Clinical Update

The Role of Aerobic Exercise on Endothelial Function and on Cardiovascular Risk Factors

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Coronary artery diseases, including atherosclerosis, have become the major cause of death in the modern civilization[1,2]. This problem results from many aspects of the modern lifestyle: irregular nutrition, smoking, excess alcoholic beverage consumption, daily stress and, above all, a sedentary lifestyle.

These habits lead to the development of risk factors related to atherosclerosis. The formation of atherosclerotic plaques or atheromas is directly related to coronary events such as infarction, ischemic heart disease, and apoplexy[3].

Primary stages of atherosclerosis may be detected through observation of some changes in the arterial wall. One of them is the decrease in endothelium-dependent vasodilation, which is related to a high risk of development of atherosclerosis[4]. Another change is the intima-media thickening, which is a primary stage of atherosclerosis[5,6] and may be used to monitor asymptomatic individuals.

Prevention, when such changes are diagnosed, may stop the progression of atherosclerosis, thus reestablishing the arterial integrity (Figure 1).

The relation between physical exercises and endothelium-dependent vasodilation and intima-media thickness has been studied. However, there are few studies on this issue. Yet, the results have suggested that aerobic exercise is efficient to improve these indexes. The objective of this study is to contribute to the current discussion through a review of the literature.

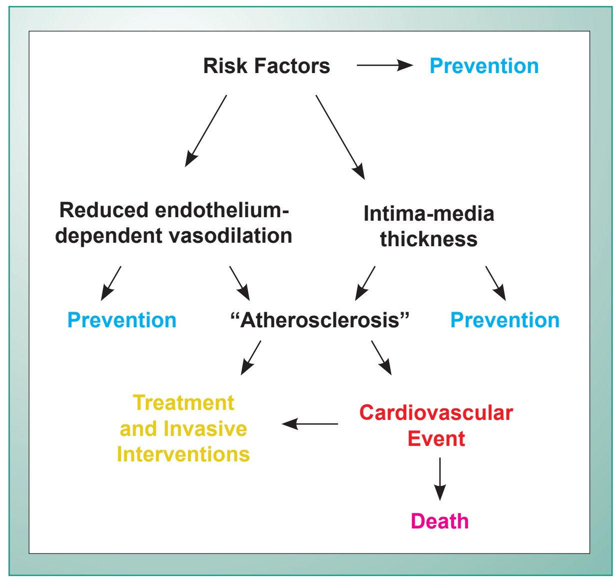

Fig. 1 *- Superficial schematization of the atherosclerotic process: with interruption through prevention, and with progression to atherosclerosis itself and further treatment, or even death.*

Aerobic exercise and atherosclerosis

Etymologically, the word atherosclerosis comes from the Greek "athero" (paste, gruel) and "sclerosis" (hardening)[2]. Atherosclerosis is a chronic degenerative disease characterized by a narrowing of the arterial lumen due to deposition of fat and formation of fibrolipid plaques[2,3,7].

Aerobic exercise is defined as that where predominant oxygen demand occurs. It enables the oxidative burning of energetic substances, including carbohydrates, fats and proteins. The proportion of utilization of these substrates depends on the exercise intensity[8].

Cardiovascular alterations are widely reported in the literature. The main of these alterations are: increase in heart volume, increase in ejection volume, increase in blood erythrocyte concentration and hemoglobin, reduction in resting heart rate and blood pressure, improvement of peripheral vascularization, and others[8-10].

However, in addition to these benefits, atherosclerotic patients may present improved arterial reactivity and intima-media thickness with aerobic training. Studies[11] have demonstrated that moderate intensity, together with regularity of training, seems to be efficient in promoting benefits to the endothelial function. In the following topics, studies on the influence of aerobic training on endothelium-dependent vasodilation, intima-media thickness, and coronary risk factors are presented.

Aerobic exercise and endothelium-dependent vasodilation

Irregular endothelial function is largely related to risk factors predisposing to atherosclerosis, such as hypercholesterolemia,

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obesity, hypertension, diabetes and smoking. The endothelium-dependent vasodilation index has been consistently used in studies as an indicator of the endothelial function. This index seems to be capable of identifying high risk patients. Yet, further investigation is necessary to confirm this possibility[4]. However, the use of endothelium-dependent vasodilation generates a parameter of the arterial integrity condition and, for this reason, many studies have used this assessment.

