Chapter 3

Oxidative Stress and Vascular Diseases: Effect of Physical Exercise

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http://dx.doi.org/10.5772/intechopen.76576

Abstract

Investigations have shown that worldwide the vascular diseases are considered independent risk factors for an increased mortality. Despite these diseases being related to factors such as sedentary lifestyle, poor diet and stress, the oxidative stress been the which most strongly explained the genesis of these vascular diseases. In this sense, the body of evidence involving an analysis and understanding of the factors and preventive variables of these diseases available in the literature is necessary. Considering this, we aimed to available information about the role of the oxidants and antioxidants enzymes in the prevention or causes of vascular diseases, and how the physical exercise can prevent the development of these vascular diseases. It was observed that endothelin-1 is an important oxidant involved in the atherosclerotic process, while the hydrogen sulfide and glutathione peroxidase have an antioxidant role. About the physical exercise, there is greater production of oxidants, however, as a mechanism of compensation, there is also greater production and release of antioxidants such as nitric oxide and glutathiones after some sessions when compared with the baseline. We conclude that the stress oxidative is involved in the vascular disease and the physical exercise could be used like prevention.

Keywords: vascular disease, oxidant enzyme, antioxidant enzyme, oxidative stress, physical exercise

1. Introduction

Vascular diseases have been reported worldwide as an independent risk factor for premature mortality [1]. It is now understood that the point in common of all vascular, cardiovascular or chronic non-cardiovascular degenerative diseases is the imbalance between oxidation and reduction profile caused by free radicals culminating in a situation denominated oxidative stress [1, 2]. This reactive oxygen species are generated from NADPH oxidases (NOx), responsible for the bioavailability of nitric oxide (NO) in vascular pathologies, through of a direct inactivation of NO, together with a reduction in NO synthesis and in oxidation of your receptor, denominated guanylyl cyclase soluble [3]. In this sense, the development of studies about the antioxidant action in vascular function are important, considering that alterations in this functions, characterized for one increase in vasoconstrictor responses, decrease in vasodilatory capacity and one increase in reactive oxygen species production, and the reduction of the activity of antioxidants enzymes are associated with the cardiovascular risk factor, as arterial hypertension and atherosclerosis [4–9].

Therefore, researches have analyzed effective therapeutic strategies in the treatment of pathologies that affect the vascular musculature. Among them, drug therapy is still the most indicated, due to its antithrombotic, vasodilatory and hypocholesterolemic pharmacological efficacy, such as statins, capable of improving the endothelial functions, due to yours antioxidants, anti-inflammatories and anti-atherosclerotic properties [10, 11]. Although the drugs administered are effective, their clinical utility is limited due to the development of tolerance and resistance. For that reason, other therapeutic strategies, with fewer collateral effects, have been indicated together with the drug treatment, since they are also able to reduce the deleterious vascular effects, such as nutraceutical biology with a diet rich in fruits, vegetables or red wine, for example [12, 13]. In the present study, the use of polyphenols in the treatment of high levels of polyphenols was studied. Then, it seems plausible to affirm that a better understanding of the relationship between oxidants and antioxidants functions in the prevention or treatment of vascular diseases should have a body of evidence amply constructed to collaborate in the prevention and treatment of diseases.

Physical exercise, in this context, has been presented as one of the elements of a healthy lifestyle capable of modulating oxidative stress, by promoting the increase of endothelial nitric oxide synthase (eNOS) activity, of the early oncogenesis protein tyrosine kinase (c-Src) [73] and the bioavailability of NO and antioxidant enzymes, leading to significant vascular protection [12, 13] .

Although to date the investigations have demonstrated the endogenous antioxidant effect on the prevention of vascular disease, obtained with or without the contribution of short- or long-term physical exercise, other mechanisms are need to be better understood, especially with regard to exercise. It is not yet possible to assert the understanding that in addition to modulation in the antioxidant action, there is also an action on inflammatory factors, reducing the inflammation so present in vascular diseases, if there is modification of the membrane proteins of some vascular cells, or if this regulation also occurs at the downstream level. The collection of the literature regarding these gaps will be best seen in Chapters 2 and 3 of this book.

Considering this, we aimed to avail information about the role of the oxidants and antioxidants enzymes in the prevention or causes of vascular diseases, and how the physical exercise can prevent the development of these same diseases.

2. What is the role of oxidative stress in vascular diseases?

At first, it is necessary to understand that free radicals are molecules that contain one or more unpaired electrons, are generated independently, and are considered highly reactive due to their ability to accept electrons from other molecules until a terminal reaction occurs [2]. Excessive production of these radicals can trigger cumulative cellular damage in proteins, lipids, deoxyribonucleic acid (DNA) and other components, resulting in several pathological processes [1].

Thus, in vitro studies have demonstrated that these molecules are important intracellular signaling factors that contribute to vascular remodeling, modulating vascular contraction/dilatation, migration, apoptosis and protein turnover of the extracellular matrix [14]. Thus, increased reactive oxygen species (ROS) formation is identified in vascular diseases such as hypertension, atherosclerosis and stroke, and is associated with a reduction in levels of nitric oxide (NO) and other vasodilators, endothelial tissue damage, protein oxidation, DNA damage and increased proinflammatory responses [14].

There are two types of reactive species, one of which is called the reactive oxygen species, a general term that refers not only to radicals derived from superoxide (O_2) metabolism, but also includes non-radical O_2-reactive derivative (e.g., hydrogen—H_2O_2) [15]. Similarly, the other class is known as nitrogen reactive species (RNS), it refers to nitrogen radicals reactive with other molecules in which the reactive center is nitrogen [15]. The most common ROS and RNS are shown in **Table 1** in an order of the ones that are the most to the least reactive in the cell [15].

A variety of enzymatic and non-enzymatic processes can generate the reactive species in mammalian cells [1]. The primary sources are: mitochondrial respiratory chain, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, dissociated nitric

Oxigen-reactive species	
Singlet oxygen	$^1O_2$
Superoxide anion	$O_2^{-\bullet}$
Hydrogen peroxide	H_2O_2
Hydroxyl radical	$HO^\bullet$
Perhydroxyl radical	$HO_2^\bullet$
Alcoxila radical	$RO^\bullet$
Peroxyl radical	$ROO^\bullet$
Hydroperoxyl radical	$ROOH^\bullet$
Hypochlorous acid	HCLO
Ozone	O_3
Nitrogen reactive species	
Nitric oxide	NO
Nitric oxide	NO_2
Peroxynitrite	ONO_2^-

Table 1. Reactive oxygen and nitrogen species.

oxide synthase (NOS), lipoxygenase and myeloperoxidase (MPO), the first four of which are responsible for aggravating the vascular diseases [1].

