

## Coronary Heart Disease, Physical Exercise and Oxidative Stress

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### Abstract

Cardiovascular diseases are the leaders in morbidity and mortality rates in Brazil and worldwide, being coronary heart disease (CHD) the cause of a large number of deaths and high expenditure on medical assistance. Quite a number of risk factors for CHD are directly related to endothelial dysfunction. Those risk factors induce decreased bioavailability of nitric oxide (NO), the increase of free radicals (FR), and increased endothelial activity. Those changes may lead to vasodilation impairment. Many interventions are performed to treat CHD. Pharmacological agents, a change in eating habits, nutritional supplements and physical exercise on a regular basis are some of those interventions. The benefits of physical exercise on a regular basis over endothelial function have been demonstrated in experiments with animals and humans. However, data in the literature are still controversial as to the required intensity level to result in significantly protective changes in endothelial function. Intense exercising is also related to higher oxygen consumption and to a resulting increase of oxygen free radicals (OFR).

### Introduction

Coronary heart disease (CHD) is characterized by insufficient blood supply to the heart through coronary arteries. DAC is directly related to the extent of blood flow obstruction by atherosclerotic plaques, with resulting narrowing of the coronary arteries (stenosis), which in its turn reduces the oxygen that reaches the heart due to coronary blood flow reduction<sup>1</sup>.

Cardiovascular diseases are the leaders in morbidity and mortality rate in Brazil and worldwide, being CHD the cause of a large number of deaths and high expenditure on medical assistance<sup>2,3</sup>. Based on data from the Summary of Social Indicators (2002), collected by the Brazilian Institute of Geography and Statistics (IBGE), cardiovascular diseases

### Key words

Coronary artery disease; exercise; endothelium, vascular; free radicals.

stand out as the main cause of death (28.8% among males and 36.9% among females) in the whole country. The Southern Region - and Rio Grande do Sul State in particular - report the highest rates: they account for 40% of deaths among women<sup>3</sup>. Smoking, obesity, diabetes mellitus, hypertension, high cholesterol levels, family history of CHD, and the lack of exercise increase the risk for CHD<sup>1,2</sup>.

Hermann and Lerman<sup>4</sup> have suggested that a number of risk factors for CHD are directly related to endothelial dysfunction. Those risk factors induce a large number of changes that are damaging to vascular biology, among them a reduction in NO bioavailability, the increase of free radicals, and an increase in endothelial activity. Those changes may lead to vasodilation impairment<sup>5-7</sup>.

Many interventions are performed to treat CHD. Pharmacological agents, a change in eating habits, nutritional supplements and physical exercise on a regular basis are some of those interventions.

Mild to moderate physical exercise on a regular basis is recommended for good health and the prevention of a number of diseases. It also reduces the production of oxidants and oxidative damage, improve antioxidant defense system, and increase the resistance of organs and tissues against the deleterious action of FR<sup>8</sup>. However, some studies<sup>9-11</sup> have presented evidence that physical exercise - particularly if too intense - is associated both to muscular damage and high formation of FR.

The benefits from regular physical exercise over endothelial function have been demonstrated in experiments with animals and humans<sup>12</sup>. The literature is still controversial, however, as to the required exercise intensity to result in significantly protective changes in endothelial function. Farsifar et al<sup>13</sup> and Wisløff et al<sup>14</sup> have reported that acute, intense exercising has shown to present significant, fast response on endothelial function. Nonetheless, some studies have demonstrated that intense exercising has also been related to higher oxygen consumption and to resulting increased formation of FR in cardiac and skeletal muscle<sup>10,11,15</sup>.

Having that in mind, the present review will address the endothelial dysfunction involved in the genesis of CHD. It will focus the role played by vascular endothelium, and the relevance of physical exercise on endothelial function as well as on the parameters of oxidative stress in CHD.

### Endothelial function and atherosclerosis

It is quite well known that coronary arteries functional characteristics are determined by endothelial cells, vascular smooth muscle cells, and connective tissue elements on arterial walls. The vascular muscle is the end of the regular

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pathway to activate artery diameter control, and therefore, vascular resistance<sup>16-18</sup>.

