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Exercise, Nitric Oxide, and Endothelial Dysfunction: A Brief Review

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ABSTRACT

Asano RY, Sales MM, Coelho JMO, Moraes JFVN, Pereira LA, Simões HG. Exercise, Nitric Oxide, and Endothelial Dysfunction: A Brief Review. **JEPonline** 2012;15(1):76-86. Nitric oxide (NO) is biosynthesized from the amino acid L-arginine, oxygen, and a variety of co-factors mediated by nitric oxide synthase (e-NOS). Nitric oxide is referenced as a relaxing factor in the endothelium, acting as a potent vasodilator that plays an important role in controlling vascular tone. Studies have demonstrated the role of NO in preserving the functional capacity of the endothelium, preventing atherosclerosis, vascular injury, and hypertension. Moreover, genotypic and/or phenotypic factors may adversely influence the bioavailability of NO, resulting in severe endothelial dysfunction and increased peripheral vascular resistance. Studies have shown exercise as an effective intervention to increase the bioavailability of NO acutely and chronically, for exercise may provide improvement in musculoskeletal and circulatory systems by increasing local blood flow and, therefore, preventing illness or increase performance. Thus, the purpose of this brief review was to elucidate the molecular mechanisms involved in the synthesis and regulation of NO, demonstrating the advances of scientific knowledge related to its bioavailability mediated by exercise and the impact of this phenomenon on endothelial dysfunction. To achieve this objective, we reviewed the scientific literature published in the following databases: Scielo, Medline, Pubmed, WebScience, SCOPUS and SportDiscuss (EBSCO), using the keywords: “nitric oxide” and “exercise.”

Key Words: Nitric Oxide, Exercise, Endothelial Dysfunction

TABLE OF CONTENTS

ABSTRACT-----	76
1. INTRODUCTION -----	77
2. Acute Effects of Exercise in the Bioavailability of NO -----	77
3. Chronic Effects of Exercise in Endothelial Dysfunction Mediated by NO -----	79
4. NO Decrease in Peripheral Tissues in Diabetes Mellitus -----	81
5. Genetic Studies on the Effects of Exercise in the Production of NO -----	82
6. CONCLUSIONS -----	83
REFERENCES -----	83

INTRODUCTION

Vascular smooth muscle cells mediate the relaxation of the endothelium (vasodilation) to maintain basal vascular tone through various vasodilators of which nitric oxide (NO) is the most potent one (29). It plays an important role in blood flow regulation by vasodilating and decreasing the peripheral vascular resistance in several tissues and organs (28).

Endothelium derived NO is produced by the endothelial nitric oxide synthase (eNOS). The expression of eNOX increases the metabolism of the L-arginine, which enhances the formation of L-citrulline in the NO of endothelial cells. Afterwards, the NO migrates to the vascular smooth muscle cells and activates guanylate cyclase that decreases the amount of intracellular calcium and, consequently, relaxing the vascular smooth musculature (19).

The occurrence of endothelial dysfunction is primarily the result of the decrease in the bioavailability of NO (18,27). Recent studies have associated this phenomenon with numerous diseases related to the endothelium that include, but not limited to, atherosclerosis (23), vasospasm and thrombosis (29), vascular injury (9), diabetes mellitus (26), hypercholesterolemia (30), cardiac fibrosis (25), osteoporosis (10), colon cancer (2), autonomic cardiac deficit (24), myocardial infarction (5), and hypertension (11).

The bioavailability of NO is influenced by genotypic and phenotypic factors. Several studies have approached the influence of genetics in the production of NO, since the gene T786C of the NO synthase (NOS) presents polymorphisms and is associated with hypertension (3). On the other hand, recent studies have also demonstrated that lifestyle, which includes regular physical exercise, has strong association with the preservation of the functional capacity of the endothelium and the capacity to produce NO (7,10,17,25).