The mitochondrial respiratory chain is the main pathway for radical generation in biological systems involving the transport of mitochondrial electrons, where oxygen is used for the production of ATP. Under physiological conditions, most of the oxygen consumed by cells is reduced to water in the mitochondria by serial oxy-reduction reactions through the action of the cytochrome oxidase complex. The reduction of oxygen to water takes place inside it in a way that leaves no intermediates. In fact, it is necessary to receive the oxygen atom to form two molecules of H_2O and this is done when it receives four electrons (H^+) and, upon receiving them, the oxygen goes through intermediate stages: superoxide, hydrogen peroxide, radical hydroxyl and finally water. All this happens inside the cytochrome oxidase complex and it does not let these intermediates leak. However, if there is an accumulation of electron flow in the chain, this increases the probability that some electron will leak out of the chain. From 1 to 5% of the passage of oxygen along the respiratory chain may give rise to $O_2^{\bullet-}$, which results in other non-radical species (H_2O_2) and radicals ($HO^{\bullet}$). This may result from the reduction of an ubiquinone (coenzyme Q) electron, generating ubisemiquinone, which then binds its unpaired electron to O_2 to form $O_2^{\bullet-}$. However, there may be other free radical generation sites in the electron transport chain [2]. Mitochondria also generate NO, which can react with $O_2^{\bullet-}$ to form peroxynitrite ($ONOO^-$), a very potent oxidant [16].

Nicotinamides adenine dinucleotide phosphate oxidases (NADPH) are a family of enzymes with multiple complex subunits that generate $O_2^{\bullet-}$ by reducing one of electron oxygen using NADPH as the source of electrons [17]. They comprise a cytochrome b558 that crosses the plasma membrane, is composed of a large catalytic subunit, $gp91^{phox}$ (nox2), and a small subunit, $p22^{phox}$ (the term "phox" is derived from "phagocytic oxidase") together with cytosolic regulatory subunits $p47^{phox}$, $p67^{phox}$, $p40^{phox}$ and the small GTPase Rac [14, 18]. Activation of NADPH oxidase is initiated by phosphorylation (in serine) of the $p47^{phox}$ cytoplasmic subunit, triggering its migration to the membrane, where, along with Rac, it associates with cytochrome b558, initiating the catalytic activity of the enzyme. The identification of subunits homologous to $gp91^{phox}$ resulted in the formation of the Nox family (of "Nonphagocytic NADPH Oxidase") (Nox1, Nox2 [formally known as $gp91^{phox}$], Nox3, Nox4, Nox5, Duox1 and Duox2 [Dual oxidase]). The main components of the complex enzymatic are nox1, nox2 and nox4 being the major catalytic subunits in vascular endothelial cells, smooth muscle cells, fibroblasts and cardiomyocytes. In the large arteries, $p22^{phox}$, $p47^{phox}$ and Rac subunits are found. While in cells of small arteries of resistance, $gp91^{phox}$ (nox2), $p22^{phox}$, $p47^{phox}$ and e $p67^{phox}$, were identified as the main responsible for the formation of intracellular ROS [19]. In cell stimulation, $p47^{phox}$ becomes phosphorylated and the cytosolic subunits form a complex, which then migrates to the membrane, where it associates with cytochrome b558 to leave the active oxidase, which transfers electrons from the O_2 substrate, leading to formation of de $O_2^{\bullet-}$ [18]. In vascular cells, nox4 is abundantly expressed and plays an important role in the production of de $O_2^{\bullet-}$ and has been associated with vascular pathophysiology [17].

There are three isoforms of nitric oxide synthase (NOS) decoupling enzymes that are termed: neuronal nitric oxide synthase (nNOS) expressed in most neural tissues, endothelial nitric oxide synthase (eNOS) expressed in cardiovascular tissues and inducible iNOS), induced by pro-inflammatory mediators [20]. NO synthesizing enzymes catalyze the conversion of

L-arginine to L-citrulline and NO. The production of NO via eNOS involves the transfer of electrons from the NADPH cofactor to adenine and flavin dinucleotide and the mononucleotide of adenine and flavin to heme [20]. All can generate $O_2^{\bullet-}$ under substrate (arginine) or cofactor (tetrahydrobiopterin—BH4) conditions. The BH4 enzyme is highly susceptible to oxidative degradation, and the initial oxidative loss of BH4 in response to increased EROS production by NADPH oxidases amplifies oxidative stress through the resulting loss in NO production and an increase in the generation of $O_2^{\bullet-}$ dependent of us. Most of the evidence linking NOS to EROS production belongs to the eNOS isoform [20].

The coupling of the electron flow through the eNOS to L-arginine is dependent on adequate levels of cofactors and under specific circumstances, eNOS can become "decoupled" and reduces the oxygen molecule rather than transfer electrons to L-arginine, generating $O_2^{\bullet-}$. Thus, the impact of eNOS on vasculature may depend on adequate levels of cofactors to support endothelial function. In fact, studies have shown the decoupling of eNOS from the arteries of individuals with diabetes [21] or atherosclerosis [22].

Xanthine and xanthine dehydrogenase are forms of the same enzyme, known as xanthine oxidoreductase. This enzyme is widely expressed in the capillary endothelium and catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid, however, only the oxidase form generates $O_2^{\bullet-}$ and H_2O_2. The enzyme typically exists in the form of dehydrogenase, but under conditions of stress or, for example, in hypoxia induced by a process of atherosclerosis, the oxidase isoform predominates. Therefore, xanthine oxidase has been implicated as a source of EROS after reperfusion of ischemic tissue in various organs [2], and its expression is upregulated by NADPH oxidase [23].

The development of vascular disease originates from an initial injury to the vessel wall by biological or mechanical factors. Both produced in response to injury can stimulate ROS production in macrophages, endothelial cells, smooth muscle cells and adventitial layer. These then impair vessel tone through endothelial dysfunction, which is characterized by inflammatory response, pro-constrictive response, increased migration of smooth muscle cells, proliferation and apoptosis (**Figure 1**), contributing to diseases such as stroke, atherosclerosis and hypertension [5–8, 24].