According to Da Luz et al[12], the major reason for the reduction of the endothelium-dependent vasodilation lies in the dysfunction of the endothelium to respond positively to nitric oxide. Guanylate cyclase activation by nitric oxide is impaired in individuals with endothelial dysfunction. For this reason, accumulation of cyclic guanosine monophosphate in the endothelium fails to occur, and, consequently, the endothelium-dependent vasodilation is affected.

The relationship between aerobic exercise and endothelium-dependent vasodilation index has been studied, although few recent studies on this subject are found . Additionally, studies have used different types of exercises and different types of populations (normal, hypertensive, coronary patients). Thus, each situation must be considered individually, and the results should not be generalized.

Studies have verified that regular aerobic exercise may prevent the loss of endothelium-dependent vasodilation, in addition to restoring previous levels in sedentary middle-aged and elderly men[13]. When compared to sedentary men, aerobically trained men show a preserved endothelium-dependent vasodilation[14].

Clarkson et al[15] found positive results of a 10-week aerobic and anaerobic exercise training program in healthy military recruits. Training increased endothelium-dependent vasodilation in these individuals. Gokce et al[16] also found a significant increase in endothelium-dependent vasodilation of the posterior tibial artery with a 10-week moderate intensity aerobic exercise program with emphasis in the legs. However, vasodilation in the arms did not increase significantly, perhaps due to the specificity of the exercise proposed.

Higashi et al[17] analyzed individuals with essential hypertension undergoing a 12-week aerobic exercise program (30 minutes, 5-7 X/week) with an intensity of 52 ± 9% of the $VO_{2\,Max}$ and found a significant increase of the endothelium-dependent vasodilation in response to acetylcholine. In that study, normotensive individuals also presented increased endothelium-dependent vasodilation. No alterations in the response to isosorbide dinitrate - an endothelium-independent vasodilator - were observed after training in both groups.

Individuals with acute myocardial infarction undergoing a 3-month aerobic exercise training (cycle ergometer) at an intensity of 75% of the peak exercise heart rate also presented an increase in endothelium-dependent vasodilation. However, one month after detraining the benefits disappeared[18]. This result suggests that even individuals with a history of a cardiac event may obtain improvement of the endothelial function.

Goto et al[11] analyzed the effect of different intensities of aerobic exercise on the arteries, and verified that moderate intensity (50% $VO_{2\,Max}$) was the only one able to improve the endothelium-dependent vasodilation. Low (25% $VO_{2\,Max}$) and high intensity exercise (75% $VO_{2\,Max}$) did not provide the endothelial function with any benefit. As regards high intensity, it was responsible for an increase in the oxidative stress, a harmful aspect to the arterial wall. For this reason, moderate intensity seems to be more appropriate for sedentary individuals who seek cardiovascular benefits through regular aerobic exercise.

Although studies state that regular aerobic exercise is responsible for the change in endothelium-dependent vasodilation, a key question arises within this context. How much does the aerobic fitness respond to these changes?

Cardiorespiratory fitness proved to be related to a slower progression of atherosclerosis in men[19]. However, the association of cardiorespiratory fitness and endothelium-dependent vasodilation has been little studied.

Higher aerobic exercise capacity ($VO_{2\,Max}$)[20] was associated with greater arterial diameter ($r=0.66$, $p<0.002$) during hyperemic response in trained elderly men (68.5 ± 2.3 years) in comparison with sedentary elderly men (64.7 ± 1.4 years). This association results from a higher endothelium-dependent vasodilation ability in individuals who trained at least 3X/week for at least 1h/day.

This result raises the possibility that the aerobic exercise capacity is being preferably related to the endothelial function, because this is a much more accurate measurement. Quite the opposite, training programs are subject to lack of attendance, lack of compliance, and to the individual physiologic response to the training itself, because these variables cannot be completely controlled in exercise programs.

Although studies with children and adolescents are not common, Watts et al[21] found a positive result in normalization of the circulatory function in obese adolescents using a circuit training program that consisted of a cycle ergometer and resisted training. Additionally, an increase in the functional capacity, muscle force and improvement in the body composition of these adolescents were observed. Studies reported that prevention of cardiovascular diseases should begin at childhood, because the risk factors are already present in this phase[22].

It seems that even with differences in the exercises and intensity used, the studies have demonstrated that aerobic exercise is able to improve and restore the endothelium-dependent vasodilation.

Aerobic exercise and intima-media thickness

Intima-media thickness is one of the stages of atherosclerosis, and, consequently, its assessment can be helpful in the diagnosis and prognosis of the atherogenic process[5]. Rosfors et al[23] verified that the intima-media thickness was related to the degree of atherosclerosis in the carotid bifurcation. Zureik et al[6] also verified that a high intima-media thickness predicted the occurrence of atherosclerotic plaques in elderly individuals.