The role played by the endothelium was traditionally thought to be basically that of a selective barrier for the diffusion of macromolecules from blood vessels lumen into the interstitial space. In the last 20 years many other functions have been described for the endothelium, such as the regulation of vagal tonus<sup>16</sup>; inflammation modulation; promotion and inhibition of neovascular growth<sup>17</sup>; and modulation of platelet aggregation and coagulation<sup>16-18</sup>. Additionally, the endothelium is responsible for the synthesis of vasoconstricting and vasodilating factors, being the nitric oxide (NO) one of the most relevant endothelium-derived relaxing factors (EDRF)<sup>19,20</sup>.

Basal vasodilating tonus in healthy individuals is shown to be moderate and constant from endothelial NO diffusion to vascular smooth muscle cells. If basal formation of NO is interrupted, vasoconstriction occurs. Low NO formation (in a number of vascular diseases) reduces tissue perfusion and promotes the formation of thrombus. High NO formation, however, promotes marked vasodilation and shock<sup>21</sup>.

A number of diseases - such as dyslipidemia, atherosclerosis, and systemic arterial hypertension - have their genesis and/or their pathophysiological mechanisms in endothelial function. Therefore, endothelial dysfunction - characterized by lower production and/or NO bioavailability - is one of the factors to contribute for the onset of cardiovascular diseases<sup>20,22</sup>.

The understanding of the genesis and of the progression of atherosclerosis has been highly elucidative in the last decade. In the mid 1970's, Ross and Glomaser<sup>23</sup> suggested that coronary atherosclerosis starts with an injury in the arterial wall, leading to endothelial denudation or to desquamation of arterial endothelium lining. Adding to that assumption, recent evidence has suggested that even the classic fat spots - the first typical injury in childhood - is an inflammatory injury made of macrophages, derived monocyte-derived, and T-lymphocytes<sup>24</sup>.

In individuals who do not present atherosclerosis the dominating effect of endothelial activation and NO release is vasodilation. Endothelial injury and denudation result in dysfunction (paradoxical vasoconstriction in response to vasodilating agents) which seems to be the starting event for the development of atherosclerosis. Endothelial dysfunction precedes physical manifestation of atherosclerosis on angiography<sup>25</sup>. Increasing knowledge that coronary lumen diameter in epicardium, in resistance vessels, and in major peripheral arteries is highly dynamic in response to flow-mediated and agonist-mediated factors (NO and endothelium-1) has contributed for the understanding of atherosclerosis. Ludmer et al<sup>26</sup> and El-Tamimi et al<sup>27</sup> were the first to observe paradoxical vasoconstriction of atherosclerotic segments in coronary arteries in response to acetylcholine infusion.

Therefore, endothelium damage and dysfunction were perceived as the starting events in atherosclerosis. Additionally, endothelial dysfunction has also been recognized as a relevant factor for acute coronary syndrome<sup>7,18,28</sup>. Rozanski et al<sup>29</sup> have compared peripheral blood flow response in

57 patients with coronary heart disease and 50 subjects apparently healthy as controls. Both groups were submitted to physical exercise on the treadmill. Results showed no evidence of vasodilation induction from exercise in the control group, whereas 53% of the coronary heart disease individuals showed progressive vasoconstriction.

While under aggression by risk factors, endothelium progressively loses its protective, physiologic function, and is turned into a source for elements that are involved in the development of atherosclerosis. Endothelium damage or activation change the regulatory functions and result in endothelial dysfunction, thus changing vasodilating response, reducing antithrombotic activity, and resulting in structural changes and, obviously, vascular damage<sup>6,7,30,31</sup>.

Therefore, atherosclerosis is the prototype of a disease characterized by endothelial dysfunction at all stages. Endothelial dysfunction is here defined as the insufficient supply of NO, which predisposes to oxidative stress, inflammation, erosion, and vasoconstriction<sup>4</sup>.

Among the factors that lead to endothelial damage, the Oxygen Reactive Species (ROS) and the Nitrogen Reactive Species (NOS) - specifically those that are NO-derived - have increasingly been recognized as those most responsible for the impairment of cellular endothelial function involved in atherogenesis<sup>7</sup>.

#### Reactive oxygen species and oxidative stress in CHD

Under normal physiologic conditions, most ROS is generated in mitochondrial respiratory chain, where from 2% to 5% of electrons are detoured for the production of free radicals. Additionally, ROS may be generated at other biochemical events in the cells, as for instance during inflammatory processes, fatty acids catabolism, in the degradation of xanthine into uric acid, and in catecholamine auto-oxidation<sup>32</sup>. Although those processes are normal in cell life, excess ROS production may induce damage to biomolecules, among them nucleic acids, proteins, and lipids - which if extensive, may lead to cellular death<sup>32</sup>.