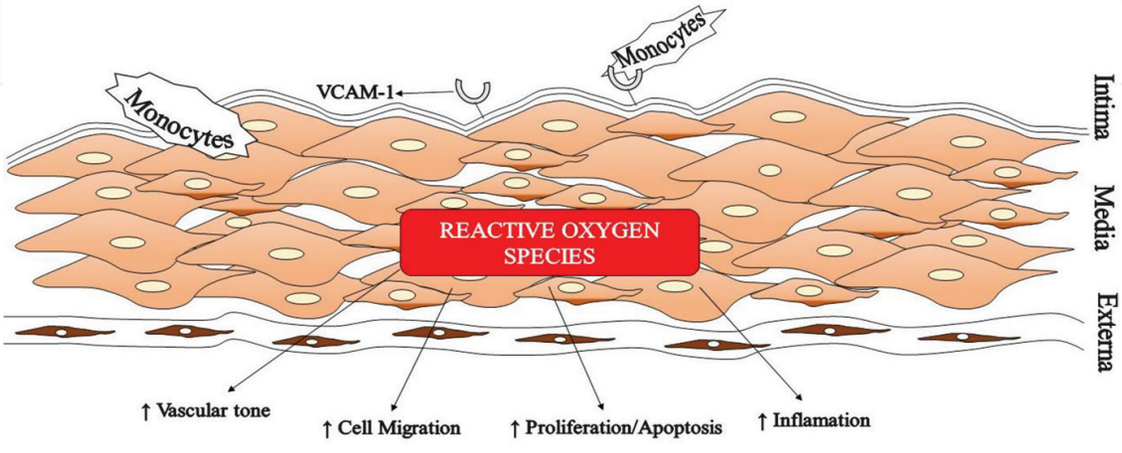

Figure 1. Role of reactive oxygen species in response to an injury.

During vascular injury, when oxidative stress is greatest, there is vessel remodeling, where agonists such as angiotensin II, platelet growth factor, cytokines/chemokines, IL-6 and IL-8, thrombin and endothelin stimulate increased activity of NADPH oxidase and its $p22^{phox}$ domain, increased proliferation, migration and adhesion activity of vascular smooth muscle cells and reduced NO bioavailability [4, 14, 20].

In this sense, it has been observed in diseases, such as hypertension, that in the aorta and mesenteric arteries there is an increase in vascular activation of NADPH oxidase, xanthine oxidase and decoupling of eNOS resulting in an increase in $O_2^{\bullet-}$ generation, whereas levels of glutathione antioxidant and activity of the endotoxin superoxide dismutase (SOD) are reduced [25]. An increase in the local and systemic vascular inflammatory process (C-reactive protein) is also observed [26]. Activation of the renin-angiotensin system stimulates NADPH oxidase activation and production of $O_2^{\bullet-}$ [27]. Vecchione et al. [28] in 2009 have shown that the reduction in endothelium-dependent vasodilation in rat arteries is associated with vascular increase in superoxide production and increased NADPH oxidase activity. However, transgenic mice with overexpression of thioredoxin 2, peroxidase that helps conversion of hydrogen peroxide into water, are resistant to hypertension induced by angiotensin II, oxidative stress and endothelial dysfunction [29]. In this sense, the present chapter aims to present the main vascular diseases, the role of the redox balance and physical exercise, in its prevention.

3. Prevention of vascular diseases

3.1. What is the role of antioxidants?

A vascular inflammation, risk of vascular disease development and oxidative stress have been widely discussed in the literature [30]. In general, oxidative stress and the inflammatory process are closely related to vascular diseases such as atherosclerosis, peripheral obstructive arterial disease, stroke, coronary artery disease and abdominal aneurysm [31].

Vascular diseases are chronic, progressive and multifactorial inflammation in which, at present, the immunological disorder, more precisely inflammatory, is perceived as a factor that plays an important role in the onset and maintenance of diseases [32, 33]. Already, oxidative stress is defined as the state of unbalance without qualifying favoring of oxidants at the expense of antioxidants that culminate in damaging effects on cells and membranes [34]. Oxidants may be referred to as reactive oxygen species, and free radicals such as superoxide ($O_2^{\bullet-}$), peroxynitrite ($ONOO^{\bullet-}$) and hydroxyl ($OH^{\bullet}$), in addition to non-radicals such as hydrogen peroxide (H_2O_2).

Antioxidant defenses consistently protect tissues and body fluids from injury caused by free radicals produced by normal metabolism, disease response or from external sources [15]. For this, they are strategically arranged throughout the cytoplasm, within several organelles, extracellular space and vascular [15].

The first defense mechanism against free radicals is to prevent their formation, mainly by inhibiting chain reactions with iron and copper. A second mechanism is through the interception of free radicals, preventing the attack on the lipids of the cell membrane causing lipid peroxidation, protein amino acids, the double bond of polyunsaturated fatty acids and

DNA bases [18]. Antioxidants obtained from the diet are extremely important in interception. Another mechanism is the repair of the lesions by removing damages of the DNA molecule and the reconstitution of damaged cell membranes [2].

Antioxidant defense mechanisms are grouped into enzymatic systems (are the first to act) and non-enzymatic [17]. Important antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT) and glutathione-dependent enzymes, such as glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), glutathione reductase (GSH) and glutathione synthetase [17].

There are three types of SOD: SOD-1, found in the cytosol and in the nucleus, dependent on zinc and copper; SOD-2, present in the inner mitochondria, dependent on manganese and SOD-3, found in the extracellular medium. All require a transitional redox active metal in the active site to perform the catalytic decomposition of the superoxide anion.

Physiologically, our body adapts daily so that the concentration of antioxidant/antioxidant substances is balanced. However, in pathological conditions, such as in the development and maintenance of vascular diseases, antioxidant defenses are unable to maintain the oxidoreduction balance, causing higher levels of active reactive oxygen species which have the need of interaction with other cells, substances or membranes [34–37].

In a vicious cycle and difficult to break, oxidative stress can generate an inflammatory process and vice versa, so that there is the progression to an inflamed environment being it internal or external to the cell, resulting in an increase in the concentration of adhesion molecules vascular wall, endothelial dysfunction and onset of atherosclerosis, progressing to stroke, peripheral obstructive arterial disease, diabetic foot, coronary artery disease or abdominal aneurysm [34–37].