Although not significantly, studies relating the intima-media thickness to training programs and types of training have been conducted.

Rauramaa et al[24] did not verify any reduction in the intima-media thickness of middle-aged men (whether or not treated with statins) who underwent a 6-year moderate aerobic exercise program and were analyzed with a carotid bifurcation ultrasonography (10 MHZ). However, when a subgroup of individuals not taking statins was analyzed separately, exercise was proven to be efficient in the reduction of the atherosclerotic progression. Thus, the authors concluded that the medication may have masked the effects of exercises on this population. Nonetheless, divergent opinions regarding Rauramaa et al's study have been recently published by authors in this field[25,26].

Dinenno et al[27] conducted a study with two distinct moments, consisting of a cross-sectional analysis and an aerobic training intervention. The authors verified the influence of the aerobic training on arterial remodeling. In the first moment, the authors analyzed 55 endurance-exercise trained men (47 ± 2 years) and 53 sedentary men (47 ± 2 years). Endurance-trained individuals were demonstrated to have a common femoral artery lumen diameter 7% greater than sedentary individuals. Additionally, the intima-media thickness and the intima-media/lumen ratio of the individuals trained was 16% and 21% lower, respectively. For the intervention study, the authors selected 22 individuals (51 ± 2 years) from the sedentary group, who underwent a 3-month aerobic training. The individuals exercised 13.5 ± 1.0 weeks, 5.3 ± 0.3 days, 45 ± 2 min. per session, on average, at 73 ± 1% of the maximum HR. After the training period, a 9% increase in the common femoral artery lumen diameter was observed, along with a reduction by 14% and 20% in the intima-media thickness and in the intima-media/lumen ratio, respectively.

However, in a later study, these authors did not find a positive result of aerobic exercises in the reduction of arterial hardening. The 3-month training program was not significantly efficient in the promotion of arterial benefits. In this study, a positive relationship between age and intima-media thickness ratio was found. Thus, exercise was not able to prevent the consequences of aging.

Dinenno et al[29] reported that age-associated arterial wall thickening is closely related to elevations in sympathetic activity.

Moreau et al[30] analyzed postmenopausal women and verified that both hormone replacement therapy and regular aerobic exercises were associated with a lower intima-media thickness ratio. In addition to the classification of individuals into sedentary or trained, the maximum aerobic capacity was also used to divide the groups. Together, hormone replacement therapy and regular aerobic exercises promoted greater changes in the intima-media thickness than each one separately. However, both the regular aerobic exercise group and the hormone replacement group were able to promote significant changes in the intima-media thickness when compared to the sedentary group not treated with hormone replacement.

Because of some controversy on the effects of the aerobic exercise on the intima-media thickness, further investigation on the subject is necessary so as to verify whether exercise is really efficient to restore the arterial integrity in this stage of atherosclerosis.

Effects of aerobic exercise on atherosclerotic risk factors

Although endothelium-dependent vasodilation and arterial thickness indexes are excellent indicators of arterial integrity, several risk factors act on the development of cardiovascular diseases. A decrease in risk factors should be promoted to prevent and control atherosclerosis[31].

Aerobic training is an excellent tool to modify risk factors (Figure 2). As demonstrated by Rique et al[32], changes in life habits, such as nutrition and regular practice of physical exercises, may lead to a reduction in cardiovascular risk factors. Exercise can attenuate dyslipidemias, diabetes, obesity and hypertension.

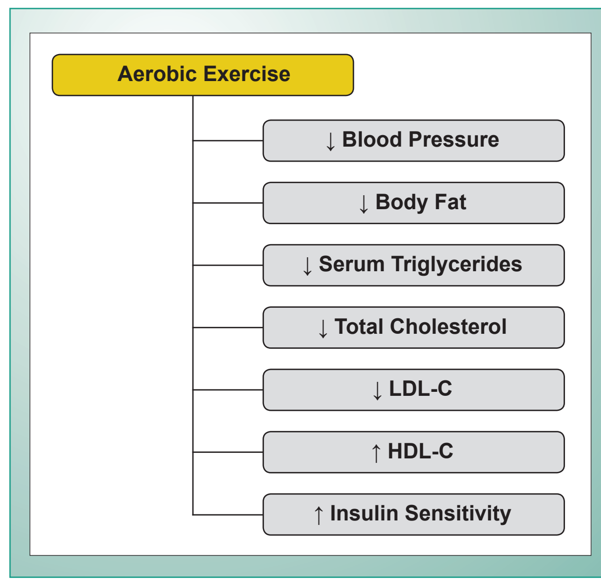

Fig. 2 - *Desirable benefits from aerobic training.*

Dyslipidemia is mainly characterized by high levels of LDL-C and triglycerides, and low levels of HDL-C[1,2,12,33]. Exercise is a tool used to modify the lipid profile, and significantly increases the levels of serum HDL-C and reduces serum LDL-C and triglycerides. In a meta-analysis, Kelley and Kelley[34] demonstrated that aerobic exercise (≥8 weeks) is able to significantly increase the levels of HDL_2-C in adults (≥18 years).