The generation of free radicals is not always damaging to the body. Quite the opposite, it is necessary for a number of biological processes such as cellular signaling, muscular contraction, and the immune system<sup>33</sup>. When the cells are under the aggression of some stressing agent, for instance (which may also be a free radical), they end up producing free radicals to fight against that agent. A big problem emerges when total level of free radicals generation is higher than defense capabilities, and when significant cellular damage may occur.

Increased oxidative stress may contribute for the pathogenesis of cardiovascular diseases<sup>2,6,7</sup>. Experimental clinical trials have suggested that those conditions are associated to increased formation of free radicals as well as to the reduction of antioxidant defense<sup>2,6,34</sup>.

Different oxidants may originate from cellular and extracellular sources, and from enzyme and non-enzyme pathways on the vascular wall. The major sources of free radicals on inflamed vascular wall with acceptable physiologic relevance in cardiovascular diseases are: NADPH

oxidase, endothelial nitric oxide synthase (eNOS) uncoupling, and inducible nitric oxide synthase (iNOS), myeloperoxidase, xanthine oxidase, lipoxigenase/cyclooxygenase, respiratory chain/oxidative phosphorylation<sup>2,7,35</sup>.

Currently, the most important mechanism through which oxidative stress is believed to change endothelial function is through NO inactivation by superoxide anions and oxidated low density lipoproteins (ox-LDLs). Those FR deactivate the endothelial receptors for acetylcholine, serotonin, thrombin, bradycinin, and other mediators, thus reducing NOS stimulation in endothelial cells, with consequent reduction in the production of NO, impairing muscle smooth cells relaxation, and predisposing to atherosclerotic plaque<sup>6</sup>.

Additionally, the generation of ROS may react with NO molecule and produce peroxynitrite anion (ONOO<sup>-</sup>) and nitrogen dioxide, and therefore start lipid peroxidation and potentialize the inflammatory injury in vascular cells, reducing NO availability and favoring thromboembolic processes<sup>2,35</sup>.

Oxidative change of circulatory lipoprotein caused by FR - particularly low density lipoproteins (LDL) - seems to be quite relevant in the development of atherosclerotic injuries, primarily the oxidation of polyunsaturated fatty acids in LDL, which seems to occur inside atherosclerotic injuries. Following oxidation process, ox-LDL stimulates the migration of circulating monocytes to the subendothelial space, and also causes endothelial cell injury. ox-LDL is then captured by macrophages - faster than usual - to form cholesterol-loaded foam cells. That early histological process leads to the development of atherosclerotic plaques<sup>6,7,35</sup>.

Additionally, ox-LDL is cytotoxic to endothelial cells, promotes cytokines expression, is pro-inflammatory, causes eNOS inhibition, promotes vasoconstriction and compliance, and increases platelet aggregation<sup>2,7,15</sup>.

Risk factors for atherosclerosis - such as smoking, *diabetes mellitus*, hypertension, hypercholesterolemia, and others - are associated to increased formation of FR. Excessive generation of ROS promotes direct generation of cytotoxic species and NO inactivation<sup>2,6</sup>. Such inactivation leads to the loss of NO protective effects such as arterial tonus regulation, inhibition of local inflammation and coagulation, and cellular proliferation<sup>16-18</sup>.

The protective effect of NO in atherosclerosis occurs through the inhibition of LDL-cholesterol molecules as well as the prevention of platelet aggregation. NO prevents the formation of ox-LDL molecule through its antioxidant action - by preventing the formation of superoxide anions that promote LDL-cholesterol molecule oxidation<sup>36,37</sup>. NO antiaggregating action is a result of its binding to the guanilatocyclase molecule, which induces the formation of cyclic guanilate monophosphate (cGMP), which in its turn promotes the reduction of calcium ions concentration inside the platelet to inhibit its activation and aggregation<sup>38</sup>.

The loss of NO impairs those protective mechanisms, thus contributing for the development of atherosclerosis. Oxidative stress is believed to induce endothelial dysfunction in coronary atherosclerosis as a result of increased degradation and inhibition of NO synthesis<sup>12</sup>.

