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Role of Oxidative Stress in Cardiovascular Diseases

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ABSTRACT

Oxidative stress is defined as an excessive bioavailability of Reactive Oxygen Species (ROS) due to imbalance of generation of ROS and antioxidant defense systems. ROS produced by vascular cells (endothelial cells, vascular smooth muscle cells, and adventitial fibroblasts) are implicated as possible underlying pathogenic mechanism in a progression of cardiovascular diseases such as ischemic heart disease (angina pectoris), atherosclerosis, hyperlipidemia, cardiac arrhythmia and hypertension. Lipid peroxidation is a major oxidative effect in which lipids after combination with oxygen through peroxyl radical formation, leads to lipid hydroperoxidation with membrane disruption and form highly cytotoxic products, leading to cardiovascular diseases mainly ischemic heart diseases like angina pectoris. Another oxidative process is an imbalance of reduced production of NO (Nitric Oxide) or increased production of reactive oxygen species (ROS), mainly by superoxides (O2·) in vascular cells that promotes atherosclerosis and hypertension. In cardiac arrhythmia, cardiac mitochondria and NADPH oxidase are involved. ROS weakly couples cardiac mitochondria under oxidative stress conditions and leads to development of fatal ventricular arrthymia and when ROS oxidize Low Density Lipoprotein to O- LDL (Oxidized LDL) it leads to hyperlipidemia. This review focuses on how oxidative stress play role in promotion of various cardiovascular diseases.

Keywords: Reactive oxygen species; Oxidative stress; Lipid peroxidation; Cardiovascular diseases.

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INTRODUCTION

Oxidative Stress

Oxidative stress in a physiological setting can be defined as an excessive bioavailability of Reactive Oxygen Species (ROS), which is the net result of an imbalance between production and destruction of ROS (with the latter being influenced by antioxidant defences). [1-5] Oxidative stress involves any condition in which oxidant metabolites (e.g., oxygen radicals) can exert their toxic effects due to increased production or altered cellular mechanisms of protection. The effects of oxidative stress can be evidenced by cellular accumulation of peroxides (e.g., lipid peroxides) or by-products, such as malondialdehyde (MDA), and by oxidized glutathione. Oxygen itself has a radical nature and can be called a diradical, but it does not exert any major reactivity. [6, 7]

Reactive Oxygen Species (ROS)

Despite the fundamental biological role of oxygen as an efficient producer of energy, an altered form of oxygen – with modifications in key chemical bonds may potentially result in alterations in cellular structure and function. Reactive oxygen species (ROS) include both free radicals (that typically have an oxygen- or nitrogen-based unpaired electron in their outer orbitals) and other species (eg, hydrogen peroxide) that act as oxidants. The mitochondria and cellular membrane oxidases (eg, NADPH oxidase) are major sources of ROS. [8] Oxidative stress is one of the most potent inductors of endothelial dysfunction and is involved at all stages of atherosclerotic plaque evolution. Oxidative modification of NO not only leads to reduced bioavailability but also produces the toxic oxidant peroxynitrite, which further aggravates the imbalance of protective and aggressive factors. As oxidative stress centrally contributes to atherothrombosis so sustained efforts have been undertaken to characterize and identify the biomarkers that enable detection of oxidative stress and allow improved risk management. [9 – 11]

ROS are formed by different generating systems, whereby they exert their physiologic actions. Oxygen radicals, moreover, are involved as key intermediates in metabolic reactions in both spontaneous and enzymatically driven physiological processes .The bulk of oxygen reduction in most cells, such as in the heart, occurs by the mitochondrial cytochrome oxidase pathway.NO radicals are also observed in granulocytes and macrophages where they react with superoxide anion to form hydroxyl radical. Phagocytic cells also synthesize hypochlorous acid through oxidation of chloride ions by hydrogen peroxide and the reaction is catalyzed by myeloperoxidase. These ROS are extremely important for the phagocytic function. [6, 12, 13]

Reactive oxygen species (ROS) can play a role in cell signalling. Oxidative stress can activate numerous intracellular signalling pathways via ROS-mediated modulation of various enzymes and critical transcription factors activated in response to an increase in ROS or oxidative damage which travel from the cytoplasm to the nucleus within a cell and bind to promoter regions of particular genes. These stress-activated pathways have a significant impact

on gene expression, which will ultimately affect the fate of a cell (e.g., apoptosis, proliferation, and cytokines). The balance between ROS production, cellular antioxidant defences, activation of stress-related signalling pathways, and the production of various gene products, as well as the effect of aging on these processes, will determine whether a cell exposed to an increase in ROS will be destined for survival or death. [1]