Roberts et al.[35] verified that aerobic exercise for three weeks improved blood pressure, oxidative stress, nitric oxide availability and the metabolic profile. Lalonde et al[36] observed that the more intense intervention (strict diet with exercises) provided better results in relation to the effects on the lipid profile and quality of life than the less intense interventions (diet, strict diet without exercise). Diet associated with exercise provided a higher reduction of LDL-C, and an increase of HDL-C.

Couillard et al[37] verified that a 20-week endurance exercise training was more effective in increasing HDL-C in individuals with high levels of triglycerides and low levels of HDL-C than in individuals with normal levels of triglycerides and low levels of HDL-C.

Bhalodkar et al[38] analyzed a group of Asian Indians and verified that the group which exercised regularly presented the best levels of HDL-C in the large subclass. Additionally, the size of HDL-C particles was significantly larger in the active group in comparison with the inactive group.

Matos and Ladeia[39] studied a rural community and verified that normal serum triglyceride levels and a normal waist-hip ratio (WHR) were related to a higher energy expenditure and a better risk profile.

Another worldwide problem is obesity, which is a secondary risk factor, although extremely related to the atherosclerotic process. Yet, central (abdominal) obesity is a better predictor of heart diseases than overall obesity. Pitanga and Lessa[40] demonstrated that waist circumference (W) and waist-hip ratio (WHR) are more appropriate than BMI to discriminate high coronary risks.

Lakka et al[41] found a relation between abdominal obesity (high waist circumference and high waist-hip ratio) and development of atherosclerosis, regardless of overall obesity and other risk factors. The major factor for this relation is that abdominal obesity is directly linked to visceral fat, which is, in turn, an indicator of unfavorable metabolic effects. These effects result in insulin resistance, glucose intolerance, hypertriglyceridemia, elevation of LDL-C levels, reduction in HDL-C levels, and others.

Kretschmer et al[42] conducted a study in Wistars rats and demonstrated that a 5-week aerobic exercise program was effective in maintaining and reducing the body weight of the rats. Because of the type of analysis of this study (post-mortem), the results are highly reliable, since fat quantification becomes much more precise.

Savage et al.[43] verified that a 4-month training program consisting of walking long duration (60-90 min) 5 to 7 days per week at an intensity of 50-60% of peak VO_2 was effective in reducing body weight (-4.6 kg) in overweight coronary patients. In addition to body weight, there was a reduction of fat percentage (-2.9%), subcutaneous adipose tissue (-12%), and visceral adipose tissue (-14%). Concurrently, lipid profile changes could also be observed, the main of which was a reduction by 23.7% in triglyceride levels.

Another risk factor for the development of atherosclerosis is diabetes, even in asymptomatic individuals[44,45]. The main reason for that is the irregular glucose metabolism in diabetics, and, consequently, an accelerated fat metabolism in this population[46].

Nishida et al.[47] verified that a 12-week training (60 minutes daily, 5 days/week) at lactate threshold intensity improved insulin sensitivity. This sensitivity resulted mainly in improved peripheral insulin sensitivity and peripheral glucose effectiveness. However, the effects of training were verified to be lost one week after detraining.

Short et al[48] verified that a 4-month aerobic training improved insulin sensitivity in younger individuals, but not in middle-aged and elderly individuals. Yet, benefits regarding mitochondrial content and aerobic capacity were observed in all age ranges.

Hypertension seems to be one of the major risk factors for the development of atherosclerosis, because it is closely related to the triggering of arterial wall inflamation[49]. This inflammation affects the normal artery vasodilation and promotes a systematic increase in systolic and diastolic blood pressure, thus triggering a vicious cycle[12].

Studies correlating reduction of blood pressure with the practice of aerobic exercises have been frequently conducted. The most stable responses of blood pressure to exercises may be observed after 1-10 weeks of training[50].