## Physical exercise and oxidative stress

High metabolic rates resulting from physical exercise may drastically increase oxygen consumption ( $VO_{2max}$ ) up to 20 times when compared to values at rest<sup>39</sup>. That increase is followed by a concurrent increase in ROS generation<sup>40</sup>. Studies elsewhere have demonstrated, however, that endurance training increases antioxidating defense, as well as muscle oxidative capacity<sup>40-42</sup>.

Oxidative stress has been associated to reduced performance, fatigue, muscular damage, and physical exercise in excess. That explains why some researchers<sup>8,39,41,43</sup> have suggested that oxidative stress reduction may improve exercise tolerance as well as physical performance.

Although the benefits of increased  $VO_{2max}$  have been quite well established, a biochemical paradox can be observed. Increased maximum consumption of  $O_2$  is crucial for cardiovascular aptitude and performance. Nonetheless, increased consumption of  $O_2$  during physical exercise causes a concurrent increase in FR formation. Depending on exercise type and intensity, different mechanisms for ROS generation have been proposed. Among them, the following should be pointed out:

1 - *Higher generation of superoxide anion ( $O_2^-$ ) in respiratory chain* - One of the major sources of free radicals during physical exercise is the release of electrons taking place in electron transport chain. Increased oxygen consumption by the tissues during intense exercise would theoretically lead to a proportional increase of  $O_2^-$ , consequently leading to increased mitochondrial lipid peroxidation, loss of protein thiol groups, and inactivation of oxidative enzymes<sup>33</sup>.

2 - *Xanthine oxidase (XO) activation* - XO catalyzes adenosine monophosphate (AMP) during muscular ischemia, leading to increased  $O_2^-$  production. During ischemia AMP - formed from adenosine triphosphate (ATP) through adenilate kinase (ADK) reaction - is degraded into hypoxanthine. XO is converted and then reduced to xanthine dehydrogenase during ischemia by intramuscular proteases, which need  $Ca^{+2}$ . XO converts hypoxanthine to xanthine and uric acid by using molecular oxygen as electrons receptor, thus forming  $O_2^-$ . Under aerobic conditions, sufficient oxygen will ensure that ATP is replaced via mitochondrial oxidative phosphorylation, and that hypoxanthine and xanthine are first converted to uric acid by xanthine dehydrogenase. Additionally, the skeletal muscle has low XO activity. However, XO may be a relevant pathway when the muscle presents adenine dinucleotide. In theory, that may occur under ischemia, isometric exercises,  $O_2$  deficit, and blood flow vascular limitation while exercising<sup>44</sup>.

3 - *Polymorphonuclear cells activation* - The fast oxygen consumption process by phagocytic cells - particularly neutrophils and macrophages - is known as respiratory burst. That process is one of the sources for superoxide, hydrogen peroxide, hydroxyl radical, hypochloride acid peroxynitrate<sup>45</sup>. In addition to presenting antitumoral action, some of those reactive oxygen intermediates are directly involved in the defense of the host against bacteria, viruses, protozoans, and fungi<sup>33</sup>.

Respiratory burst results from the activity of NADPH oxidase - an enzyme that catalyzes electrons transfer from

NADPH to  $O_2$  to form superoxide. Superoxide dismutation occurs when superoxide dismutase is present, thus forming an important microbicidal agent - hydrogen peroxide<sup>45</sup>. Hydrogen peroxide may be catalyzed by myeloperoxidase - found particularly in neutrophils, resulting in an even more powerful toxin in its microbicidal action called hypochlorite acid (HOCl)<sup>46</sup>.

Once formed, HOCl is bound to oxidize aminoacids to chloramine synthesis. Those last derivatives lose Cl- and  $CO_2$ , thus forming amines that are hydrolyzed to aldehydes. As for treonin, resulting hydroxyaldehyde undergoes dehydration and produces acrolein (cancerigenous, destroys elastic fibers, irritates mucosae)<sup>46</sup>. HOCl also reacts with hydrogen peroxide to form singlet oxygen ( $1O_2$ ). Hydroxyl radical (OH·) may also be formed by Haber-Weiss reaction<sup>32</sup>.