Based on the evidence described, the aim of the present study was to review the literature related to the effects of exercise in the production and bioavailability of NO in the prevention and treatment of vascular dysfunction. We conducted a bibliographical research in the following databases: SCIELO, Medline, Pubmed, WebScience, SCOPUS and SportDiscuss (EBSCO) using the keywords “nitric oxide” and “exercise.”

Acute Effects of Exercise in the Bioavailability of NO

One acute exercise session can increase NO and its biomarkers in the plasma that result in vasodilation of the endothelium during and after exercise. This has been shown in studies using both

animal and human models. A recent study in our group (20) showed that after a single aerobic exercise session (e.g., 20 min at 90% of the anaerobic threshold) the activity of plasma kallikrein augmented. In addition, it is known that this substance mediates positively the reaction that releases NO in the bloodstream.

Faria et al. (11) submitted hypertensive rats to a squat session using weight vests, the authors observed a decrease in blood pressure (BP), a lower vascular reactivity, and an endothelial dependent relaxation mediated by NO after exercise. Yang et al. (31), with the purpose to investigate the effects of an aerobic exercise session on the vasodilatory effects of insulin and IGF-1 by stimulating NOS and PI3K submitted hypertensive rats to an aerobic exercise bout in a treadmill at a speed of $21 \text{ m} \cdot \text{min}^{-1}$ for 1 hr. The authors observed an increase of the endothelium dependent vasodilation through the mechanism described.

Long et al. (15) examined the preventive effects of exercise in coronary blood flow and macrovascular atherosclerosis. They aerobically trained Yucatan pigs and submitted them to a high fat and cholesterol diet during 36 weeks. After this period of hypercholesterolemia, the animals were submitted to a short term aerobic training, which preserved the endothelium independent (adenosine) coronary microvascular responses and enhanced the endothelium dependent coronary responses through the action of bradikinin, which is a mediator of NO production and reducer of the possibility of macrovascular atheroma in aerobically trained pigs.

Physical training in rats adapts the Porta Vein to vigorously respond to sympathetic stimuli, even when the animals are exposed successively to exercise. Based on this point of view, Chies et al. (6) evaluated the effects of angiotensin II in the Porta Vein and the Vena Cava in sedentary rats and trained rats while they were at rest or after an exercise bout. The exposure of trained animals to consecutive bouts of acute exercise in the treadmill improved the responses of the Porta Vein in rats with the presence of angiotensin II. This improvement seems to be specific to the Porta Vein, since there were no alterations in the Vena Cava. The authors, therefore, concluded that these adaptations were influenced by NO, endothelin and vasodilating prostanoids.

The eNOS is associated with several physiological regulations related to muscular metabolism, such as muscular signaling and the use of resources during exercise. However, the real role played by eNOS is still poorly understood. Lee-Young et al. (14) found that in sedentary mice without the presence of eNOS, ATP stocks were reduced in 40%. Consequently, the tolerance to exercise was badly impaired during an aerobic exercise session. One observed effect that is eNOS dependent, cited by the authors, was related to the AMP Kinase protein, activated in muscular signaling and perfusion. In addition, the authors showed that muscular glucose uptake, long chain fatty acids and glucogenolysis, and hepatic muscular functions were augmented during exercise in mice with absence of eNOS when compared to mice with partial presence of eNOS and to wild mice. The finding that a partial decrease in the expression of eNOS is enough to induce physiological alterations in ATP production, NO release and, therefore, intolerance to exertion makes it possible to conclude that the decrease in eNOS expression can lead to metabolic chronic diseases such as obesity and insulin resistance.

Lasta et al. (13) tested the hypothesis that the inhibition of NOS alters the responses of arterial and venous vessels of the retina in healthy adults during the performance of isometric exercise. This hypothesis is based on the theory that blood flow in the retina is self-regulated, which means that the flow does not depend on perfusion pressure. The authors concluded that NO plays an important role in the control of the vascular tone of the retina since the vascular response to isometric exercise was less pronounced when NOS was inhibited.