One of the oxidizing mechanisms that may explain the onset of vascular diseases such as atherosclerosis and peripheral arterial obstructive disease [38, 39] refers to the exacerbated concentrations of endothelin-1 (ET-1). ET-1 is a peptide with pro-inflammatory and pro-oxidant properties commonly secreted when there is damage to the endothelium as a signaling medium for tissue repair mechanisms. ET-1 directly causes increased NADPH activity and consequent increase in the concentration of reactive oxygen species. This is only the beginning of a reaction cascade that leads to an increase in the activity of adhesion molecules in the vascular cell (VCAM-1), with a consequent increase in macrophage and monocyte infiltration, calcium influx and vasoconstriction. Already indirectly, ET-1 participates in the generational process of atherosclerosis since it decreases the vasodilatory property of the arteries considering that there is redistribution of the eNOS to the mitochondria, thus decreasing the NO bioavailability [38]. In **Figure 2**, we observe the above-mentioned effects of ET-1.

For the antioxidant processes of prevention or deceleration of vascular diseases, proteins, enzymes or transmitting gases are involved [39–43]. In view of this, hydrogen sulfide (H_2S), paraoxonase and glutathione peroxidase (GSH-PX) are reported in the literature as the main antioxidant sources capable of preventing or treating vascular diseases, especially atherosclerosis and obstructive arterial disease peripheral [39–43].

H_2S is currently considered the third gas transmitter after NO and carbon monoxide (CO) [40, 41]. It is known that due to its interaction with ion channels [44], second messengers [45–47], post-translational modification [44, 48, 49] and antioxidant defense [50], this compound plays an important role in the prevention of vascular diseases.

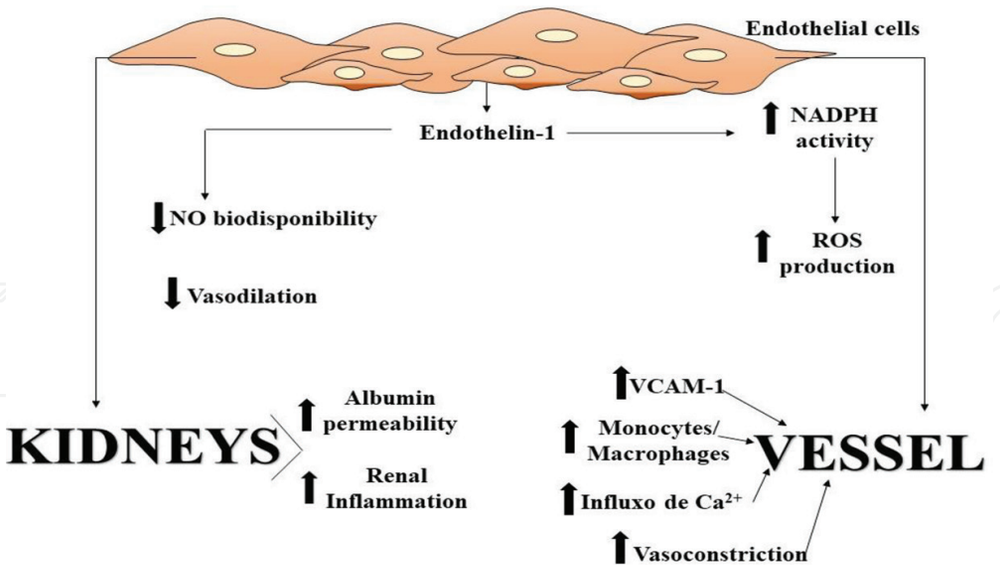

Figure 2. Principal effects of ET-1 on the vascular system and surrounding tissues. VCAM-1, vascular cell adhesion molecule 1.

Vasoprotection promoted by H_2S involves a cascade of effects that culminate in the prevention or deceleration of the atherosclerotic process once it has been initiated. Thus, the effects cascade is composed of: (1) inhibition of atherogenesis by modifying low density lipoprotein (LDL) molecules [51]; (2) inhibition of monocyte aggregation in endothelium [1, 52]; (3) inhibition of proliferation and migration of vascular smooth muscle cells in the atherosclerotic process once it is established in the vascular wall [53, 54]; (4) inhibition of the formation of spongy cells [55]; (5) angiogenesis [56]; (6) improvement of vasorelaxative mechanisms [57]; (7) reduction of vascular wall stiffening or calcification [58] and (8) prevention of platelet aggregation and thrombogenesis [59, 60]. Some of these effects can be visualized in **Figure 3**.

H_2S demonstrates its antioxidant and, consequently, vasoprotective action when it reduces pexonitrite ($ONOO^-$) molecules to nitrous acid ($HSNO_2$) and hydroxyl radical (OH^-) in a chemical representation, proposed by Filipovic et al. [61], as described below:

$$H_2S + ONOO^- \rightarrow HSNO_2 + OH^- \quad (1)$$

Carballal et al. [62] in 2011 proposed that the antioxidant action of H_2S is minimal, or of no physiological significance. However, Filipovic et al. [61] demonstrated that, unlike the initial hypothesis, H_2S has a potent antioxidant and vasoprotective effect and is similar to glutathione.

It is also emphasized that all cells are susceptible to the action of reactive oxygen species, however, the lipid matrix of cell membranes is one of the most affected sites of these active species causing lipid peroxidation [63]. In this sense, although H_2S is able to reduce peroxynitrite molecules, its main and vasoprotective antioxidant action is to reduce lipid hydroperoxides by limiting the pathobiological potential for the development of vascular diseases through lipid peroxidation. The chemical representation can be seen below:

$$LOOH + H_2S + O_2 \rightarrow LOH + SO_2 + H_2O \quad (2)$$

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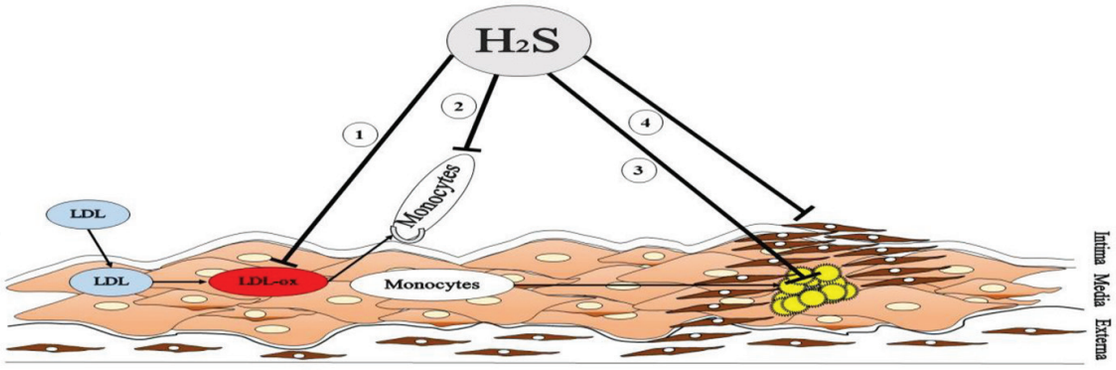

