overload after an ingestion of aminoacids. By its turn, the arginine induces the endogen synthesis of the creatine, generating an additional source of the creatinine to be excreted. Regarding to this, the arginine together with the glycine and S-adenosylmethionine are the precursor aminoacids of the creatine, what in our study could be an additional energy to improve the performance, and this did not happen. The increase in the creatine synthesis demands a complex process that includes the captation of the arginine by the synthesizer organs of the creatine, to form phosphate creatine and to the dephosphorylation of the creatine, and consequently, the circulation[53].

Results related to the glycosis did not change along the test in the different phases, and this can explain the absence of an increase in the arginine-mediated flowing to the formation of the NO, as several authors have already shown the fundamental role of the formation way to the NO in the skeletal-muscle system as to the glycosis transport[47]. Thus, we point out the inefficiency of the supplement used in our research.

Despite the study has suggested that the oral administration of 4 to 5 g of arginine could bring benefits such as reduction in the lactate and ammonia concentrations and maybe an improvement in the performance, our results suggest that studies with other dosages and other administration schedule would be further performed maybe trying to attain an increase in the tolerance to the fatigue[13].

Finally, this study had the purpose to study the effect of the acute supplement of the arginine aspartate in trained healthy individuals submitted to an exhaustion protocol in an ergometric bicycle. But in face of the results attained, it can be concluded that the acute supplement of the arginine aspartate in the 4,5 g dosage it was impossible to increase the physical performance, characterizing the fact it did not help in the tolerance to the muscular fatigue.

All the authors declared there is not any potential conflict of interests regarding this article.

REFERENCES

1. Lucia A, Hoyos J, Pardo J, Chicharro JL. Effects of endurance training on the breathing pattern of professional cyclists. Jpn J Physiol 2001;51:133-41.
2. Hargreaves M, Mckenna MJ, Jenkins DG, Warmington SA, Li JL, Snow RJ, et al. Muscle metabolites and performance during high-intensity, intermittent exercise. J Appl Physiol 1998;84:1687-91.
3. Bangsbo J, Krustrup P, Alonso JG, Saltin B. ATP production and efficiency of human skeletal muscle during intense exercise: effect of previous exercise. Am J Physiol Endocrinol Metab 2001;280:956-64.
4. Dahlstedt AJ, Westerblad H. Inhibition of creatine kinase reduces the rate of fatigue-induced decrease in tetanic [Ca^{2+}], in mouse skeletal muscle. J Physiol 2001;533:639-49.
5. Hicks AL, Kent-Braun J, Ditor DS. Sex differences in human skeletal muscle fatigue. Exerc Sports Sci Rev 2001;29:109-12.
6. Kirkendal DT. Mechanisms of peripheral fatigue. Med Sci Sports Exerc 1990;22: 444-9.
7. Marquezi ML, Lancha Junior AH. Possível efeito da suplementação de aminoácidos de cadeia ramificada, aspartato e asparagina sobre o limiar anaeróbio. Rev Paul Educ Fis 1997;11:90-101.
8. Green HJ. Cation pumps in skeletal muscle: potential role in muscle fatigue. Acta Physiol Scand 1998;162:201-13.
9. Harmer AR, Mckenna MJ, Sutton JR, Snow RJ, Ruell PA, Booth J, et al. Skeletal muscle metabolic and ionic adaptations during intense exercise following sprint training in humans. J Appl Physiol 2000;89:1793-803.