Crecelius et al. (8) investigated whether the increase in muscular blood flow, induced by ascorbic acid (AA), during dynamic exercise in an elderly population, occurred through endothelium dependent vasodilation mediated by NO or prostaglandins. Fourteen elderly volunteers used an ultrasonography Doppler during a handgrip exercise at an intensity of 10% of the maximum voluntary contraction. Afterwards, the same subjects repeated the procedure using a NOS inhibitor. As a result, the authors found that AA coupled with the NOS inhibitor reduced the blood flow in 20%, but no significant changes were observed with the prostaglandins. The authors concluded that the administration of AA in the elderly augments the blood flow due to the increase in NO bioavailability during dynamic exercise and not due to prostaglandins.

It has recently been shown that supplementary diets with nitrite increases its levels in blood plasma. Nitrite is a well known marker of bioavailability of NO in blood plasma which enhances the efficiency and tolerance to exercise in healthy adults. Bailey et al. (4) hypothesized that the supplementation with L-arginine, which is a substrate of NOS, could reveal similar results as nitrite supplementation. The authors administered L-arginine to 9 healthy adults and, 1 hr later, submitted them to moderate and high intensity exercise. The results showed that plasma nitrite was significantly higher in the group that ingested L-arginine. There was also a decrease in systolic blood pressure (SBP). The submaximal $\dot{V}O_2$ was 7% lower in the moderate intensity exercise session, and the high intensity exercise resulted in smaller amplitude of the slow component and an extended time until exhaustion. They concluded that L-arginine does present similar results when compared to nitrite, increasing the bioavailability of NO and time until exhaustion during high intensity exercise, and reducing the oxygen cost during moderate intensity exercise.

Cubbon et al. (9) studied the association of the NO induced by exercise in the proliferation and mobilization of circulating progenitor cells (CPC), which is a potential mediator of muscle repair. The CPC mobilization is critically dependent on NO, and South Asians are associated with low CPC. The purpose of their study was to determine the response of CPC mobilization during a moderate intensity exercise, the role of NO in CPC mobilization, and to compare the results between South Asians and white Europeans. The findings showed that vasodilating mediators and CPC were lowered in South Asians when compared to white Europeans. A decrease in the bioavailability of NO can contribute to an inadequate balance between vascular injury and muscle repair mechanisms.

In summary, the recent studies show that a single bout of exercise can increase the bioavailability of NO in blood plasma and, therefore, acutely augment the blood flow to several organs. In addition, exercise is a useful tool (among others) in the prevention of hypertension, hypercholesterolemia, and diabetes mellitus. It also increases peripheral blood flow and helps with the repair of vascular muscle tissue.

Chronic Effects of Exercise in Endothelial Dysfunction Mediated by NO

Recent studies have demonstrated that exercise is an efficient non-pharmacological treatment to dysfunctions in the endothelium, especially because of its chronic effects in the enhancement of eNOS and subsequent NO production (23,29).

Studies related to the chronic effects of exercise and the bioavailability of NO have approached several tissues and organs. In the cardiac tissue, Souza et al. (25) studied the effects of an 8-week aerobic training (swimming) program on rats with NOS inhibition. At first, the NOS inhibited rats were characterized as hypertensive, but after the training period the increase in BP in NOS inhibited rats was significantly smaller when compared to other NOS inhibited rats that remained sedentary. In addition, the trained rats presented higher cardiac weight index, macroscopic cardiac area, and

cardiac fibrosis than the control group. The authors concluded that a short term blockage of NOS in sedentary rats could induce hypertension. On the other hand, after exercise the inhibition of the synthesis of NO attenuated hypertension and promoted cardiac hypertrophy with a significant increase in cardiac muscle fibrosis. This suggests that NO plays an important role in the adaptations of cardiac tissues induced by aerobic physical training.

