Physical Exercise and Endothelial Dysfunction

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Abstract

The role of the endothelium was considered mainly as a selective barrier for the diffusion of macromolecules from the lumen of blood vessels to the interstitial space. During the last 20 years, many other functions have been defined for the endothelium, such as the regulation of the vagal tonus, the promotion and inhibition of neovascular growth and the modulation of inflammation, of platelet aggregation and coagulation. This finding is considered one of the most important concepts in modern vascular biology. Currently, atherosclerosis is the prototype of the disease characterized in all its phases by an endothelial dysfunction, defined as an insufficient offer of nitric oxide (NO), which predisposes the endothelium to oxidative stress, inflammation, erosion and vasoconstriction. In this sense, several experimental studies have demonstrated that physical exercise is capable of restoring and improving the endothelial function. The impact of exercise on the endothelium has been broadly discussed. Considering its vasodilating effect and the risk factors, the possibility of treating coronary artery disease and its outcomes without the inclusion of physical exercise became unconceivable. However, the literature is still controversial regarding the intensity of physical effort that is necessary to cause significant protective alterations in endothelial functions. Moreover, the association between intense physical exercises and increased oxygen consumption, with a consequent increase in free radical formation, is also discussed.

Introduction

The mechanisms involved in endothelial function control are multifactorial and, most of the times, can be altered due to the association of a pathological process[1]. Several studies have demonstrated the association between abnormal endothelial function and cardiovascular diseases, considering endothelial dysfunction as the triggering factor of the atherogenesis process[2-4].

Keywords

Exercise; endothelium; endothelium, vascular; coronary artery disease.

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Among several functions, the vascular endothelium is responsible for the synthesis of vasoconstrictor and vasodilating factors, with nitric oxide (NO) being one of the most important endothelium-derived relaxation factors[1,5,6]. NO also has many antiatherogenic properties, which include monocyte, leukocyte and platelet adhesion inhibition, antioxidative properties and inhibition of smooth muscle cell proliferation. The decrease in the bioavailability of NO - endothelial dysfunction - seems to be present in the cardiovascular diseases[7].

Moderate exercises are known as stimulators of NO release; considering this fact, the regular physical exercise can be considered as a protective factor against cardiovascular diseases[8,9].

As the o vascular endothelium is constantly exposed to several chemical and mechanical stresses, the endothelial cells have a variety of defenses; however, the development of several diseases associated with the cardiovascular system can overcome these defenses, causing structural damage and subsequent function failure. The complexity and importance of the vascular endothelium in the disease suggest that multiple processes are involved with the endothelial adaptations to exercise training[10].

Studies have demonstrated that the vascular endothelium-mediated vasodilation is initially reduced in the atherosclerosis process, even before the morphological angiographic alterations occur[3,11].

This vasodilation progressively decreases as the atherosclerosis severity increases and also due to the associated risk factors, such as hypertension, dyslipidemia and sedentary life style[7,12-14].

Evidence supports the protective effect of exercise on the decrease of oxidative stress, which has a direct impact on the use of exercise practice as treatment of cardiovascular diseasesproporcionas[1,5,15]. This review tries to associate physical exercise and endothelial function, not only under normal physiological patterns, but also related to cardiovascular diseases.

The evascular endothelium

The cells that constitute the intimal layer of the blood and lymphatic vascular systems, typically epithelial concerning its structure, position and function, develop from the mesoderm and are called endothelial cells. The membrane that is constituted by these cells is called the endotheliums[10,16].

The vascular endothelium is considered an active and dynamic tissue. This actual "organ" controls important functions, such as the regulation of vascular tonus, fluidification, coagulation, maintenance of blood circulation, as well

as inflammatory responses. Therefore, the endothelium represents an interface between the circulation elements and the several systems in the body[10].

In the 80s, the first evidence appeared that the endothelial cells release nitric oxide (NO) through the action of several enzymes that regulate the arterial tonus. Moreover, studies demonstrated that the NO inhibits platelet and leukocyte action and modulates smooth muscle cell proliferation in the medial layer of the arteries. These actions are altered when there is a decrease in the synthesis of NO[4,10]. Thus, the NO is one of the most important endothelium-derived factors[7,13]. NO is synthesized from L-arginine by the nitric oxide synthase (NOS) enzyme. Three isoforms of NOS have been identified: the neural, the inducible and the endothelial isoforms. The so-called constitutive forms (neural and endothelial NOS) produce the NO that participates in neural transmission, as neurotransmitter and neuromodulator, in endothelium-mediated vasodilation and also have platelet antiaggregation action. On the other hand, the inducible isoforms produces large amounts of NO, which are important in the cytotoxicity process against invading microorganisms and tumor cells[17]. The basal NO production seems to be the main protector of immune, nervous and cardiovascular stimulation[18].

Physiologically, the force that the blood exercises on the arterial walls (shear stress) is a stimulus for the release of vasorelaxation factors produced by the vascular endothelium, such as NO. This fact is more evident in the arteries in which the amount of NO produced is higher than in the veins. Thus, when there is an increase in shear stress, the release of NO is accelerated. In coronary circulation, this stress force also has an important role in the adaptation of the coronary flow that can increase several times during the exercises[6,19,20].