Cardiovascular Diseases

Cardiovascular diseases are the leading cause of death globally. Considerable progress has been made in the past years to define, identify, and modify risk factors for cardiovascular disease (e.g., hypertension, dyslipidemia, obesity, type 2 diabetes, cigarette smoking, physical inactivity and oxidative stress). Major cardiovascular diseases includes ischemic heart disease mainly angina pectoris, atherosclerosis, hyperlipidemia, cardiac arrthymia and hypertension. [14]

Oxidative Stress in Progress of Cardiovascular Disease

Oxidative stress has a major role in development of cardiovascular diseases (figure1). The production of reactive oxygen species and lipid peroxidation plays a significant role in the progression of cardiovascular diseases. Oxidative stress also plays a central role in the pathogenesis of atherosclerosis, cancer, aging and other chronic diseases. Ischemic heart disease is probably the human condition in which the role of oxidative stress has been investigated in more detail. Reactive oxygen species and consequent expression of oxidative damage have been demonstrated during post-ischemic reperfusion in humans and the protective role of antioxidants has been validated in several experimental studies addressing the pathophysiology of acute ischemia. [6]

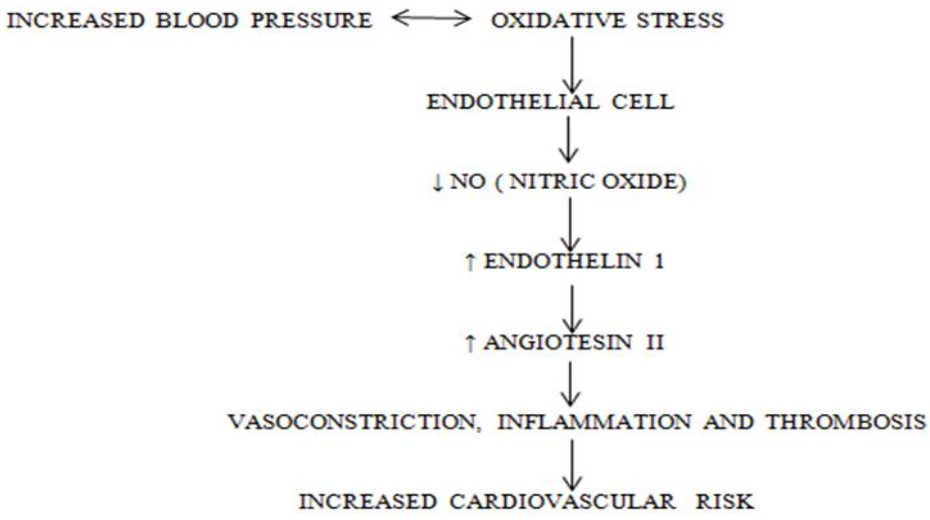

Figure 1. Oxidative stress and Cardiovascular disease.

Oxidative Stress in Ischemic Heart Disease or Coronary Artery Disease (CAD)

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Angina Pectoris

An important indicator of CAD is Angina Pectoris which can be defined as a syndrome of substernal chest discomfort, with a characteristic quality and duration, provoked by exertion or emotional stress, and is relieved by rest or administration of nitroglycerine. The main pathologic abnormality in stable angina is the presence of an intimal plaque within the coronary artery lumen that limits flow to a portion of the left ventricle. Inflammatory processes are a major driving force of atherosclerosis and are involved in the disruption of plaques and the resulting thrombosis. Anginal pain is most likely mediated by adenosine released from ischemic myocardium that activates sensory nerves in the heart. [15]