The blocking of the NO synthesis is characterized by the increase in cardiac sympathetic activity. However, exercise promotes the decrease of sympathetic activity. Therefore, Rossi and colleagues (24) investigated the effects of NO synthesis blockage on the autonomic cardiac control of Wistar rats that were submitted to a 10-week aerobic training period. The trained rats were treated with the NOS inhibitor (L-NAME) only during the last week of training. After the total training period, the authors observed that exercise prevented the deficit of autonomic cardiac control induced by the NOS inhibition. However, it did not prevent the increase in systolic blood pressure variability.

Exercise is a known method to improve functional capacity and life quality in patients that suffer from peripheral arterial insufficiency. However, it is still not known how exercise influences the collateral veins. Colleran et al. (7) studied the effects of exercise on the vasomotor properties of the isolated peripheral collateral arteries. Specifically, they used rats submitted to a femoral artery occlusion surgery that performed 3 months of aerobic exercise in a treadmill. The authors showed that exercise did augment the vasodilation of the collateral artery's endothelium, apparently due to the increase of the production of hyperpolarizing factors derived from the endothelium. According to the authors, these findings can contribute to increases in the collateral artery's functions and to develop a better tolerance to exercise during the training period.

Exercise performance is limited by peripheral artery diseases due to the decrease in local blood flow, which results in less O₂ availability. Nitrite is the biggest product of NO oxidation, and has recently been suggested as a donor of NO to tissues with hypoxia, providing vasodilation by the mediation of endocrine functions. Allen et al. (1) hypothesized that chronic exercise could enhance endothelial function and nitrite levels in blood plasma. The authors submitted peripheral arterial disease carriers to 3 months of daily activity exercises. After the intervention, the authors found an increase in time to the beginning of limping (feel pain during walking due to insufficient O₂ irrigation to muscles), increase in peak time of walking and peak VO₂, increase in brachial blood flow due to vasodilation and nitrite increase in blood plasma. However, there were no significant changes in the peripheral arterial disease. According to the authors, the results suggest that alterations of nitrite levels in blood plasma are related to endothelial function and predict exercise performance in peripheral arterial disease carriers.

In regards to bone tissue, Domingues and colleagues (10) researched the association between endurance exercise and the bone vasculature function. Because there is a decrease in blood flow in the elderly, there is also a commitment to vasodilation mediated by NO. On the other hand, endurance training is associated with the restoration of several vascular runways and improves bone properties. The authors submitted 344 elderly Fischer rats to treadmill exercise for a 12-week period. The results showed that the exercise resulted in an increase in bone and medullary blood flow. Also, there was an increase in the femur's trabecular volume which was associated with NOS signaling.

The chronic effects of exercise are also related to cancer. Several epidemiological studies have suggested that exercise can prevent colon cancer. However, it is not at all clear how this mechanism works. Frequent high expressions of immune cell NO synthase (iNOS) are initial symptoms of tumor genesis and development of colon-rectal cancer. Aoi et al. (2) investigated the effect of exercise in the genesis of colon tumors, associated with iNOS, in mice. The authors observed that 6-weeks of aerobic training (treadmill) reduced iNOS and tumor necrosis factor- α (TNF- α) in the colon and blood

plasma. Therefore, they concluded that regular exercise can prevent the genesis of tumors in the colon, in part, by suppressing the iNOS expression.

Nitric oxide is also associated with the concentration of satellite cells and skeletal muscle cells, once it is capable of activating the proliferation of satellite cells. In the muscle, NO is produced by nNOS, which enhances its activity during muscular contractions. It is still not known if NO levels are decreased during muscle functional discharge and if this reduction is associated with muscle atrophy and satellite cell reduction. Using rats supplemented with L-arginine for 14 days, Kartashkina et al. (12) investigated whether muscular atrophy and decrease in satellite cells during functional discharge could be related to a decrease in NO muscle levels. The results showed a negative association between the increase in muscle NO levels and a decrease in atrophy during functional discharge. Therefore, the authors concluded that there really is an association between the proliferation of the satellite cells and the increase in NO levels.