Figure 3. Main effects of hydrogen sulfide (H2S) in vascular system. 1—inhibition oxidation of low density lipoprotein; 2—diminution of monocyte aggregation in tunica intima; 3—inhibition of formation of spongy cells; 4—inhibition of proliferation and migration of vascular smooth muscular cells. The order of these effects was adopted for didactic purposes. LDL, low density lipoprotein; LDL-ox, oxidized low density lipoprotein.

Another proposed antioxidant and vasoprotective mechanism involves the action of paraoxonases, universally accepted proteins as capable of protecting cells from oxidative stress [4]. The paraoxonase family includes paraoxonase-1, 2 and 3 (PON-1, PON-2 and PON-3), with PON-1 and PON-3 being found in plasma and directly associated with high density lipoprotein fractions (HDL) promoting action against the formation of reactive oxygen species, oxidation of low density lipoprotein (LDL) and macrophages leading to blockage or reduction of atherosclerotic lesions [4]. As for PON-2, it is a cell-associated complex, it is not found free in plasma, but in some tissues, especially in the kidneys, in which its antioxidant and anti-inflammatory effects are more evident [42].

In recent years, it has been observed that glutathione peroxidase (GSH-PX), an endogenous antioxidant enzyme, attenuates the development of atherosclerosis in a similar action to H_2S, that is, reducing hydroperoxides [64]. In fact, when blocked, GSH-Px elevates oxidative stress in macrophages and increases ox-LDL activity. In addition, some elements when in non-physiological concentrations decrease GSH-PX activity, such as homocysteine [64]. Porter et al. [65] and Blann et al. [66] demonstrated that volunteers affected by atherosclerotic disease showed a reduction of approximately 29% of the peroxidase activity compared to healthy volunteers, demonstrating that the performance of this enzyme may be more related to prevention than to the repair process after vascular disease.

3.2. Effects of physical activity and physical exercise on oxidative stress: molecular mechanisms and antioxidant effect of physical exercise

The antioxidant defense system has the function of inhibiting and/or reducing the damage caused by the action of free radicals. For this, the mechanisms of action may be the impediment in formation of free radicals or non-radical species (prevention systems), preventing the action of these molecules (sweep systems) or favoring the repair and reconstitution of damaged biological structures [67].

In response to the increased oxygen consumption that occurs in intense physical exercise, the reactive oxygen species (ROS) are generated by activating at least three main mechanisms: mitochondrial, cytoplasmic and favored production by iron and copper ions [68]. At the same time,

physical exercise may also promote adaptation able to reduces the oxidative damage caused by the action of such agents. One such mechanism is the increased expression of the enzyme nitric oxide synthase (eNOS), through phosphorylation of residues by the proto-oncogenesis protein tyrosine kinase (c-SRC) and the activation of eNOS induced by other ROS in response by shear stress; while other mechanisms are triggered by oxidative stress, such as concomitant production of the enzyme superoxide dismutase (SOD), increased glutathione dismutase (GPx) activity, increased NO production induced by adenosine and the NO signaling pathway dependent on cyclic guanosine monophosphate (cGMP) (**Figure 4**). In addition, there is reduced mRNA expression and activity of pro-oxidant enzymes such as NADPH oxidase, angiotensin II receptor type I and increased expression of angiotensin II receptor type II in mammalian arteries [69].

Exercise-induced cardioprotection is probably a multifaceted phenomenon, with potential effector tissues including the myocardium, endothelial cells, inflammatory cells and coronary smooth muscle (CSM) [70]. Several mechanisms explain the positive effects of physical training regarding vascular adaptations [71].

The improvement of endothelial function by physical exercise is dependent on factors such as frequency and magnitude of physical exercise, which can cause shear stress and autoregulation of eNOS expression in endothelial cells [72]. Physical exercise results in increased heart rate and, consequently, increased blood flow and shear stress, which increases the activity of the early oncogenesis protein tyrosine kinase (c-Src) and increased eNOS production.

In the same sense, apparently the adaptations to physical exercise also occur in those vessels where there is no change in perfusion/blood flow during exercise [73]. It is important to highlight that, during exercise, the signal triggering endothelial adaptations in blood vessels perfusing tissues outside actively contracting muscle may not only be increased mean shear stress but also the alteration in shear profiles [74] that result from hemodynamic changes (e.g., heart rate and pressure) during exercise. It is suggested that alterations in the frequency of cyclic shear, and