The damage to the vascular endothelium caused by risk factors such as dyslipidemia and systemic arterial hypertension causes the progressive loss of these physiological protective functions, characterizing the endothelial dysfunction[1,4,5,19,21]. Figure 1 shows this association[22].

Endothelial dysfunction

Since the 1970s on, the understanding of the genesis and progression of atherosclerosis has progressively increased. In 1973, Ross and Glomaser[23] suggested that the coronary atherosclerosis started with an injury to the arterial wall leading to the denudation of the endothelium or desquamation of the arterial endothelial lining. This hypothesis was supported by recent evidence that indicated that even the classic fatty streaks - the first lesion common in childhood - are inflammatory lesions consisting of monocyte-derived macrophages and T lymphocytes[24].

The vascular endothelium, when affected by risk factors, progressively loses its physiological protective function and starts to be a source of elements that participate in the progression of atherosclerosis. This damage - endothelial activation - alters the vasodilating response, reducing the antithrombotic activity, causing structural alterations and, obviously, causing vascular damages[12-14,24].

The endothelial dysfunction is considered a characteristic feature of patients with atherosclerosis of the coronary arteries, which influences the start and progression of this disease and its adverse events[25]. Physiologically, the vascular endothelium produces biological substances - such as NO, prostacyclin and bradykinin - which contribute to maintain the vascular tonus with predominance of vasodilation, with the objective of regulating the blood flow and maintain a non-adherent endothelial surface[26].

The growing knowledge that the lumen diameter of the coronaries of the epicardium, resistance vessels and major peripheral arteries is highly dynamic in response to flow-mediated factors (NO and endothelium-1) has caused an advance in the understanding of atherosclerosis[27,28]. In

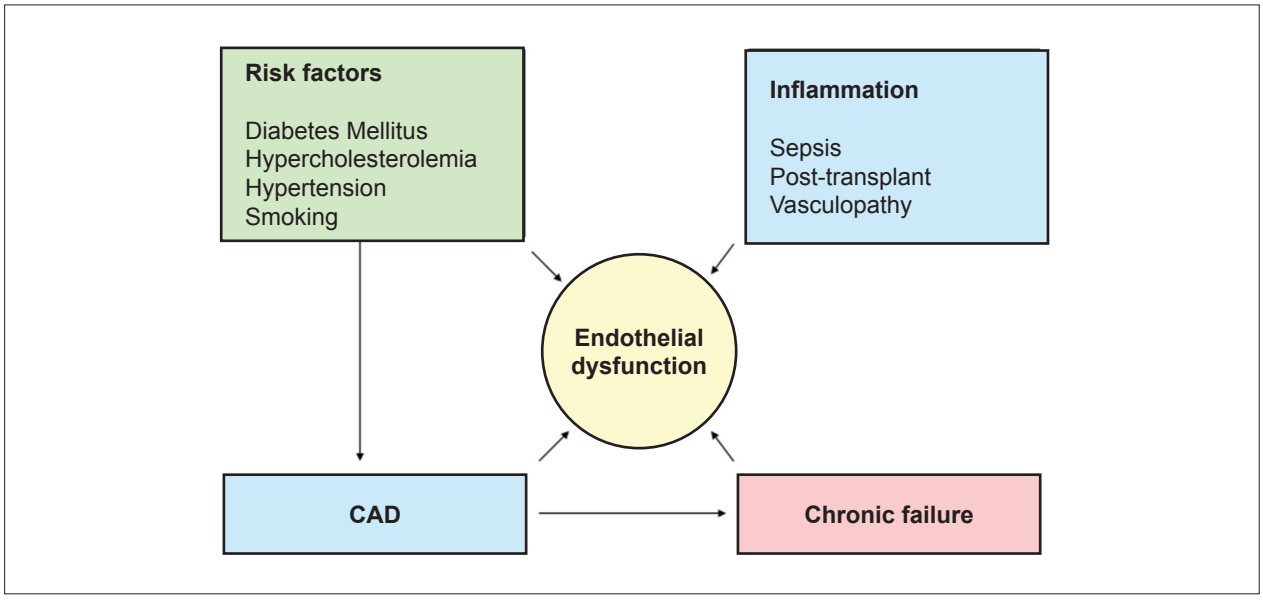

Figure 1 - Association between endothelial dysfunction, coronary artery disease (CAD), risk factors, inflammation.

a study with acetylcholine (Ach) infusion, which causes a vasodilating response that depends on the endothelial NO release, Ludmer et al[27] observed a paradoxical vasoconstriction of atherosclerotic segments of coronary arteries in response to this infusion[28]. According to the authors, the study of the flow-mediated vasodilation is a good indicator of endothelial functions[27,29,30].

Among the factors that cause damage to the vascular endothelium, the reactive oxygen species (ROS), and more specifically the free radicals (FR), are considered one of the main factors that impair the endothelial function and trigger atherogenesis,[14,25].

Currently, it is believed that the main mechanism by which the oxidative stress alters the endothelial function is the inactivation of NO by free radicals such as superoxide anion (O_2^-) and oxidated LDL. These FR deactivate the endothelial receptors for acetylcholine, serotonin, thrombin, bradykinin and other mediators, decreasing the stimulation of NOS in the endothelial cells and consequent decrease in the NO production, impairing smooth muscle cell relaxation and predisposing to the formation of atheroma plaques[13,31,32].