In summary, exercising on a regular basis seems to be associated with higher availability of NO and a higher blood flow to bone, cardiac tissues, and muscles, This is in addition to enhancing the endothelial wall function, which is primordial to coronary disease prevention. However, more research is needed to clarify the association between endothelial dysfunction and NO, since McAllister and Price (17) related that the increase in the expression of eNOS during chronic aerobic training did not accompany an enhancement of its vascular function and sensibility to NO.

NO Decrease in Peripheral Tissues in Diabetes Mellitus

Type 2 diabetes mellitus can induce dysfunctions in capillary and arterial endothelium that are close to insulin sensitive and metabolic active tissues, such as the skeletal muscle. A decrease in vasodilation due to NO can result in a reduction of insulin, which can promote peripheral resistance to insulin. Until recently, NO was considered limited in the vascular endothelium where it was produced, for the NO is easily inactivated in the vasculature (26).

In diabetes, hyperglycemia reduces the endothelium's products that are derived from NO via NOS, and the inactivation of NO by the final products of advanced glycation and oxygen reactive species. This inability to carry NO from other distant sites can help in the development of cardiovascular diseases and microvascular commitments in diabetics (16,23). In fact, preliminary data from Stabler et al. (26) showed that the difficulty of transportation of NO and transport mechanisms in the red blood cells in blood plasma can be present in diabetics. This could enhance the peripheral reduction of tissue blood flow and oxygen transport, and therefore, contribute to the increase in the incidence of diseases in the vasculature of diabetics.

Nitric oxide reduction in diabetics can result in platelet aggregation, lack of adherence, and smooth cell proliferation and, therefore, to atherosclerosis (26). In addition, the nitric autonomic and endothelial function show dysfunctions in diabetic animals and humans, resulting in a decrease of regional blood flow. However, the pathological phenomenon is caused by the reduction of NO or by the activity or availability of NO, by the increase in the production of oxygen reactive species and endogenous inhibitors of NO, and also by the action of vasoconstrictive factors.

In summary, the evidence indicates the efficiency in the increase of the bioavailability of NO due to exercise. But, even though the mechanism as to how exercise affects the production of NO in diabetics is still inconclusive, it seems reasonably clear that diabetics can benefit from the regular exercise in the treatment or prevention of the possible endothelial dysfunctions induced by the disease.

Genetic Studies on the Effects of Exercise in the Production of NO

The association between exercise and NO has been being studied under the genetics' point of view. The T786C gene of eNOS shows a polymorphism that can reduce the production and bioavailability of NO and also be associated with hypertension (3). Zago et al. (32) investigated the effects of aerobic training in the connection between the eNOS polymorphisms (T786C and G894T), and in blood pressure and oxidative stress in pre-hypertensive elderly women, once the C allele produces less eNOS activity than the T allele. The authors submitted volunteers to a 6-month aerobic training program at 70% of VO_2 max. Before the 6-month intervention, the women with both polymorphisms (T786C and G894C) had less products derived from NO metabolism (NOx) than the subjects that did not show any polymorphisms or than the ones who showed only the G894T polymorphism. After the training period, NOx increased in the group with both polymorphisms and there was a decrease in blood pressure. The group that only had the T786C polymorphism, no polymorphism, and both polymorphisms presented improvements in oxidative stress. Aerobic exercise also improved oxidative stress and NOS activity in the allele T (T786C) and allele C (G894T) carriers. The authors concluded that the effects of exercise in the production of NO were not influenced by eNOS polymorphisms.

Another study by Zago et al. (33), investigated the influence of 6 months of aerobic training and the T786C polymorphism in the levels of NOx, blood flow (BF), and blood pressure in pre-hypertensive elderly women. The pre-intervention evaluations showed that the NOx levels were lower in the carriers of the alleles TC+CC when compared to the TT. The TT group showed association between NOx and BF-0 ($r = 0.60$), and between diastolic blood pressure (DBP) and BF-0 ($r = -0.70$). However, there were no associations in the TC+CC group. After the intervention, the results in the TT group remained significant, and the TC+CC group showed associations between DBP and BF-1 ($r = -0.80$), DBP and BF-2 ($r = -0.60$) and DBP and BF-3 ($r = -0.60$). There were also significant associations between NOx and BF-1 ($r = 0.80$) and between NOx and DBP ($r = -0.70$). The authors concluded that 6 months of aerobic training can contribute to increase the associations that exist between NO, blood pressure, and BF in elderly women that carry the C allele.