Exercise-induced neutrophil activation occurs as a result of the migration (catecholamine mediated) of neutrophils from endothelial tissues and bone marrow (cortisol mediated)<sup>47</sup> That leads to the removal of damaged proteins and cells, as well as dead cells. Although that is a desirable reaction, if not well regulated it may be one of the causes for acute inflammations due to the largely increased production of pro-inflammatory mediators (interleukin 1, 8, TNF-alpha) and prostaglandins, thus leading to the induction and intensification of additional inflammatory processes and increasing the generation of ROS - NF-kB<sup>48</sup> factor transcription activators.

However, even if intense exercising induces significant change in ROS generation, recent studies have shown that regular endurance exercise may turn antioxidant defense system more efficient as well as improve the oxidative capacity of organic systems, thus establishing equilibrium between ROS-induced damages and antioxidant repair systems<sup>39-43</sup>.

### Physical exercise and endothelium

Quite a number of studies have demonstrated that moderate to intense exercising is associated to significant reduction in the incidence of cardiovascular events, thus ranking physical exercise as a relevant therapeutic regimen for the prevention and prognosis of those conditions<sup>49,50</sup>. In the most recent years, many benefits have been described from regular exercising for cardiopaths, in addition to improving functional capacity<sup>51</sup>.

Exercising stands for physiologic stress on the body from the high energy demand when compared to resting, which results in high release of heat and intense change in muscular and ischemic chemical milieu. Consequently, regular exposure to exercise in the long term (physical training) promotes a set of morphological and functional adaptations that provide the body with higher capacity to respond to the stress from exercising. It is important to point out that chronic effects from exercising depend primarily on peripheral adaptation, which involves both better control and distribution of blood flow, as well as specific adaptations of skeletal musculature<sup>52</sup>.

Most patients with established cardiovascular diseases refer reduced functional capacity, which is related to the reduction of  $VO_{2max}$  obtained during ergospirometric test. Exercise capacity for those patients is determined by the complex

interaction between cardiovascular, respiratory, metabolic, and muscular systems, added to autonomic nervous system modulation. Therefore, any unbalance in that interaction may reduce individual functional capacity<sup>53</sup>.

The correlation between physical exercise and primary and secondary CHD prevention has been widely discussed. Results from quite a number of studies have shown the impact of physical exercise on the treatment for the condition<sup>54,55</sup>. From all those studies, two meta-analyses are to be pointed out: they have confirmed a significant reduction - from 20% to 25% - in mortality rate from cardiovascular diseases in patients that have been submitted to cardiac rehabilitation<sup>56,57</sup>.

Human and laboratory animal studies have shown that shear stress (blood force on artery wall) induced by physical exercise is a powerful stimulus for the release of vascular endothelial vaso-relaxing factors, such as NO. It has been demonstrated that moderate physical training increases the relaxation of vascular and non-vascular smooth muscle resulting from higher generation of NO by endothelial cells in response to physical exercise<sup>12,58-60</sup>. Additionally, it has been observed that exercise-induced shear stress increases endothelial and neuronal NOS expression<sup>60-63</sup>.

Therefore, during physical exercise, cardiac debit is increased, with blood flow redistribution to skeletal musculature and coronary circulation. That mechanism is mediated by eNOS, whose genetic expression may be potentialized with regular aerobic exercises<sup>62,64</sup>.

Taddei et al<sup>65</sup> have demonstrated that physical training may prevent endothelial dysfunction through NO availability repair as a result of oxidative stress prevention. Such evidence suggests that physical exercise may prevent or attenuate the reduction of endothelium-dependent vasodilation.

Therefore, the benefits from regular exercising on cardiovascular diseases are primarily associated to a higher generation of endothelium-derived vasodilating agents, with resulting reduction of peripheral vascular resistance, of LDL cholesterol levels, and platelet aggregation inhibition<sup>22,60</sup>.

Results from recent studies have demonstrated that physical training provides significant myocardial perfusion improvement<sup>1</sup>. The following are among the components involved:

*1 - Endothelial function* - Frequent increase of transmural pressure in blood flow resulting from repeated exercise results in endothelial function improvement, thus contributing for easier myocardial perfusion. Such vasodilating mechanism - mediated by endothelial action - has been referred to as one of the main vascular adaptations from physical training<sup>49,59,62,66</sup>. Animal studies elsewhere have also demonstrated endothelial vasorelaxing factors resulting from physical exercise<sup>60</sup>.