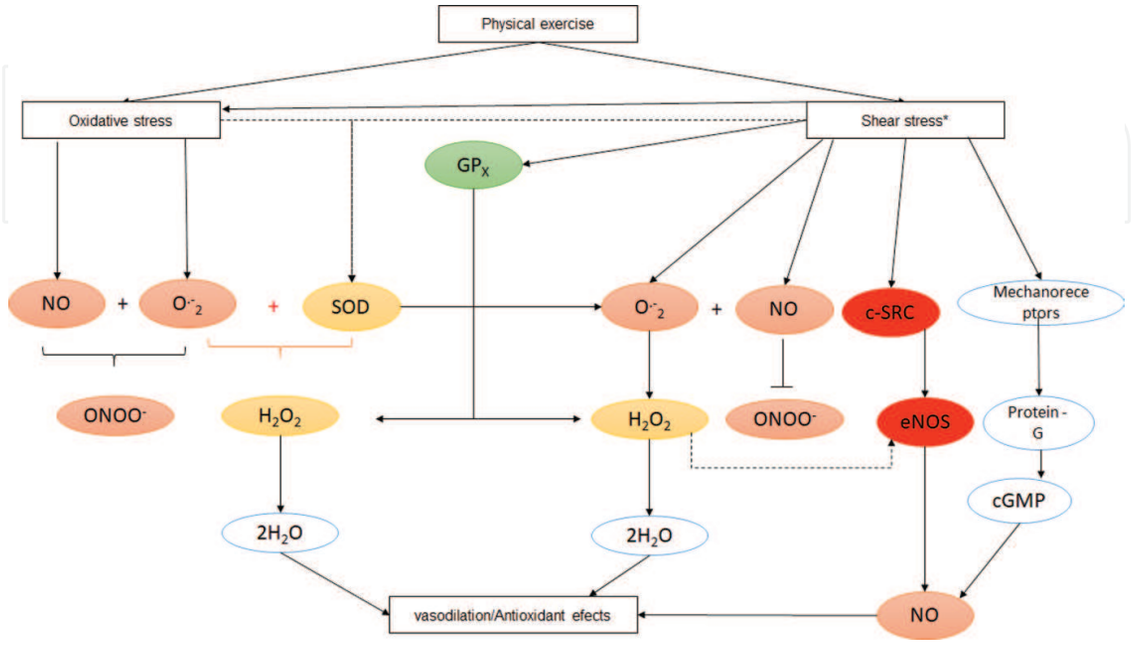

Figure 4. Possible pathways of antioxidant effect occurring as a result of physical exercise.

hence the profile of the shear waveform, may activate highly different signaling pathways than do increases in average shear stress. More research is warranted to isolate the influence of shear patterns from other exercise-related signals to fully evaluate the hypothesis that exercise-induced acute changes in shear waveforms modulate endothelial health systemically with training [75].

Several considerations should be taken into account when viewing the hypothesis that shear stress is an exercise-induced signal for endothelial adaptations in nonworking tissues. Shear stress is directly related to blood flow and viscosity but inversely related to arterial diameter [76]. Given vascular tone (and hence diameter) is constantly regulated by central and local factors (e.g., shear stress), changes in blood flow through a given vessel do not always correspond with alterations in shear stress. In this regard, the extent to which enhanced blood flow or viscosity results in increased shear stress may be dependent on the caliber of the vessel and/or its ability to dilate in response to shear. Contrary to conduit arteries, given the remarkable capacity of arterioles to dilate and constrict, it is unclear to what degree changes in blood flow in the microvasculature translate into alterations in shear [75].

Moreover, shear stress may not be the only hemodynamic exercise-induced signal for systemic endothelial adaptations. Endothelial cells are also exposed to stress from distention of arteries caused by relaxation of smooth muscle in the wall or by increased transmural pressure across the arterial wall. Since endothelial cells are exposed to cyclic distention within each cardiac cycle and during exercise the frequency and magnitude of this distention is augmented, cyclic strain should be considered as a potential exercise-induced signal. In this regard, Awolesi et al. [77] have shown that cyclic strain increases transcription of eNOS in cultured endothelial cells. Similarly, it is demonstrated that distention of isolated arteries is a stimulus for increased expression of the eNOS gene [78].

However, it is important to note that cyclic strain has also been associated with increased production of ROS and expression of adhesion molecules including vascular cell adhesion protein 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), E-selectin and monocyte chemoattractant protein-1 (MCP-1) [79]. Although chronic exposure of endothelial cells increasing cyclic strain (as occurs with hypertension) may produce negative adaptations, based on the classical physiological concept of hormesis, it is plausible that recurring periods of exercise-induced cyclic strain and consequent oxidative stress may increase the tolerance of endothelial cells to withstand subsequent doses and hence stimulate a long-term protective effect [75].

In addition to evidence in the literature that exercise-induced adaptations of the endothelium result from increases in shear stress and/or cyclic strain [80], there is also growing evidence suggesting that changes in chemical signaling (i.e., hormones, cytokines and adipokines) may contribute to systemic benefits of chronic exercise on endothelial cells. Hemodynamic forces may interact with anti-atherogenic mediators such as insulin, adiponectin and IL-6 and with inflammatory cytokines (pro-atherogenic mediators) in the determination of endothelial cell phenotype/function. It appears that substances such as signal remodeling and altered phenotype of endothelial and smooth muscle cells are also released in response to increased shear stress [71].

Regarding the positive adaptations on coronary smooth muscle (CSM) by physical training, some other points need discussion. The beneficial adaptations of physical training can occur both at the sarcoplasmic level (rianodine-sensitive Ca^{2+} channels—RyR-) and sarcolemma (voltage-dependent Ca^{2+} channels and K^{+} channels) [70].

A study by Newcomer et al. [78] demonstrated a postdepolarization, time-dependent decline in the caffeine-releasable SR Ca^{2+} store in cells from exercise-trained animals, but not sedentary control subjects. This phenomenon (termed SR Ca^{2+} unloading) was further determined to result from a slow release of SR Ca^{2+} via RyR. Of noteworth is that the Ca^{2+} released through SR Ca^{2+} unloading seems to be extruded from the cell, not resequestered by the SR or other organelles, and was demonstrated to occur with no increase in bulk Ca_m (myoplasmic free Ca^{2+} concentration) [81]. It was concluded that the net effect of this training-induced SR Ca^{2+} unloading would be a lower SR Ca^{2+} content and an increased subsarcolemmal Ca^{2+} gradient, with no effect on bulk Ca_m. In this way, it was proposed that a lower SR Ca^{2+} content caused by SR Ca^{2+} unloading may contribute to attenuated contractile responses to vasoactive agonists in the exercise trained state because of both diminished SR Ca^{2+} release and increased SR buffering of influx Ca^{2+}.

L-type Ca^{2+} channels are associated with endothelin response, so they may be associated with changes due to physical exercise. It is known that endurance training increases L-type Ca^{2+} channel current density approximately twofold in all three arterial sizes, with no effect on voltage-dependent activation or inactivation characteristics [81]. Additionally, a significant correlation between treadmill endurance time and peak L type Ca^{2+} current density was demonstrated in all three arterial sizes, supporting a direct association between endurance capacity and coronary smooth muscle L-type Ca^{2+} current density. The increase in L-type Ca^{2+} current density could result from an increase in the number of L-type Ca^{2+} channels in the sarcolemmal membrane and/or increased activity of existing channels. Future studies will be necessary to determine the basis for this training-induced adaptation.