On the other hand, the allele T of eNOS has been associated with the increase of coronary heart disease mortality and the susceptibility of endothelial dysfunction. Augeri et al. (3) examined the influence of the T786C of eNOS in post-exercise hypotension and NO after a low intensity exercise session at 40% of VO_2 max, a moderate intensity exercise session at 60% of VO_2 max, and a control session using a cycle ergometer in pre-hypertensive caucasian volunteers. They found that 9 hrs after exercise the TT allele carriers had less post-exercise hypotension than the heterozygous subjects.

Negrão et al. (21) investigated if exercise induced muscular vasodilation is attenuated in homozygous allele T carriers, and if training augments muscular vasodilation in response to exercise in the same population. The subjects were divided in two groups (homozygous TT allele carriers and TC+CC carriers) that underwent 18 weeks of exercise at an intensity that corresponded to their anaerobic threshold. Forearm's vascular conductance and mean blood pressure were the same between the groups. However, during the handgrip exercise, vascular conductance was smaller in the TT group. Oxygen uptake was improved in both groups. The intervention increased the forearm's vascular conductance in response to the handgrip exercise in the TT group, but not in the TC+CC group. The authors concluded that training improved muscular vasodilation in response to exercise in the TT allele carriers, suggesting that genetic variations can influence the outcome of interventions.

In summary, the exercise responses of the T786C gene polymorphisms are still inconclusive. However, there is an effort to enhance the research related to this topic so there can be a solid foundation to aid future studies.

CONCLUSIONS

The recent studies presented in this paper suggest that both the acute and chronic effects of exercise are a potential factor to augment the availability of NO in blood plasma, thus increasing the blood flow to several tissues such as: cardiac, bone, muscular, retina, and others. In each tissue, the production of NO induced by exercise can act as a protective agent against atherosclerosis, including in individuals that have hypertension and diabetes, since they are more likely to develop endothelial dysfunctions.

Genetic studies are advancing to elucidate the influence of exercise in the expression and activity of the proteins present in the polymorphisms of eNOS. However, future researches are needed to better clarify the results found and aid in the prescription of regular exercise. There is also a need to amplify the studies that associate the use of proteomics, since the increase in the bioavailability of NO derived from exercise is not accompanied by an improvement of the sensibility of the endothelium's smooth muscle cells to NO.

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REFERENCES

1. Allen JD, Stabler T, Kenjale A, Ham KL, Robbins JL, Duscha BD, Dobrosielski DA, Annex BH. Plasma nitrite flux predicts exercise performance in peripheral arterial disease after 3 months of exercise training. *Free Radical Biology & Medicine* 2010;49:1138-1144.
2. Aoi WA, Naito Y, Takagi T, Kokura S, Mizushima K, Takanami Y, Kawai Y, Tanimura Y, Hung LP, Koyama R, Ichikawa H, Yoshikawa T. Regular exercise reduces colon tumorigenesis associated with suppression of iNOS. *Biochemical and Biophysical Research Communications* 2010;399:14-19.
3. Augeri AL, Tsongalis GJ, Van Heest JL, Maresh CM, Thompson PD, Pescatello LS. The endothelial nitric oxide synthase - 786 T>C polymorphism and the exercise-induced blood pressure and nitric oxide responses among men with elevated blood pressure. *Atherosclerosis* 2009;204:28–34.
4. Bailey SJ, Winyard PG, Vanhatalo A, Blackwell JR, Dimenna FJ, Wilkerson DP, Jones AM. Acute L-arginine supplementation reduces the O₂ cost of moderate-intensity exercise and 3 enhances high-intensity exercise tolerance. *J Appl Physiol* 2010;19.
5. Bansal A, Daí Q, Chiao YA, Hakala KW, Zhang JQ, Weintraub ST, Lindsey ML. Proteomic analysis reveals late exercise effects on cardiac remodeling following myocardial infarction. *Journal of Proteomics* 2010;73:2041-4049.