10. Danion F, Latash ML, Li ZM, Zatsiorsky VM. The effect of fatigue on multifinger co-ordination in force tasks in humans. J Physiol 2000;523:523-32.
11. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81:1725-89.
12. Santos RS. Estudo do efeito da administração oral de l-arginina na resistência muscular em voluntários sadios por meio de dinamometria isocinética 2001; f.62. Dissertação (Mestrado em Engenharia Biomédica) – Instituto de Pesquisa e Desenvolvimento, Universidade do Vale do Paraíba.
13. Schaefer A, Piquard F, Geny B, Doutreleau S, Lampert E, Mettaure B, et al. L-Arginine reduce exercise-induced increase in plasma lactate and ammonia. Int J Sports Med 2002;23:403-7.
14. Lees SJ, Franks PD, Spangenburg EE, Williams JH. Glycogen and glycogen phosphorylase associated with sarcoplasmatic reticulum: effects of fatiguing activity. J Appl Physiol 2001;91:1638-44.
15. Tsopanakis C, Tsopanakis A. Stress hormonal factors, fatigue, and antioxidant responses to prolonged speed driving. Pharmacol Biochem Behav 1998;60:747-51.
16. Rassier DE, Macintosh BR. Coexistence of potentiation an fatigue in skeletal muscle. Braz J Med Biol Res 2000;33:499-508.
17. Bilodeau M, Henderson TK, Nolta BE, Pursley PJ, Sandfort GL. Effect of aging on fatigue characteristics of elbow flexor muscle during sustained submaximal contraction. J Appl Physiol 2001;91:2654-64.
18. Favero TG, Zable AC, Colter D, Abramson JJ. Lactate inhibits Ca^{2+}-activated Ca^{2+}-channel activity from skeletal muscle sarcoplasmic reticulum. J Appl Physiol 1997;82:447-52.
19. Febbraio MA, Dancey J. Skeletal muscle energy metabolism during prolonged, fatiguing exercise. J Appl Physiol 1999;87:2341-7.
20. Baldwin J, Snow RJ, Gibala MJ, Garnham A, Howarth K, Febbraio MA. Glycogen availability does not affect the TCA cycle or TAN pools during prolonged, fatiguing exercise. J Appl Physiol 2003;94:2181-7.
21. Grassi B, Quaresima V, Marconi C, Ferrari M, Cerretelli P. Blood lactate accumulation and muscle deoxygenation during incremental exercise. J Appl Physiol 1999;87:348-55.
22. Brooks GA, Dubouchaud H, Brown M, Sicurello JP, Butz CE. Role of mitochondrial lactate dehydrogenase and lactate oxidation in the intracellular lactate shuttle. Proc Natl Acad Sci USA 1999;96:1129-34.
23. Von Grumbckow L, Elsner P, Hellsten Y, Quistorff B, Juel C. Kinetics of lactate and pyruvate transport in cultured rat myotubes. Biochim Biophys Acta 1999;1417: 267-75.
24. Ferrington DA, Reijneveld JC, Bar PR, Bigelow DJ. Activation of the sarcoplasmic reticulum Ca^{2+}-ATPase induced by exercise. Biochim Biophys Acta 1996;1279: 203-13.
25. Favero TG. Sarcoplasmic reticulum Ca^{2+} release and muscle fatigue. J Appl Physiol 1999;87:471-83.
26. Kabbara AA, Allen DG. The role of calcium stores in fatigue of isolated single muscle fibres from the cane toad. J Physiol 1999;519:169-76.
27. Chin ER, Allen DG. The contribution of pH-dependent mechanisms to fatigue at different intensities in mammalian single muscle fibres. J Physiol 2000;512:523-32.
28. Modin A, Björne H, Herulf M, Aluin K, Weitzbeg E, Lundberg JON. Nitrite-derived nitric oxide: a possible mediator of 'acidic-metabolic' vasodilation. Acta Physiol Scand 2001;171:9-16.
29. Jacob TL, Segal SS. Attenuation of vasodilatation with skeletal muscle fatigue in hamster retractor. J Physiol 2000;524:929-41.
30. Barros Neto TL. A controvérsia dos agentes ergogênicos: estamos subestimando os efeitos naturais da atividade física? Arq Bras Endocrinol Metab 2001;45: 121-2.