Moreover, the production of ROS can react with the NO molecule and produce the peroxynitrite anion ($ONOO^-$) and nitrogen dioxide (NO_2), which can increase the inflammatory injury in vascular cells, decreasing the availability of NO for cells and favoring the thromboembolic processes[31,33].

The association between endothelial function and coronary artery disease (CAD) was confirmed by Al Suwaidi et al[34], who demonstrated the predictive value of the endothelial dysfunction and atherosclerosis progression, regardless of the traditional risk factors. A total of 157 patients with coronary disease were followed for a period of 2.3 years, divided in three groups: (normal endothelial function, moderate dysfunction and severe dysfunction). The results showed a higher number of cardiovascular events in the group with severe endothelial dysfunction, whereas there were no events in the other groups. This association was observed in other studies[30,35-38].

Rozanski et al[39] compared the peripheral blood flow response in 57 coronary patients and 50 apparently healthy individuals, submitted to physical exercise on an ergometric treadmill. The results showed that, among the healthy individuals, 76% showed vasodilation throughout the exercise, whereas 35% of the individuals with CAD showed progressive vasoconstriction.

Regarding the treatment of the endothelial dysfunction, there are currently several interventions that can attenuate this dysfunction in humans[1]. Studies have demonstrated a significant increase in the endothelial function when the plasma lipid levels are treated with a therapy that promotes their decrease[40]. One study demonstrated the increase in endothelial function in patients with type II diabetes with a 3-day treatment based on cerivastatin[41]. Another study showed an increase in the endothelial function in patients that decreased LDL and underwent antioxidant therapy with vitamin C[42]. Furthermore, important studies have shown that interventions including angiotensin-converting enzyme inhibitors (ACEI), HMG-CoA reductase inhibitors, folic acid supplementation in hyperhomocysteinemic patients and, currently, angiotensin II receptor blockers, attenuate endothelial dysfunction in patients with CAD[43,44].

Among the interventions, the aerobic physical exercise is shown to be the most important tool to maintain and/or recover the endothelial function[9].

Physical exercise and the vascular endothelium

Since the 1908s, studies have demonstrated that the physical exercise can modify the control of vascular resistance and the neural control of coronary circulation[45]. Di Carlo et al[46] observed in animals that the physical training results in an increase in the coronary artery resistance, sensitive to alpha and beta adrenergic agents and adenosine. When the alpha-adrenergic agents are blocked, the adenosine promotes an important vasodilation, in addition to decreasing the concentration of phenylephrine, which is an important coronary vasoconstrictor.

The association between physical exercise and CAD prevention has been extensively discussed and the results of several studies have shown the impact of physical exercise on the treatment of this disease[47-50]. The classic studies of Oldridge et al[51] and of O'Conner et al[52] confirmed an important decrease of 20% to 25% in the mortality due to cardiovascular diseases in patients submitted to cardiac rehabilitation. Moreover, in another study carried out with more than 3,000 apparently healthy men and women in the USA, the association between the regulatory effect of physical activity on inflammation and the decrease in the risk of cardiovascular events was confirmed[53].

Regarding the molecular mechanisms, the physical training is associated with significant physiological adaptations involving the skeletal and cardiac musculature, the circulating blood volume and several metabolic modifications. Studies have shown that the exercise also leads to a significant increase in endothelial NOS, which almost always results in an increase in the amount of NO. Moreover, the exercise induces the release of extracellular superoxide-dismutase, which can also contribute to improve the amount of NO. It is known that the NO does not produce only vasodilation, but also inhibits platelet aggregation and has antioxidant, antiproliferative and antiapoptotic properties. These effects suggest that the increase in the NO production and exercise rate can also decrease the progression of vascular diseases[1,4,6,8-10,54].

Therefore, the physical training can prevent endothelial dysfunction by maintaining the availability of NO consequent to the prevention of oxidative stress. This evidence suggests that the physical exercise can prevent or attenuate the decline in endothelium-dependent vasodilation[55].

The beneficial effects of the regular practice of exercises on cardiovascular diseases are especially associated with the higher production of vasodilating agents derived from the vascular endothelium, with the consequent decrease in peripheral vascular resistance, decreasing the levels of LDL-cholesterol and inhibiting platelet aggregation[54].

Study results have demonstrated that the physical training results in significant improvement in myocardial perfusion[56]

(Figure 2)[22]. Among the components involved in this coronary circulation improvement are: endothelial functionf. sm[9,20,57]; the velocity of production and oxidation of NO[6,58]; microcirculation[9,20,57,59]; the regression of atherosclerotic lesions[3,60,61]; the neoformation of collateral vessels[3,60,61]; the decrease in blood viscosity[18] and the increase in the diastolic perfusion time[59].

Although it has been defined that the physical exercise results in these benefits in patients with coronary diseases, the processes by which these benefits are established are yet to be clarified. Studies have suggested that the mechanism by which the physical exercise reduces the progression of atherosclerosis and the risk of recurrent events is related to the improvement in muscle tonus and endothelial function[62-71].

Haskell et al[64], using quantitative angiography, compared the vascular coronary reactivity in long-distance runners and sedentary individuals. Initially, they did not find any significant differences between the groups regarding the basal diameter of epicardial coronary arteries; however, when sublingual nitroglycerin was used, the coronary arteries of the runners were 200% more reactive to vasodilation when compared to the group of sedentary individuals.