Another channels that plays major role in control of smooth muscle tone are K^+ channels, by determining Ca_m, through regulation of membrane potential (V_m) and voltage-gated Ca^{2+} channel activity. Activation of K^+ channels produces membrane hyperpolarization, acting as a negative feedback on voltage-gated Ca^{2+} channel activation to limit contraction or produce vasodilation. Various K^+ channels are expressed in vascular smooth muscle, including large-conductance, Ca^{2+}-activated K^+ channels (K_{Ca}), voltage-dependent K^+ channels (K_v), inward rectifier K^+ channels (K_{ir}) and ATP sensitive K^+ channels (K_{ATP}).

Preliminary research [82] indicates that exercise training increases the relative contribution of both K_{Ca} and K_v channels to regulate basal tone of coronary arteries. Thus, K^+ channels play a greater role in regulating basal coronary tone in the exercise-trained state. Interestingly, it is concluded that stretch is a requisite factor for expression of this training-induced adaptation because K_{Ca} and K_v, currents, determined by voltage-clamp in enzymatically isolated smooth muscle cells, exhibited no difference in current density in cells from exercise trained and sedentary groups.

An intense physical exercise session can generate large amounts of reactive oxygen species, which increases oxidative stress and superoxide production ($O_2^{\bullet -}$) [83]. The superoxide radical is highly reactive, however, it crosses with difficulty the plasma membrane, being converted quickly to hydrogen peroxide (H_2O_2) by the enzyme superoxide dismutase (SOD), whose concentration also increases with physical exercise [84]. Hydrogen peroxide (H_2O_2) is catalyzed by the enzyme glutathione oxidase (GPX), which reduces it to two molecules of water, reducing the oxidant damage of the superoxide radical.

The antioxidant mechanisms induced by shear stress are not yet completely clarified by the literature, so other mechanisms are studied [83]. The mechanism of NO signaling dependent on cyclic

guanosine monophosphate (cGMP), refers to endothelial cells that present mechanoreceptors. These receptors directly activate G-proteins, enzymes and other protein kinases that generate a second messenger, such as cGMP, which leads to vasodilation. Another mechanism increased NO production stimulated by adenosine. Studies have shown that erythrocyte membranes tend to release ATP in response to shear stress and that during the strenuous physical exercise in the cincunflex artery, there is NO production stimulated by adenosine [84].

Despite the exhaustive studies, there are controversies regarding the antioxidant effect of physical exercise related to issues such as eNOS measurement after a training period, eNOS status in the animal and human baseline, and the existence of polymorphisms in the gene promoter of eNOS [83]. It has been shown that eNOS activation induced by shear stress does not depend on the increase of intracellular calcium, but on enzyme phosphorylation [85]. This post-transcription modification occurs at serine 1177 and is mediated by the serine/threonine protein kinase Akt (protein kinase B) [86]. This alters the sensitivity of the enzyme to Ca^{2+}, making its activity maximal at subphysiological concentrations of Ca^{2+}. In the presence of Ca^{2+}/calmodulin, the serine 1177-mediated eNOS phosphorylation occurs in the skeletal and cardiac muscle of rats by the activation of AMPK (activated protein kinase), an enzyme activated by vigorous exercise and ischemic stress [87]. Boo et al. [88] suggested that a coordinated interaction between Akt and PKA may be an important mechanism by regulating eNOS activity in response to shear stress. These results are confirmed in humans with coronary artery disease who underwent 4 weeks of supervised physical exercise training lasting 60 min/day. The increase in the levels of phosphorylation of eNOS-mediated enzyme ser-1177 increased fourfold in the left mammary artery region. This was associated with a two-fold increase in eNOS and a significant increase in endothelium-dependent vasodilation in this artery [89]. Together, the current evidence suggests that phosphorylation induced by shear stress caused by physical exercise contributes to the improvement of endothelium-dependent vasodilation.

The acute effects of aerobic and anaerobic physical exercise are related to the increase of vascular oxidative stress and damages to lipid cells, nucleic acids and the glutathione system (GSH). Very intense physical exercise for 4 weeks may induce increased plasmatic activity of the glutathione peroxidase enzyme (GPx) and decrease of antioxidant substances in the resting plasma, in the pre-exercise period, and mainly, in the post-exercise period and accompanied by a reduced glutathione (GSH) and oxidized glutathione (GSSG, GSH/GSSG) and an increase in plasma thiobarbituric acid reactive substances (TBARS) [90]. Thus, acute periods of exhaustive training may decrease the antioxidative capacity of tissues, such as skeletal muscle and vascular cells [83]. On the other hand, adaptations to moderate exercise appear to occur after a few weeks of training; in fact, endurance training has been shown to be able to reduce oxidative stress, such as lipid peroxidation in membrane erythrocytes, when compared to exhaustive exercise in young men trained [91]. The increase in eNOS expression by physical exercise is followed by increased expression of SOD3 [84]. Self-regulation of SOD by physical exercise not only provides efficient detoxification of superoxide but also reduces the generation of peroxynitrite, a strong oxidant with important pathophysiological effects [92]. While manganese protein levels, superoxide dismutase (SOD2) was not altered, levels of the $p67^{phox}$ protein, a subunit of the pro-oxidant enzyme NADPH oxidase, were reduced by physical training [93]. These observations demonstrate that the antioxidant effects of physical exercise can not only be mediated by increased expression of antioxidant enzymes, but also by reduced expression of pro-oxidant enzymes [83].