6. Chies AB, Rossignol PS, Daniel EF. Exercise increases the angiotensin II effects in isolated portal vein of trained rats. *Peptides* 2010;31:883-888.
7. Colleran PN, Li Z, Yang HT, Laughlin MH, Terjung RL. Vasoresponsiveness of collateral vessels in the rat hindlimb: influence of training. *J of Physiol* 2010;15:1293-1307.
8. Crecelius AR, Kirby B, Voyles HF, Dinunno FA. Nitric Oxide but not Vasodilating Prostaglandins Contributes to the Improvement of Exercise Hyperemia via Ascorbic Acid in Healthy Older Adults. *Am J Physiol Heart Circ Physiol* 2010;299:H1633-H1641.
9. Cubbon RM, Murgatroyd SR, Ferguson C, Bowen TS, Rakobowchuk M, Baliga V, Cannon D, Rajwani A, Abbas A, Kahn M, Birch KM, Porter KE, Wheatcroft SB, Rossiter HB, Kearney MT. Human Exercise-Induced Circulating Progenitor Cell Mobilization Is Nitric Oxide-Dependent and Is Blunted in South Asian Men. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2010;30:878.
10. Dominguez JM, Prisby RD, Muller-Delp JM, Allen MR, Delp MD. Increased nitric oxide-mediated vasodilation of bone resistance arteries is associated with increased trabecular bone volume after endurance training in rats. *Bone* 2010;46:813-819.
11. Faria TO, Targueta GP, Angeli JK, Almeida EAS, Stefanon I, Vassallo DV, Lizardo JHF. Acute resistance exercise reduces blood pressure and vascular reactivity, and increases endothelium-dependent relaxation in spontaneously hypertensive rats. *Eur J Appl Physiol* 2010;110:359-366.
12. Kartashkina NL, Turtikova OV, Kuznetsov SL, Kalamkarov GR, Bugrovac AE. Corresponding Member of the RAS O. I. Orlova, and T. L. Nemirovskaya, Effect of NO on Satellite Cell Proliferation during Functional Unloading and Muscle Stretching. *Doklady Biological Sciences* 2010;432:167-170.
13. Lasta M, Polak K, Luksch A, Garhofer G, Schmetterer L. Effect of NO synthase inhibition on retinal vessel reaction to isometric exercise in healthy humans. *Acta Ophthalmologica* 2010.
14. Lee-Young RS, Ayala JE, Hunley CF, James FD, Bracy DP, Kang L, Wasserman DW. Endothelial nitric oxide synthase is central to skeletal muscle metabolic regulation and enzymatic signaling during exercise in vivo. *Am J Physiol Regul Integr Comp Physiol* 2010;298:1399-1408.
15. Long X, Bratz IN, Alloosh M, Edwards JM, Sturek M. Short-term exercise training prevents micro- and macrovascular disease following coronary stenting. *J Appl Physiol* 2010;108:1766-1774.
16. Lundberg JO, Weitzberg E. NO generation from nitrite and its role in vascular control. *Arterioscler. Thromb Vasc Biol* 2005;25:915-922.
17. McAllister RM, Price EM. Effects of exercise training on vasodilatory protein expression and activity in rats. *Europ J Appl Physiol* 2010;110:1019-1027.
18. Möbius-Winkler S, Linke A, Adams V, Schuler G, Erbs S. How to improve endothelial repair mechanisms: the lifestyle approach. *Expert Rev Cardiovasc Ther* 2010;8:573-580.