The American College of Sports Medicine (ACSM)[51] established patterns for exercise intensity aiming at reducing blood pressure, stating that hypertensive individuals should practice moderate exercises at a 40-60% $VO_{2\ max}$. This is, therefore, a 10% reduction in relation to the 1993 position stand. As regards exercise time, approximately 30 continuous or accumulated minutes or more of moderate daily exercises are recommended. The ACSM explains that blood pressure reduction occurs by means of several factors, including reduction of the sympathetic nervous activity; reduction of the renin-angiotensin system action; improved vascular responsiveness; increased capillarization; increased arterial lumen, and others.

Moreira et al[52] verified that aerobic training at two different intensities (20% and 60% of the maximum workload) in a cycle ergometer for 10 weeks provided similar results in the reduction of ambulatory blood pressure.

Takata et al[53] found a positive relation between physical activity and blood pressure reduction. The study was conducted among 207 untreated subjects with stage 1 and 2 essential hypertension. The researchers divided the subjects into groups based on the weekly activity level: sedentary control, 30-60 min/week, 61-90 min/week, 91-120 min/week, and > 120 min/week. The analysis was made at the end of an 8-week program. The results showed that those who exercised had systolic and diastolic pressure reductions, and that the control group did not present any change in these pressures. The 61-90 min/week group obtained better results than the 30-60 min/week group. No greater reductions were observed for the groups with further increases in exercise volume.

Therefore, aerobic exercise promotes a significant reduction of cardiovascular risk factors, as observed in the studies described. Thus, aerobic exercise may be used in risk populations with the purpose of decreasing the prevalence of cardiovascular diseases.

Inflammation markers and response to aerobic exercise

Technological progress has led to the investigation of inflammation or atherogenic markers of chronic and acute exercise. Ersöz et al[54] found increased collagen-induced platelet aggregation in submaximal exercise. When maximal incremental exercise was performed, the same increased collagen and ADP-induced platelet aggregation was verified, in addition to increased levels of thromboxane B_2. In Duncan et al's study[55], individuals who trained at high intensity and high frequency showed higher levels of serum homocysteine, although with a reduction of fasting insulin.

Killewich et al.[56] found positive results in a 6-month endurance training on fibrinolytic activity, in subjects with intermittent claudication. Exercise proved to be efficient on the reduction of plasminogen activator inhibitor-1 (PAI-1), and on the increase of tissue plasminogen activator (tPA), therefore, an increased fibrinolytic activity. Endurance training proved to be efficient in the treatment of peripheral arterial disease in this study.

Recommendations

Currently, the differentiation between physical activity and physical exercise is evident. The first consists of any bodily movement resulting in energy expenditure beyond resting levels. Exercise, in turn, is a subset of physical activity that is planned, structured and repetitive with the purpose of improving or maintaining physical fitness. Despite these differences, it seems reasonable to suggest the practice of physical activity as a means of modifying sedentary habits of the population, and as a preparation for engaging in a program of physical exercises.

The American Heart Association (AHA)[57] has a recommendation for the practice of physical activities in the prevention of atherosclerosis (Table 1). This recommendation in based on the ACSM position stand on physical activity[58], which has been adopted worldwide by the majority of the programs related to this issue. With the adoption of this recommendation, it is possible to reduce the frequency of heart diseases and risk factors, as well as to change the lipid profile.

For a higher adhesion to the recommendations, both the AHA and the ACSM suggest the performance of daily activities, such as gardening, climbing flights of stairs, walking, bicycle riding, etc. Minimum duration of each activity bout should be 10 minutes. Thus, three bouts of10 minutes each can be performed during the day. Peterson et al[59] found identical results as regards calorie expenditure with 30 continuous minutes and with three bouts of 10 minutes. Yet, further research is necessary to verify differences regarding changes in risk factors in these two types of situations.

Conclusion

We can observe, therefore, that aerobic exercise has demonstrated to be efficient in the prevention of atherosclerosis, and to be able to restore the normal endothelial function and attenuate risk factors in several studies mentioned. Moderate intensity seems to be the most appropriate to prevent atherosclerosis. Additionally, physical activity seems to be a great strategy to start changing sedentary habits, as well as preparing the individual to engage in a physical exercise program.

Although the majority of the studies show the benefits of aerobic exercise on atherosclerosis, further investigation on the subject is necessary to better explain the underlying physiological mechanisms.

Daily amount	Weekly frequency	Intensity
30 continuous or intermittent minutes (3 X 10 min.)	Most of the week days, preferably all.	Moderate (40-60 % of the VO_2 Max).

Chart 1 - Recommendations for Physical Activity AHA[57] and ACSM[58]

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