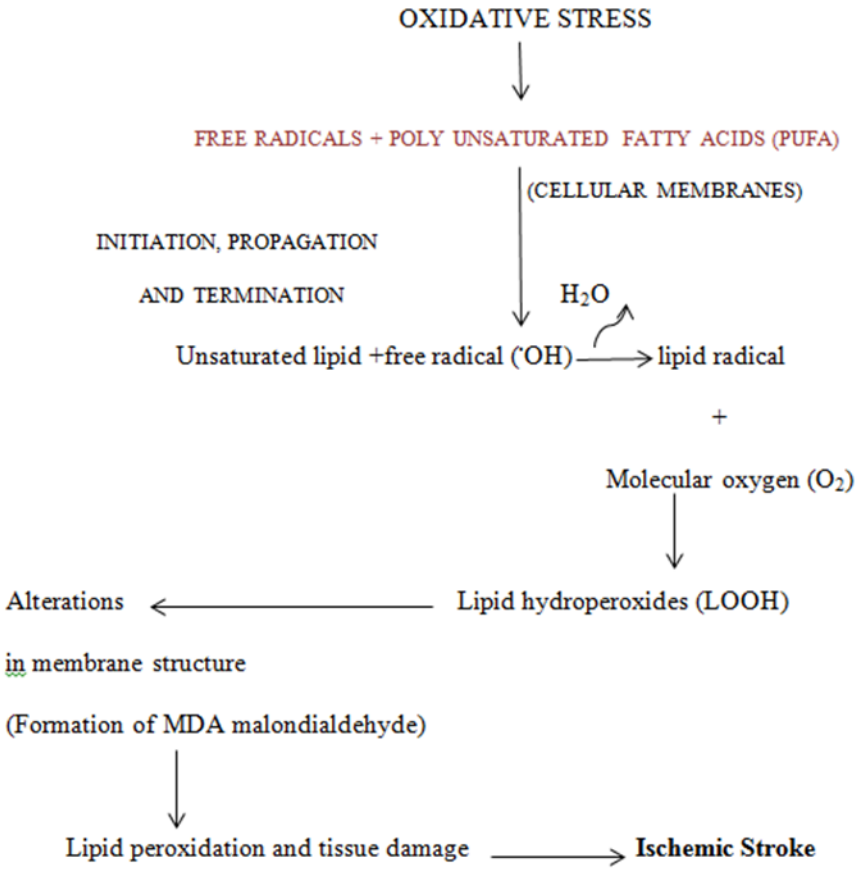

Figure 2. **ROS induced Lipid peroxidation**

ROS mediate a wide range of pathological processes in the endothelium, smooth muscle cells, and inflammatory cells. Disturbed lipid profile or Lipid peroxidation is one of the most important and potent risk factors in ischemic heart disease (IHD) as shown in figure 2. It has been demonstrated that raised oxidative stress promotes several undesirable pathways including the formation of oxidized LDL (O-LDL) and oxidized cholesterol which encourages cholesterol accumulation in arterial tissues. [16] Lipid peroxidation is a form of oxidative damage in cell membranes determined as free radicals reacting with polyunsaturated fatty acids (PUFAs) which are abundant in cellular membranes and also in low-density lipoproteins

(LDL). They comprise mainly n-3 and n-6 PUFAs which are sensitive to free radicals. The interaction of ROS and lipids consists of three different steps: initiation, propagation and termination. In the initiation phase, conjugated dienes are formed as hydrogen atom is abstracted from a lipid methylene group and absorb ultraviolet light at 230–235 n. Then in propagation and termination phase, the molecular oxygen reacts with lipid radical and thus lipid hydroperoxides (LOOH) are formed. LOOH may cause alterations in membrane structure and function, leading to the formation of malondialdehyde (MDA) causing alterations in membrane structure which ultimately lead to ischemic heart disease (IHD). [17 – 20]

Unstable angina pectoris often leads to acute myocardial infarction. Lipid peroxidation is thought to be causally related to chronic and acute events in atherosclerosis and coronary artery disease. [21] Unstable angina pectoris (UAP) and acute myocardial infarction are hallmarks of acute coronary syndromes. [22–24] Underlying pathophysiological mechanisms of UAP are multifactorial, and include plaque rupture and consecutive thrombus formation as well as vasospasm. [25] There is increasing evidence that oxidatively modified lipoproteins play a key role in the pathogenesis of atherosclerosis and that antioxidants may prevent atherosclerosis by inhibiting lipid peroxidation. [26–30]

Atherosclerosis

Atherosclerosis is a leading cause of coronary heart disease and stroke. [31] Oxidized low-density lipoprotein (ox-LDL) is an independent marker of the progression of atherosclerosis. [32 -35] The pathophysiology relates to macrophage ingestion of excess ox-LDL and the formation of foam cells, triggering atherosclerosis. [36] Both high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol contain the antioxidant enzyme glutathione peroxidase embedded in the lipoprotein, and a continuous supply of glutathione (GSH) is needed to prevent the oxidation of HDL and LDL cholesterol. [37]