19. Moncada S. Nitric oxide. *J Hypertens Suppl* 1994;12(10):S35-9.
20. Motta DF, Lima LCJ, Arsa G, Russo PS, Sales MM, Moreira SR, Morais PK, Almeida WS, Araujo RC, Moraes MR, Pesquero JL, Simões HG, Campbell CSG. Effect of type 2 diabetes on plasma kallikrein activity after physical exercise and its relationship to post-exercise hypotension. *Diabetes & Metabolism* 2010;36:363-8.
21. Negrão MV, Alves CR, Alves GB, Pereira AC, Dias RG, Laterza MC, Mota GF, Oliveira EM, Bassaneze V, Krieger JE, Negrão CE, Rondon MUPB. Exercise training improves muscle vasodilatation in individuals with T786C polymorphism of endothelial nitric oxide synthase gene. *Physiol Genomics* 2010;42A:71-77.
22. Rassaf T, Preik M, Kleinbongard P, et al. Evidence for in vivo transport of bioactive nitric oxide in human plasma. *J Clin Invest* 2002;109:1241-1248.
23. Ribeiro F, Alves AJ, Duarte JA, Oliveira J. Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *Int J Cardiol* 2010;141(3):214-221.
24. Rossi BRO, Mazer D, Silveira LCR, Jacinto CP, Di Sacco THR, Blanco JHD, Cesarino EJ, Souza HCD. O Exercício Físico Atenua o Déficit Autonômico Cardíaco Induzido pelo Bloqueio da Síntese do Óxido Nítrico. *Arq Bras Cardiol* 2009;92:31-38.
25. Souza HCD, Penteadó DMD, Martin-Pinge MC, Neto OB, Teixeira VPA, Blanco JHD, Silva VJD. O Bloqueio da Síntese do Óxido Nítrico Promove Aumento da Hipertrofia e da Fibrose Cardíaca em Ratos Submetidos a Treinamento Aeróbio. *Arq Bras Cardiol* 2007;2:99-104.
26. Stabler T, Katherine AK, Ham K, Jelesoff N, Allen J. Potential mechanisms for reduced delivery of nitric oxide to peripheral tissues in diabetes mellitus. *Annals Of The New York Academy Of Sciences* 2010;1206:101-106.
27. Teixeira JAM, Félix A, Santos CF, Moura AS, Lacerda CAM, Carvalho JJ. Exercise training enhances elastin, fibrillin and nitric oxide in the aorta wall of spontaneously hypertensive rats. *Experimental and Molecular Pathology* 2010;89(3):351-357.
28. Toda N, Imamura T, Okamura T. Alteration of nitric oxide-mediated blood flow regulation in diabetes mellitus. *Pharmacology and Therapeutics* 2010;127:189-209.
29. Vanhoutte PM. Regeneration of the Endothelium in Vascular Injury. *Cardiovascular Drugs and Therapy* 2010;24(4):1-5.
30. Woodman CR, Thompson MA, Turk JR, Laughlin MH. Endurance exercise training improves endothelium-dependent relaxation in brachial arteries from hypercholesterolemic male pigs. *J Appl Physiol* 2005;99:1412-1421.
31. Yang AL, Yeh CK, Su CT, Lo CW, Lin KL, Lee SD. Aerobic exercise acutely improves insulin- and insulin-like growth factor-mediated vasorelaxation in hypertensive rats. *Exp Physiol* 2010;95(5):622-629.

32. Zago AS, Kokubun E, Stewart NF, Park JY, Attipoe S, Hagberg J, Brown M. Efeito do Exercício Físico e do Polimorfismo T-786C na Pressão Arterial e no Fluxo Sanguíneo de Idosas. *Arq Bras Cardiol* 2010 [online].
33. Zago AS, Silveira LR, Kokubun E. Effects of aerobic exercise on the blood pressure, oxidative stress and eNOS gene polymorphism in pre-hypertensive older people. *Eur J Appl Physiol* 2010;110:825-832.

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