In two clinical trials carried out by Hambrecht et al[65,66], with patients with congestive heart failure (CHF), a significant improvement in myocardial perfusion was observed, In the first study[65], 20 patients underwent physical training for six months. In the experimental group, the peripheral blood flow increased significantly in response to acetylcholine *versus* no change in the control group. There was also an increase in peak oxygen uptake, which was correlated with the increase in endothelium-dependent changes in the peripheral flow. The results were similar in the second study[667].

Higashi et al[63] studied the blood flow in the forearm of 17 patients with mild hypertension that participated in a regular program of physical exercises and a control group. After 12 weeks, the blood flow response in the forearm of the physical training group was significantly increased when compared to the control group. There was also an increase in the Ach-stimulated NO release. This study demonstrated an improvement in the endothelium-dependent vasodilation mediated by the increase in endothelial NO[24].

DeSouza et al[68], in a study with 68 sedentary men and endurance runners, aged 22-35 years and 50-67 years, did not find an age-related decrease in the blood flow of the forearm in response to Ach in the endurance runners. Also in this study, 13 middle-aged sedentary men were submitted to a 12-week running and walking program (5-6 days a week, 40-45 minutes per session and 70%-75% of maximal HR). It was observed that the increase in the blood flow of the forearm (mediated by the acetylcholine) was significant (30%) for similar levels of young individuals, middle-aged adults and elderly individuals that were endurance runners.

It is accepted that the vascular inflammation, vascular oxidative stress and aging are important factors associated with cardiovascular diseases[3]. Yung et al[21] embrought evidence of the protective role of exercise in different populations - metabolic syndrome, diabetes, aging, hypertension, menopause, stroke - focused on the coronary artery disease. The authors believe that there is no doubt about the benefits that regular physical exercises can bring to patients with cardiovascular diseases - by decreasing the degree of endothelial dysfunction - and to young and healthy individuals - by preventing the development of cardiovascular disorders by maintaining a normal endothelial function.

Other studies have demonstrated that the physical training can prevent age-related endothelial dysfunction by repairing the availability of NO consequent to the prevention of oxidative stress[55]. This clinical and epidemiological evidence suggests that the physical exercise can prevent or attenuate the decline in the age-related endothelium-dependent vasodilation and reestablish the levels in sedentary adults and elderly individuals.

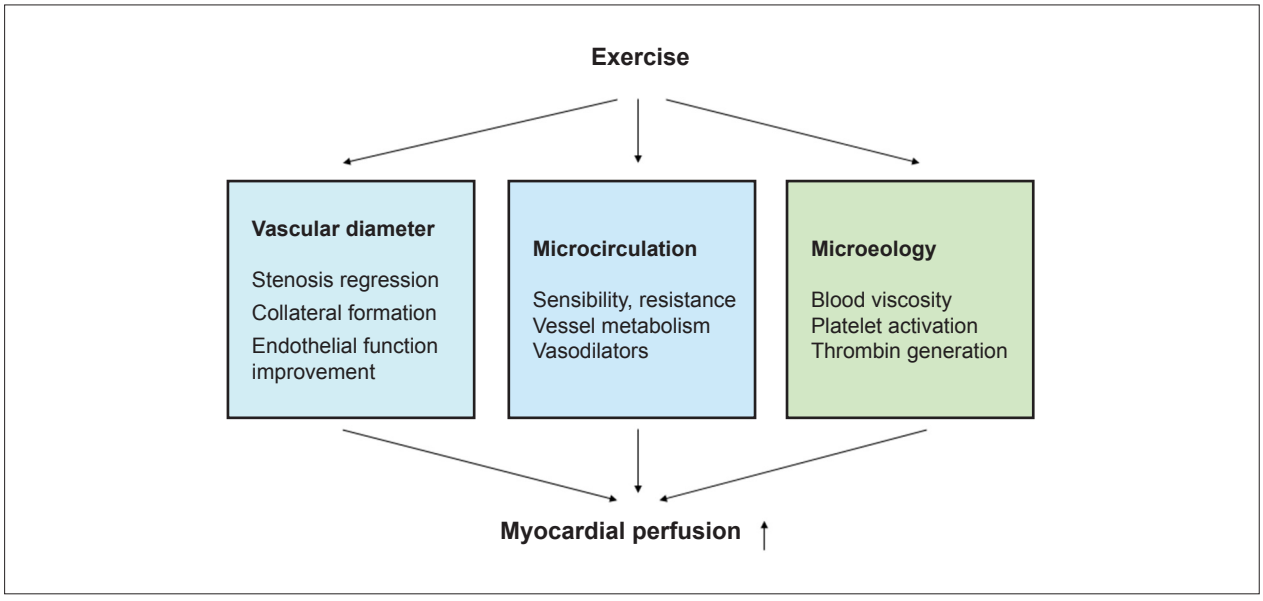

Fig. 2 - Exercise-induced improvement that leads to increased endothelial perfusion.