Oxidative Stress and Atherosclerosis

The common risk factors for atherosclerosis increase production of reactive oxygen species (ROS) by endothelial, vascular smooth muscle, and adventitial cells. These ROS initiate processes involved in atherogenesis through several important enzyme systems, including xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and nitric oxide synthase. The signalling cascade for activation of the NAD (P) H oxidase by angiotensin II has recently been elucidated. [10]

According to the theory of oxidative stress, atherosclerosis is the result of the oxidative modification of low density lipoproteins (LDL) in the arterial wall by reactive oxygen species (ROS). The common risk factors for atherosclerosis increase the risk of the production of free ROS, not only from the endothelial cells, but also from the smooth muscle cells and the adventitial cells. [38-39]The main sources of oxidative substances and ROS in atherosclerotic vessels are macrophages and smooth muscle cells .The production of free oxidative radicals is believed to induce endothelial dysfunction, an initial step of atherogenesis. [40] ROS depending

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on the intensity of their production cause: a) oxidation of LDL to form oxidized- LDL (varying from mildly oxidized LDL to highly oxidized LDL). The oxidized-LDL loses its inconsistent character for its movement between blood and vascular cells and gets accumulated in the cells forming foam cells which ultimately are converted into fatty streaks (figure 3), forming integral part of atheromatous plaques; b) endothelial dysfunction; c) exaggerated platelet aggregation and adhesion and d) dyslipidemia and hypertension. [16]

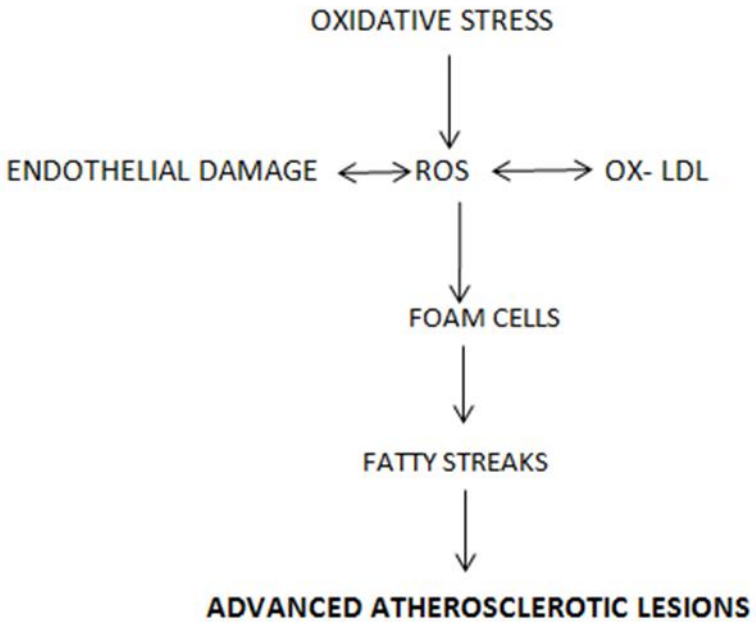

Figure 3. Interaction of Oxidative stress and Atheromatosis

Interaction of NO and ROS in the Vessel Wall

The ROS group includes superoxide anion, hydroxyl radical and peroxynitrite. Although hydrogen peroxide (H_2O_2) and hypochlorous acid are not free radicals, they also have oxidative properties, especially in the presence of metal anions. Hydrogen peroxide (H_2O_2), which is more stable, plays a principal role and can be diffused easily and converted into hydroxyl radicals of high efficacy in the presence of metal ions (e.g. Fe2+). [41] The interaction with NO leads to the production of peroxynitrite, a substance less effective for the activation of guanylyl cyclase. Therefore, NO bioavailability becomes remarkably reduced. In stages of advanced atherosclerosis, despite the fact that NO production remains the same, decomposition of NO from ROS is increased. [42]

DNA Damage in Atherosclerosis

Oxidative damage to DNA occurs spontaneously from ROS produced during normal metabolic events in all organisms, and can be induced by environmental agents, some of which

are linked to atherogenesis. ROS (Reactive Oxygen Species) has also effect on mtDNA (Mitochondrial DNA) damage in vascular cells. [43-46] The mtDNA (Mitochondrial DNA) damage occurs in vascular cells exposed to atherogenic stimuli in animal models of atherosclerosis. This appeared as a correlation between mtDNA damage and human atherosclerosis. It is possible that a measurement of oxidative DNA damage (such as measurement of mtDNA damage) may reflect oxidative stress and could be used to measure the response to antioxidant therapy. [43]