*2 - Nitric oxide synthesis and degradation velocity* - In an attempt to make up for the formation of peroxynitrate, vessel smooth muscle cells produce an antioxidative enzyme - superoxide dismutase (SOD) - which blocks the action of free radicals, thus reducing NO degradation. Animal and human studies have demonstrated that physical training increases the expression of that antioxidative enzyme, as well as NOS production and expression<sup>12,67</sup>.

3 - *Microcirculation* - Some studies have raised the assumption that physical training would also stimulate NO generation in microcirculation, with resulting vasodilation action; Evidence has shown that the vasodilating capacity of resistance vessels (microcirculation) is intensified after four weeks of training, which is of key relevance for myocardial perfusion<sup>59,62,63</sup>. Results from a study conducted by Yoshinaga et al<sup>68</sup> have shown that the differences between the coronary flow reserve in both abnormal and normal segments after physical training do reflect microcirculation vasodilating action. The authors believe that response to exercise in microcirculation is complex and multifactorial, also involving smooth muscles function, endothelial function, capillary density, the regression of the condition, and collateral circulation.

4 - *Regression of atherosclerotic lesions* - Studies have demonstrated that physical exercise associated to cholesterol level control (hypofat diet) attenuates coronary injury development in the long term (four to six years of exercise), and may even lead to the regression of myocardial atherosclerotic plaque<sup>69-71</sup>. The phenomenon is seen as controversial by many, but what has been left out of the discussion is the possibility of improvement in myocardial perfusion<sup>69-71</sup>. On the other hand, the benefit of physical exercise in the short term is uncertain<sup>72</sup>.

5 - *Neof ormation of collateral vessels* - Animal research has demonstrated that the narrowing of coronary artery caliber induces the onset of collateral circulation. That increase in circulation is potentialized when those animals are submitted to an exercise program<sup>70,71</sup>. However, myocardial perfusion studies have shown conflicting results on the scintigraphy of coronary patients who have been submitted to a regular exercise program. In the light of the facts presented, it can be observed that physical training effect on the formation of collateral vessels is still uncertain<sup>63,68,69,73</sup>. Generally speaking, human angiographic studies have found it difficult to find evidence of collateral circulation increase in coronary patients submitted to physical exercise - which may be explained by the fact that the exam cannot identify small size collateral arteries (< 100  $\mu$ m).

6 - *Blood viscosity reduction* - Regular physical exercise results in plasma volume increase in addition to the reduction of some plasma proteins such as fibrinogen and globulin - a process called chronic hemodilution<sup>74,75</sup>. Despite plasma volume increase, there is no consensus in regard to hematocrit reduction from chronic exercising<sup>75,76</sup>. Concurrent reduction of plasma viscosity occurs, which may reach up to 8% in endurance athletes<sup>75,77</sup>. Viscosity reduction from physical exercise has not, however, been demonstrated in coronary patients. Whether physical exercise actually affects blood

viscosity in those patients remains to be proven<sup>73,78</sup>.

7 - *Increased diastolic perfusion time* - A study conducted with coronary patients submitted to a regular program of physical exercise showed basal heart rate (HR) reduction, with longer time of diastolic perfusion at rest. Again, the longer time in diastolic perfusion was shown at exercise peak, thus attenuating the ischemic manifestations on the ECG<sup>63,79</sup>.

Therefore, it is clear that physical exercise improves physical performance, tolerance to exercise, and symptoms in coronary artery disease patients, and reduces mortality rate. However, the biochemical mechanisms through which those benefits are established have not yet been fully understood. Although endothelial function improvement is the earliest phenomenon (within 4 to 6 weeks) in coronary flow increase in trained individuals, it is too early to say that this is the only mechanism involved in myocardial perfusion improvement<sup>1,68</sup>.

## Final considerations

In the light of what has been presented, it is clear that oxidative stress does play a role in the genesis and development of cardiovascular diseases, among them, coronary artery disease. From the many therapeutic interventions used to treat those conditions, physical exercise stands out as a key tool for the maintenance and/or recovery of endothelial function. The benefits from physical exercise have been extensively documented in current literature.

However, further studies are required to shed light on all mechanisms involved in that therapeutic action, as well as to sponsor an analysis of the most appropriate level of physical training for those patients, to serve as guidance to the professionals working on the prescription and orientation of physical exercise for cardiovascular disease patients in the attempt to reduce the prevalence of the condition in world population.

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