A study carried out by Hambretch et al[61] demonstrated, by angiography, that the high-intensity aerobic physical exercise improved the endothelial function and the coronary circulation associated to non-stenotic coronary atherosclerosis and that its probable cause was the recruitment of collateral vessels and possible blood flow increase in the ischemic areas of the myocardium. In this study, the patients were submitted to an exercise program for 4 weeks, 6 times a week, for 10 minutes, with an intensity of 80% of maximal HR. The results showed a decrease of 54% in the paradoxical vasodilation of the coronary arteries in response to the infusion of Ach in the exercise group, when compared to the control group. The physical exercise also resulted in a significant improvement in the coronary flow reserve and flow-dependent coronary vasodilation and no changes in the control group.

This study was the first to demonstrate an improvement in the endothelial function with high-intensity aerobic physical exercises in the coronary arteries of patients with CAD and documented endothelial dysfunction.

In a study employing an animal model, Johnson and Parker[71] investigated a group of pigs submitted to training, with induced coronary occlusion of the pulmonary arteries. The findings showed that the arteries demonstrated improvement in the maximal relaxation for Ach. Moreover, the inhibition of NO synthesis significantly decreased the Ach-induced relaxation, with a significant improvement in the exercise group outcome. It was concluded that the physical exercise improves the endothelium-dependent vasorelaxation in pulmonary arteries by increasing the NO release and by a decreased production of a prostanoid constrictor.

Link et al[70] investigated the systemic effect of physical training on the lower limbs, on the endothelial function of the radial artery in 22 men with CHF. After 4 weeks, the exercise group showed a significant increase in the internal diameter of the radial artery in response to Ach infusion, when compared to the control group. The authors concluded that the increase in endothelium-dependent vasodilation was associated with changes in the functional workload capacity.

Vona et al[72] carried out a study with 54 patients post-recent acute myocardial infarction (AMI), divided in two groups: untrained and trained with moderate workload. After a three-month follow-up, the results showed that the physical training improved the vasodilation of the vascular endothelium of the individuals that underwent training and that this response was associated with a significant increase in exercise tolerance. Moreover, the study showed that the benefits on the endothelial function disappeared one month after training withdrawal.

Allen et al[7] demonstrated an association between regional endothelial function (BAR) and plasma NO availability following a physiological stress - a physical test of symptomatic tolerance. Individuals with risk factors for cardiovascular diseases or with established disease demonstrated a lack of response to this physiological stress in both markers. Conversely, the healthy young individuals showed a significant increase in NO with exercise and in BAR. Moreover, the physical training in the patients at risk seems to increase both responses, as the responses in the risk group start to get close to those in the healthy group, suggesting that the endothelial function might be restored. The results also suggest that the amount of plasma NO is related to the endothelial function, to the cardiovascular diseases and responds favorably to physical training.

Johnson et al[73] presented a study in which the short-term exercise associated with the increase in the pulmonary blood flow was correlated with the improvement in the endothelium-dependent vasodilating response in the pulmonary arteries of animals, divided in training group (low intensity) and sedentary group. The effectiveness of the training was demonstrated by comparing the body weight-heart ratio and evaluating the musculoskeletal oxidative capacity. After one week of experiment, the results showed significant improvement in the body weight-heart ratio and in the endothelium-dependent maximal relaxation in the training group. As for the endothelium-independent response, there were no significant differences. The data indicated that this short-term exercise protocol results in the increase of the protein expression of NOS and improves the pulmonary artery relaxation mediated by acetylcholine.

Roberts et al[74] submitted obese children to daily physical activity and a low-fat, high-fiber diet and observed that after these changes in habits, there was a decrease in the production of ROS; increase in the production of NO; improvement in lipid levels; decrease in the endothelial activation and adherence; decrease in the inflammation and platelet destabilization. These responses occur rapidly in young individuals and, according to the authors, the changes must be started before 20 years of age.

A study carried out by Lippincott et al[75], analyzing individuals who had sedentary professions, observed that 15 to 20 minutes a day of daily exercises at the workplace for 3 months improved endothelial function. Moreover, there was an improvement in blood pressure and LDL-c and total cholesterol levels, which contributed to the decrease in the risk of cardiovascular events.

What still seems to be unclear are the effects of different exercise intensities on endothelial fucntion[21]. A study carried out by Farsidfar et al[76] ouevaluated the anaerobic threshold and the peak oxygen uptake in the flow-mediated dilation by acute exercise in patients with stable CAD. The vasoreactivity was increased with elevated levels of exercise; however, it decreased significantly at the peak thresholds. Other studies also concluded that moderate levels of exercise (close to the anaerobic threshold) can be considered therapeutic and preventive for coronary patients[76,77].

The physical exercise and the oxidative stress have been the object of many researches aimed at analyzing their association and as the cause of several vascular diseases[25,26,50,76-78]. Performing acute vigorous exercise constitutes a physiological stress to the body due to the great energy demand, which causes heat release and intense modifications in the muscular and systemic chemical environment, followed by concomitant increase in the production of free radicals[1]. The regular exposure to exercise - physical training - promotes a set of morphological and functional adaptations that increase the body's capacity to respond to the exercise stress[1].

According to Goto et al[6] it is essential to understand the biochemical paradox observed in this situation, not only to correlate stress and exercise, but also to associate them to the treatment of cardiovascular diseases.

Conclusion and future considerations

Atherosclerosis is no longer studied as a disease of lipids, but is now seen as a dynamic and progressive process, resulting from endothelial dysfunction and inflammation. The study of the pathogenesis of this process is crucial, as well as the understanding of the cellular and molecular mechanisms to better create preventive interventions. The scientific evidence suggests that the alteration in the endothelial function occurs well before the clinical manifestations and vascular alterations and that its clinical assessment can be used as a predictor of cardiovascular events.