Author (date)	Population and/or sample	Characteristics of the intervention*	Frequency and Period of intervention	Main outcomes	Conclusions
Miyazaki et al (2001) [91]	Untrained male	High intensity endurance training-cycle ergometer 60 minutes/session 60r.p.m(15W)/minute	Five times a week for 12 weeks	SOD GPx CAT	↗SOD ↗GPx ↔CAT
de Moffarts et al (2006) [100]	Horses TM: treadmill test RT: run on track	Acute: standard treadmill test (running)	-	SOD GPx GSH GSSG GRR PSH	↔ GPx, SOD, GSSG e GRR As diferenças entre TM e RT foram significantes no E15 para UA, AA e PSH
Wycherley et al(2008) [96]	Overweight and obese patients with type 2 diabetes	Diet alone (D) or diet plus exercise (DE) Walking/jogging exercise 20 to 60minutes/session Intensity: 60% 80% HRmáx	Four to five times a week for 12 weeks	TAS MDA	**D** ↘MDA ↔TAS **DE** ↘MDA ↔TAS
Venojarvi et al (2013) [94]	Middle-aged men	Aerobic Nordic walking (NW) or resistance exercise training (RT) 60 minutes NW (55 -75% FCR) RT (50 -85% 1RM)	Three times a week for 12 weeks	MDA LPO ORAC	**NW** ↔ MDA ↔LPO ↔ORAC **RT** ↔ MDA ↔LPO ↔ORAC
Malardé et al (2014) [101]	Diabetic rats	Endurance training (a treadmill run of 60 min/day, 25 m/min)	Five days a week	SOD GPx ORAC	↔ SOD e GPx, ORAC
Duggan et al (2016) [97]	Women Obese	Moderate- to-vigorous intensity aerobic exercise. 45 minutes 70–85% (HRmáx). Activities of ≥4 METs Exercice Diet + Exercice	Five days a week for 12 moths	FOP F2-isoprostanes Oxidized-LDL	**-Exercice** ↔FOP ↘F2-isoprostanes ↔ Oxidized LDL **-Diet + Exercice** ↗FOP ↘F2-isoprostanes ↘ Oxidized LDL
Seawright et al. (2016) [103]	Male rats	-Increase in intraluminal pressure and shear stress (SS), to mimic two mechanical signals associated with a bout of exercise -90 (P90) or 130 (P130) cmH2O and exposed to no SS (0 dyn/ cm2) or high SS (~65 dyn/cm2) for 1 h	-	L-NNA	-Incubation with L-NNA eliminated flow-induced dilation in Old P130 + SS (soleus muscle feed arteries - SFA)
Chunyan LI et al (2016) [98]	Males Obese adolescents	-Aerobic exercise included jogging, table tennis, badminton, swimming, and aerobics and spinning (exercise training and dietary restriction.) - 60–80% (HRmax)	3 times/day and 6 times/week; 35 min/day for 4 weeks.	MDA SOD GPx	↔ MDA ↗ SOD ↗ GPx
Dantas et al (2016) [95]	Hypertensive elderly women	- Strength training -10 rep. of nine exercises	2 to 3 times/week for 6 weeks.	MDA TAC	↘MDA ↗TAC
Alghadir, Gabr, Al-Eisa (2016) [99]	Healthy older adults	-Moderate aerobic exercise - 45–60 min/day - (60 to 70% of Training heart rate-THR)	24 weeks	MDA TAC	↘MDA ↗TAC
Alaca et al (2018) [102]	Diabetic rats	- Swimming exercise -(CE) Continuous exercise: (30 minutes/day) - (BE) Short bouts of exercise (3x10 minutes/day) - (WWE) Weekend warriors (35+40 minutes/day, 2 days/week).	Five days a week for 6 weeks	MDA	**CE, BR and WWE** ↗MDA

Legend: *Intervention duration/modality, Weekly frequency and session duration and Intensity. Superoxide dismutase, SOD; Glutathione peroxidase, GPx; Glutathione reduced, GSH; Glutathione oxidized, GSSG; Glutathione redox ratio, GRR; Protein thiol, PSH; Catalase, CAT; Total antioxidant status, TAS; Malondialdehyde, MDA; Lipid hydroperoxides, LPO; Absorbance capacity, ORAC; Fluorescent Oxidation Products, FOP; Nitric oxide, NO; Nω-nitro-l-Arginine, L-NNA; Total antioxidant capacity, TAC; ↗, increased; ↘, decreased; ↔, did not have significant changes.

Table 2. Review of articles about effects of physical exercise and oxidative stress in humans and animals.

A review with studies that verified the influence of physical exercise on oxidative stress is presented in **Table 2**. Overall, human studies with interventions ranging from 4 weeks to 12 months, either with strength training [91, 94, 95] or aerobic training of moderate to vigorous intensity [94, 96–99] have demonstrated an improvement in antioxidant capacity by increasing SOD, CAT, GPx, total antioxidant capacity (TAC) and/or decrease of malondialdehyde (MDA). Only one study that demonstrated the acute effect of horse racing did not show significant changes in GPx, SOD, GSSG and glutathione redox ratio (GRR) [100]. In diabetic rats that performed moderate intensity exercise also did not significantly alter SOD, GPx and oxygen radical absorbance capacity (ORAC) [101] or increased MDA [102].

Considering that the acute effects of vigorous physical exercise are related to the increase in oxidative stress, while the chronic effects of training with moderate exercise can favor changes in gene expression and increase of the antioxidant effect, it is possible to speculate that the antioxidant effect of physical exercise is dependent of the occurrence of oxidative stress in an intermittent way [83]. Briefly, physical exercise may, in the medium term (about 3 weeks, for example) increase vascular hydrogen peroxide and, consequently, eNOS expression [83, 87]. It is possible that physical exercise training in the medium term reduces oxidative stress by the measurement of lipid peroxidation in the erythrocyte membrane in response to strenuous exercise in young, untrained males [91]. Furthermore, eNOS activity was shown to be a crucial factor for vascular expression of the antioxidant enzyme SOD3, and 4 weeks of physical training reduced the expression of potentially pro-oxidant proteins, such as NADPH oxidase and type 1 angiotensin II receptor, while the expression of vascular antioxidant proteins such as angiotensin II receptor type 2 is reduced [104]. Additionally, the potentially beneficial effects of exercise and/or regular physical activity as increased eNOS expression is reversible by a sedentary lifestyle as induced by forced physical inactivity [105].

Thus, regular physical exercise becomes beneficial for healthy people and patients with cardiovascular disease. While exercise training may hinder the development of pro-oxidative vascular gene expression associated with endothelial dysfunction in individuals, it corrects and/or improves already established endothelial dysfunction and increased vascular oxidative stress in cardiovascular diseases such as hypertension, diabetes, encephalic stroke, coronary artery disease and heart failure [83, 103, 106].

4. Conclusion

The present chapter demonstrates that the oxidative stress is heavily involved in most of vascular diseases considering your effect for elevated the aggregation of monocytes in endothelium, low density lipoprotein oxidation, proliferation of vascular smooth muscular cell, among others. On the other hand, endogenous enzymes or compounds like glutathione peroxidase and sulfide hydrogen have the antagonistic effects like inhibition of the pathophysiological processes involved in vascular diseases. Therefore, although the physical exercise be able to elevated the concentration of reactive oxygen species after your practice, is be able to promoted the elevation in the production and secretion of antioxidants like superoxide dismutase, resulting in scavenging effects, responsible for the defenses against the development of the atherosclerotic process, present in the most of the vascular diseases can be observed.

Conflict of interest

There is no conflict of interest.

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