Hyperlipidemia and Oxidative Stress

Hypercholesterolemia or high cholesterol is a disorder that causes severe elevations in total serum cholesterol and low-density lipoprotein cholesterol. The normal range for total blood cholesterol is between 140 and 200 mg per decilitre (mg/dL) of blood. There are two types of cholesterol -- HDL (high density lipoproteins, or "good" cholesterol) and LDL (low density lipoproteins, or "bad" cholesterol). The amount of HDL relative to LDL is considered a more important indicator of heart failure and stroke. In hyperlipoproteinemia, cell membranes and the extracellular matrix can change their lipid composition and expected to more free radical generation. [47] Hypercholesterolemia has been reported to increase superoxide anion production in endothelial cells. [48] Oxidative modification of lipids is able to lead to a self-perpetuating cycle of oxygen radical generation and modification of proteins. [49] Reactive oxygen species (ROS) oxidize low-density lipoprotein (LDL), and contribute to the formation of foam cells in arterial walls during the early stages of atherosclerosis, and the oxidized LDL further enhances the generation of ROS by polymorphonuclear leukocytes (PMN). [50-54] NADPH oxidase is the primary source for ROS generated by PMN, and protein kinase C (PKC) plays a critical role in activation of the enzyme, which further contributes to hyperlipidemia. Statins reduced both oxidative stress and smooth muscle cell migration via PKC. [55-59]

Arrhythmia

Cardiac arrhythmia is any abnormality or perturbation in the normal activation sequence of the myocardium. The sinus node, displaying properties of automaticity, spontaneously depolarizes, sending a depolarization wave over the atrium, depolarizing the atrioventricular (AV) node, propagating over the His-Purkinje system, and depolarizing the ventricle in systematic fashion. There are different types of cardiac arrhythmias. The normal rhythm of the heart, so called normal sinus rhythm, can be disturbed through failure of automaticity, or through overactivity, such as inappropriate sinus tachycardia. In general, the cardiac arrhythmias depend on the presence or absence of structural heart disease. The most common example of benign arrhythmia is atrial fibrillation.

Oxidative Stress and Arrhythmia

Cardiac mitochondria are involved in the genesis of arrhythmia and play a role in altering the heart's electrical function by introducing heterogeneity into the cardiac action potential. ROS weakly couples mitochondria under normal conditions but becomes a strong

coupling messenger under oxidative stress conditions due to which the mitochondrial network attains critical stage. This critical stage of mitochondria is achieved when a threshold of ROS is overcome and a certain density of mitochondria forms a cluster covering whole cell. This triggers a wide collapse of mitochondrial membrane potential leads to energetic failure, temporal and regional alterations in action potential (AP), development of zones of impaired conduction in the myocardium and ultimately a fatal ventricular arrhythmia. [60]

NOX (NADPH Oxidase) in Cardiac Arrthymia

There is evidence that oxidative processes have a major influence on the expression of Atrial Fibrillation (AF). [61-62] Reactive oxygen species (ROS) are known to cause AF and antioxidant and statin therapies associated with the modulation of ROS, redox and improved nitric oxide regulation modulate the expression of AF. Nox-2 is present in human cardiac myocytes, and that AF appears to be associated with increased activation. Atrial stretch and increased angiotensin II could be initiating factors for Nox activation during the early stages of AF. Nox oxidase activation and NOS uncoupling could be important factors in the initiation of mitochondrial ROS generation. [63] NADPH oxidase family of enzymes plays a central role in generation of reactive oxygen species (ROS) in arrthymia. [64-66] It catalyzes the formation of superoxide anion (O2•-) responsible for respiratory burst by transferring an electron to molecular oxygen to generate millimolar concentrations of superoxide anion ($O^{2\ \bullet}$) in the extracellular or intra-phagosomic spaces. The main NADPH oxidase subunit (Nox) has multiple isoforms; Nox_2 is the most common form in neutrophils and is also present in myocardium. [67-68] Superoxide anion is reduced to hydrogen peroxide (H_2O_2) by superoxide dismutases (SODs). While not a free radical, hydrogen peroxide is an oxidant capable of initiating lipid peroxidation chain reaction and in the presence of transitional metals, hydrogen peroxide is decomposed into hydroxyl radical ($OH^{\bullet}$), one of the most reactive of ROS, [69] and this could contribute to the observations made in atrial tissue from AF patients. Oxidative damage in human AF alters myofibrillar energetics, and the oscillations in mitochondrial energetics activated by ROS to cause synchronized changes in action potential duration, a process which potentially contributes to arrhythmias during ischemia-reperfusion injury. Thus, mitochondrial ROS could potentially be a contributing factor to persistent arrhythmias in the atria. [61]