For a long time, it remained unclear how the physical exercise could improve the myocardial perfusion in coronary patients. Currently, the theories of atherosclerosis regression and formation of collateral circulation have been more broadly discussed. Although it is believed that there is a possibility of lesion regression as a result of large amounts of aerobic exercise, it is unlikely that this will result in a significant improvement in myocardial perfusion, observed much before that.

The new possibilities for coronary endothelial function investigation *in vivo* and *in vitro* have increasingly demonstrated the impact of aerobic exercise on endothelial dysfunction and, consequently, on the coronary disease. As described before, the endothelial dysfunction has been well documented as an initial phenomenon of atherosclerosisu[1,14,21,47], as it seems to precede structural changes and clinical manifestations of CAD. The focus of detection of endothelial dysfunction in many studies is criticized by researchers[80], who believe that efforts should be made to its treatment, not to its causes.

Regardless of that, further studies are recommended so that all mechanism involved in the association between exercise and vascular endothelium can be better understood, including which intensity of aerobic exercise is the ideal one to attain the indicated changes, including other questions. We believe it is imperative to rule out the hypothesis that endothelial dysfunction is an indicator of plaque instability or an independent prognostic marker, so that physical exercises can de definitively added to the treatment strategy.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Leung FP, Yung LM, Laher I, Yao X, Chen ZY, Huang Y. Exercise, vascular wall and cardiovascular diseases: an uptade (part1). Sports Med. 2008; 38 (12): 1009-24.
2. Stary HC, Chandler AB, Glagow S, Guyton JR, Insull W Jr, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis: a report from the committee on vascular lesions of the Council on Atherosclerosis, American Heart Association. Circulation. 1994;89 (5): 2462-78.
3. Linke A, Möbius-Winkler S, Hambrecht R. Exercise training in the treatment of coronary artery disease and obesity. Herz. 2006; 31 (3): 224-33.
4. Rush JWE, Ford RJ. Nitric oxide, oxidative stress and vascular endothelium in health and hypertension. Clin Hemorh Microc. 2007; 37 (1-2): 185-92.
5. Vanhoute PM, Shimokawa H, Tang EHC, Feletou M. Endothelial dysfunction and vascular disease. Acta Physiol. 2009; 196: 193-222.
6. Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, et al. Effect of different intensities of exercise on endothelium-dependent vasodilatation in humans: role of endothelium-dependent nitric oxide and oxidative stress. Circulation. 2003; 108 (5): 530-5.
7. Allen JD, Cobb FR, Kraus WE, Gow AJ. Total nitrogen oxide following exercise testing reflects endothelial function and discriminates health status. Free Rad Biol Med. 2006; 41 (5): 740-7.
8. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, et al. Walking compared with vigorous exercise for prevention of cardiovascular events in women. N Engl J Med. 2002; 347 (10): 716-25.
9. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000; 342 (7): 454-60.
10. Marsh SA, Coombes JS. Exercise and the endothelial cell. Int J Cardiol. 2005; 99 (2):165-9.
11. Reddy KG, Nair RN, Sheeran HM, Hodgson JM. Evidence that selective endothelial dysfunction may occur in the absence of angiographic or ultrasound atherosclerosis in patients with risk factors for atherosclerosis. J Am Coll Cardiol. 1994; 23 (4): 833-43.
12. Tsao PS, Niebauer J, Buitrago R, Lin PS, Wang BY, Cooke JP, et al. Interaction of diabetes and hypertension on determinants of endothelial adhesiveness. Arterioscler Thromb Vasc Biol. 1998; 18 (6): 947-53.
13. Antoniades C, Tousoulis D, Tentolouris C, Toutouzas P, Stefanadis C. Oxidative stress, antioxidant vitamins, and atherosclerosis. Herz. 2003; 28 (7): 628-38.
14. Singh U, Jialal I. Oxidative stress and atherosclerosis. Pathophysiology. 2006; 13 (3): 129-42.
15. Hamburg NM, McMackin CJ, Huang AL, Shenouda SM, Widlansky Me, Schulz E, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. Arterioscler Thromb Vasc Biol. 2007; 27 (12): 2650-6.
16. Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation oxidative stress and insulin resistance in children. Atherosclerosis. 2008; 203 (1): 311-9.
17. Michel T, Feron O. Nitric oxide syntethases: which, where, how, and why? J Clin Invest. 1997; 100 (9): 2146-52.
18. Seals DR, DeSouza CA, Donato AJ, Tanaka H. Habitual exercise and arterial

aging. J Appl Physiol. 2008; 105 (4): 1323-32.

19. Schulz E, Jansen T, Wenzel P, Daiber A, Munzel T. Nitric oxide, tetrahydrobiopterin, oxidative stress and endothelial dysfunction in hypertension. Antioxid Redox Signal. 2008; 10 (6): 1115-26.

20. Rush JWE, Denniss SG, Graham DA. Vascular nitric oxide and oxidative stress: determinants of endothelial adaptations to cardiovascular disease and to physical activity. Can J Appl Physiol. 2005; 30 (4): 442-74.