31. Ohtani M, Maruyama K, Sugita M, Kobayashi K. Amino acid supplementation affects hematological and biochemical parameters in elite rugby players. Biosci Biotechnol Biochem 2001;65:1970-6.
32. Lemon PWR. Protein and exercise: update 1987. Med Sci Sports Exerc 1987; 19:179-90.
33. Rossi L, Tirapegui J. Aspectos atuais sobre exercício físico, fadiga e nutrição. Rev Paul Educ Fís 1999;13:67-82.
34. Stevens BR, Godfrey MD, Kaminski TW, Brainth RW. High-intensity dynamic human muscle performance enhanced by metabolic intervention. Med Sci Sports Exerc 2000;32:2102-8.
35. Lawrence ME, Kirby DF. Nutrition and sports supplements. J Clin Gastroenterol 2002;35:299-306.
36. Tricarico D, Casini G, Conte Camerino D. Effects of high energy phosphates and L-arginine on the electrical parameters of ischemic-reperfused rat skeletal muscle fibers. Eur J Pharmacol 1995;287:17-25.
37. Marin J, Rodriguez-Martinez A. Role of vascular nitric oxide in physiological and pathological conditions. Pharmacol Ther 1997;75:111-34.
38. Newsholme E, Hardy G. Supplementation of diets with nutritional pharmaceuticals. Nutrition 1997;13:837-9.
39. Harrison DG. Cellular and molecular mechanisms of endothelial cell dysfunction. J Clin Invest 1997;100:2153-7.
40. Hiroaki K. Nitric oxide and hemoglobin interactions in the vasculature. Biochim Biophys Acta 1999;1411:370-7.
41. Marareli MRT. Oxido nítrico: un gás contaminante con propiedades biológicas: su importancia en fisiopatologia cardiovascular. Rev Sanid Mil 2000;54:164-75.
42. Abdelhamed AI, Reis SE, Sane DC, Brosnihan KB, Preli RB, Herrington DM. No effect of an l-arginine-enriched medical food (HeartBars) on endothelial function and platelet aggregation in subjects with hypercholesterolemia. Am Heart J 2003; 145:e15.
43. Field CJ, Johnson I, Partt VC. Glutamine and arginine: immunonutrients for improved health. Med Sci Sports Exerc 2000;32:5377-88.
44. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. Educ Heart 2001;85:342-50.
45. Koller-Strametz J. Role of nitric oxide in exercise-induced vasodilation in man. Life Sci 1998;62:1035-42.
46. Reid MB. Nitric oxide, reactive oxygen species, and skeletal muscle contraction. Med Sci Sports Exerc 2001;33:371-6.
47. Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. FASEB J 2000;14:1685-96.
48. Racké K, Hey C, Mösner J, Hammermann R, Stichnote C, Wessler I. Activation of l-arginine transpot by protein kinase C in rabbit, rat and mouse alveolar macrophages. J Physiol 1998;511:813-25.
49. Maxwell AJ, Ho HV, Le CQ, Lin PS, Bernstein D, Cooke JP. L-arginine enhances aerobic exercise capacity in association with augmented nitric oxide production. J Appl Physiol 2001;90:933-8.
50. Eto B, Peres G, Le Moel G. Effects of an ingested glutamate arginine salt on ammonemia during and after long lasting cycling. Arch Int Physiol Biochim Biophys 1994;102:161-2.
51. Billat VL, Sirvent P, Py G, Koralsztein JP, Mercier J. The concept of maximal lactate steady state: a bridge between biochemistry, physiology and sport science. Sports Med 2003;33:407-26.
52. Roecker K, Mayer F, Striegel H, Dickhuth HH. Increase characteristics of the cumulated excess-CO_2 and the lactate concentration during exercise. Int J Sports Med 2000;21:419-23.
53. Bello E, Caramelo C. Increase of tubular secretion of creatinine by l-arginine: mechanism of practical significance in the assessment of renal function based on creatinine clearance. Nefrologia 2000;20:517-22.