21. Yung LM, Laher I, Yao X, Chen ZY, Huang Y, Leung FP. Exercise, vascular wall and cardiovascular diseases: an uptade (part2). Sports Med. 2009; 39 (1): 45-63.

22. Gielen S, Hambrecht R. Effects of exercise training on vascular function and myocardial perfusion. Cardiol Clin. 2001; 19 (3): 357-68.

23. Ross R, Glomaser JA. Atherosclerosis and arterial smooth muscle cell: proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis. Science. 1973; 180 (93): 1332-9.

24. De Meyer G, Herman AG. Vascular endothelial dysfunction. Prog Cardiovasc Dis. 1997; 39 (4): 325-42.

25. Yokoyama M. Oxidant stress and atherosclerosis. Curr Opin Pharmacol. 2004; 4 (2): 110-5.

26. Desjardins F, Balligand JL. Nitric oxide-dependent endothelial function and cardiovascular disease. Acta Clinica Belgica. 2006; 61 (6): 326-34.

27. Ludmer PL, Selwin AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary segments. N Engl J Med. 1986; 315 (17): 1046-51.

28. El-Tamimi H, Mansour M, Wargovich TJ, Hill JA, Kerensky RA, Conti CR, et al. Constrictor and dilator responses to intracoronary acetylcholine in adjacent segments of the same coronary artery in patients with coronary artery disease. Endothelial function revisited. Circulation. 1994; 89 (1): 45-51.

29. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiol Rev. 2008; 88 (3): 1009-86.

30. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000; 101 (16): 1899-906.

31. Beckman J, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci USA. 1990; 87 (4): 1620-4.

32. Hobbs AJ, Moncada S. Antiplatelet properties of a novel, non-NO-based soluble guanylate cyclase activator, BAY 41-2272. Vascul Pharmacol. 2003; 40 (3): 149-54.

33. Yung LM, Leung FP, Yao X, Chen ZY, Huang Y. Reactive oxygen species in vascular wall. Cardiovasc Hematol Disord Drug Targets. 2006; 6 (1): 1-19.

34. Al Suwaidi J, Hamsaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation. 2000; 101 (9): 948-54.

35. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Munzel T. Endothelial dysfunction, oxidative stress and risk of cardiovascular events in patients with coronary artery disease. Circulation. 2001; 104 (22): 2673-8.

36. Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation. 2001; 104 (2): 191-6.

37. Halcox J, Schenke W, Zalos G, Mincemoyer R, Prasad A, Waclavlw MA, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation. 2002; 106 (6): 653-8.

38. Schindler TH, Hornig B, Buser PT, Olschewski M, Magosaki N, Pfisterer M, et al. Prognostic value of abnormal vasoreactivity of epicardial coronary arteries to sympathetic stimulation in patients with normal coronary angiograms. Arterioscler Thromb Vasc Biol. 2003; 23 (3): 495-501.

39. Rozanski A, Qureshi E, Bauman M, Reed G, Pillar G, Diamond GA. Peripheral arterial responses to treadmill exercise among healthy subjects and atherosclerotic patients. Circulation. 2001; 103 (16): 2084-9.

40. O'Driscoll G, Green D, Taylor RR. Simvastatin an HMG-CoA reductase inhibitor, improves endothelial function within 1 month. Circulation. 1997; 95 (5): 1126-31.

41. Tsunekawa T, Hayashi T, Kano H, Sumi D, Natsui-Hirai H, Thakur MK, et al. Cerivastatin, a hydroxymethylglutaryl CoA redutase inhibitor, improves endothelial function in elderly diabetic patients within 3 days. Circulation. 2001; 104 (4): 376-9.

42. Solzbach U, Hornig B, Jeserich M, Just H. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. Circulation. 1997; 96 (5): 1513-9.

43. Holven KB, Holm T, Aukrust P, Christensen B, Kjekshus J, Andreassen AK. Effect of folic acid treatment on endothelium-dependent vasodilation and nitric oxid-derived end products in hyperhomocysteinemic subjects. Am J Med. 2001; 110 (7): 536-42.

44. Prasad A, Halcox MA, Weclawiw MA, Qiuyyumi AA. Angiotensin type 1 receptor antagonism reverses abnormal coronary vasomotion in atherosclerosis. J Am Coll Cardiol. 2001; 38 (4): 1089-95.

45. Gwirtz PA, Stone HL. Coronary vascular response to adrenergic stimulation in exercise-conditioned dogs. J Appl Physiol. 1984; 57 (2): 315-20.

46. DiCarlo SE, Blair RW, Bishop VS, Stone HL. Daily exercise enhances coronary resistance vessel sensitivity to pharmacological activation. J Appl Physiol. 1989; 66 (1): 421-8.

47. Sasaki JE, Santos MG. O papel do exercício aeróbico sobre a função endotelial e sobre os fatores de risco cardiovasculares. Arq Bras Cardiol. 2006;87 (5): e227-33.

48. Marchionni N, Fattirolli F, Fumagalli S, Oldridge N, Del Lungo F, Morosi L, et al. Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial. Circulation. 2003; 107 (17): 2201-6.

49. Ricardo DR, Araújo CGS. Reabilitação cardíaca com ênfase no exercício: uma revisão sistemática. Rev Bras Med Esporte. 2006; 12 (5): 1-7.

50. Schumacher A, Peersen K, Sommervoll L, Seljeflot I, Arnesen H, Otterstad JE. Physical performance is associated with markers of vascular inflammation in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2006; 13 (3): 356-62.

51. Oldridge NB, Guyatt G, Fischer M. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. JAMA. 1988; 260 (7): 945-50.

52. O'Connor G, Burng Y, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenberger RS Jr, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation. 1989; 80 (2): 234-44.

53. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch Intern Med. 2002; 162 (11): 1286-92.

54. Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. FASEB J. 2000; 14 (12): 1685-96.

55. Taddei S, Galetta F, Virdis A, Gheadoni L, Salvetti G, Franzoni F, et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. Circulation. 2000; 101 (25): 2896-901.

56. Franco FGM, Matos LDNJ. Exercício físico e perfusão miocárdica. In: Negrão CE, Barreto AC, editores. Cardiologia do exercício: do atleta ao cardiopata. São Paulo: Manole; 2005. p. 179- 259.

57. Sun MW, Zhong MF, Gu J, Qian FL, Gu JZ, Chen H. Effects of different levels of exercise volume on endothelium-dependent vasodilation: roles of nitric oxide synthase and heme oxygenase. Hypertens Res. 2008; 31 (4): 805-16.

58. Fukai T, Siegfried MR, Ushio-Fukai M, Cheng Y, Kojda G, Harrison DG. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. J Clin Invest. 2000; 105 (11): 1631-9.

59. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiol Rev. 2008; 88 (3): 1009-86.

60. Niebauer J, Hambrecht R, Marburger C, Hauer K, Velich T, von Hodesberg E, et al. Impact of intensive physical exercise and low-fat diet on collateral vessel formation in stable angina pectoris and angiographically confirmed coronary

artery disease. Am J Cardiol. 1995; 76 (11): 771-5.

61. Hilberg T. Physical activity in the prevention of cardiovascular diseases: epidemiology and mechanisms. Hamostaseologie. 2008; 28 (1): 9-15.

62. El-Sayed MS, Ali N, El-Sayed AZ. Haemorheology in exercise and training. Sports Med. 2005; 35 (8): 649-70.

63. Higashi Y, Sasaki S, Kurisu S, Yoshimizu A, Sasaki N, Matsuura H, et al. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects - role of endothelium-derived nitric oxide. Circulation. 1999; 100 (11): 1194-202.

64. Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultra-distance runners. Circulation. 1993; 87 (4): 1076-82.

65. Hambrecht R, Fiehn E, Weigt C, Gielen S, Hamann C, Kaiser R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998; 98 (24): 2709-15.

66. Hambrecht R, Hilbrich L, Erbs S, Gielen S, Fiehn E, Schoene N, et al. Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation. J Am Coll Cardiol. 2000; 35 (3): 706-13.

67. Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, et al. The effect of combined aerobic and resistance training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001; 38 (3): 860-6.

68. De Souza CA, Shapiro LF, Clevenger CM, Dinemo FA, Monahan KD, Tanaka H, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation. 2000; 102 (12): 1351-7.

69. Taddei S, Galetta F, Virdis A, Ghiadoni L, Salvetti G, Franzoni F, et al. Physical activity prevents age-related impaiment in nitric oxide availability in elderly athletes. Circulation. 2000; 101 (25): 2896-901.

70. Link A, Schoence N, Gielen S, Hofer J, Erbs S, Schuler G, et al. Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training. J Am Coll Cardiol. 2001; 37 (2): 392-7.

71. Johnson LR, Parker LP, Laughlin MH. Chronic exercise training improves ACh-induced vasorelaxation in pulmonary arteries of pigs. J Appl Physiol. 2000; 88 (2): 443-51.

72. Vona M, Rossi A, Capodaglio P, Rizzo S, Servi P, De Marchi M, et al. Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent acute myocardial infarction. Am Heart J. 2004; 147 (6): 1039-46.

73. Johnson LR, Rush JWE, Turk JR, Price EM, Laughlin MH. Short-term exercise training increases ACh-induced relaxation and eNOS protein in porcine pulmonary arteries. J Appl Physiol. 2001; 90 (3): 1102-10.

74. Roberts CK, Chen AK, Barnard RJ. Effect of a short-term diet and exercise intervention in youth on atherosclerotic risk factors. Atherosclerosis. 2007: 191 (1): 98-106.

75. Lippincott MF, Desai A, Zalos G, Carlow A, De Jesus J, Blum A, et al. Predictors of endothelial function in employees with sedentary occupations in a worksite exercise program. Am J Cardiol. 2008; 102 (7): 820-4.

76. Farsidfar F, Kasikcioglu E, Oflaz H, Kasikioglu D, Meric M, Umman S. Effects of different intensities of acute exercise on flow-mediated dilatation in patients with coronary heart disease. Int J Cardiol. 2008; 124 (3): 372-4.

77. Peschel T, Sixt S, Beitz F, Sonnabent M, Muth G, Thiele H, et al. High, but not moderate frequency and duration of exercise training induces downregulation of the expression of inflammatory and atherogenic adhesion molecules. Eur J Cardiovasc Prev Rehabil. 2007; 14 (3): 476-82.

78. Frick M, Weidinger F. Endothelial function: a surrogate endpoint in cardiovascular studies? Curr Pharm Des. 2007; 13 (17): 1741-50.