Hypertension

Hypertension is one of the most important risk factors for cardiovascular disease and is associated with coronary heart disease, cerebrovascular disease and renal disease therefore is a major cause of morbidity and mortality, hence become an increasingly important contributor to the global health burden. [70-71] Hypertension may be categorized as either essential or secondary. Essential hypertension is diagnosed in the absence of an identifiable secondary cause (Essential hypertension is also called primary or idiopathic hypertension). Genetic factors appear to play a major role in the occurrence of essential hypertension, while secondary hypertension is associated with an underlying disease, which may be renal, neurologic, or endocrine in origin; examples of such diseases glomerulo nephritis , atherosclerosis of blood vessels in the brain, and Cushing syndrome (hyperactivity of the adrenal glands). [72-73]

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Oxidative Stress and Hypertension

Activation of the renin angiotensin system is critically involved in the pathogenesis of hypertension and atherosclerosis. [74-76] A major mechanism whereby angiotensin II, the principal effector peptide of the renin-angiotensin system, may contribute to vascular pathology is stimulation of superoxide ($O^{2\cdot}$) formation in vascular cells. [76] Treatment with liposome-encapsulated superoxide dismutase (SOD) or the membrane-permeable SOD diminishes the increase in blood pressure caused by angiotensin II administration, suggesting that stimulation of ($O^{2\cdot}$) formation is critically involved in the blood pressure response to angiotensin II. One source of ($O^{2\cdot}$) that is stimulated by angiotensin II in endothelial and vascular smooth muscle cells is the nicotinamide adenine dinucleotide phosphate (NAD [P] H) oxidase. Superoxides rapidly inactivate endothelium-derived nitric oxide (NO), the most important endogenous vasodilator, thereby promoting vasoconstriction. [77] Oxidative stress may account for endothelial dysfunction, but it is unknown whether this abnormality is a primary event or a consequence of increased blood pressure. [76] Serum lipid peroxides or ROS released from isolated vessels are increased in essential hypertensive patients or hypertensive animal models. It has been reported that such antioxidants as vitamin E, glutathione peroxidase, or superoxide dismutase (SOD) are decreased in essential hypertensives. Although ROS thus generated oxidize a variety of substances, the most important mechanism in blood pressure regulation is ROS' reaction with endothelium-released NO and the ensuing inactivation of NO. NO also directly inhibits cell proliferation or LDL oxidation. As NO production decreases, therefore, it is expected that vasoconstriction will occur and leads to hypertension. [78-79]

CONCLUSION

Reactive oxygen species (ROS) are involved in the cell growth, differentiation, progression, and death. Low concentrations of ROS may be beneficial and higher amounts of ROS play a role in a number of human disease states like cardiovascular diseases, aging, cancer etc. Deficiency of an antioxidant nutrient can severely hamper the antioxidant system and impair exercise induced oxidative stress and tissue damage. A fine balance between free radicals and a variety of endogenous antioxidants is believed to be existing. The "oxidative stress theory" holds that a progressive and irreversible accumulation of oxidative damage caused by ROS impacts on critical aspects of the aging process and contributes to impaired physiological function, increased incidence of disease, and a reduction in life span. Emerging evidence suggests that reactive oxygen species (ROS) such as nitric oxide (NO), superoxide (O^{2-}), and peroxynitrite (OONO) undergo reactions according to the oxidative stress of the environment and mediate numerous effects in the cardiovascular system promoting various disease like hypertension, angina, arrthymia etc. ROS can also damage ETC (Electron transport Chain) components and mitochondrial DNA, leading to further increases in intracellular ROS levels and a decline in mitochondrial function. Disturbed lipid profile or Lipid peroxidation due to ROS is one of the most important and potent risk factors, which cause alterations in membrane structure and function and lead to ischemic heart disease (IHD) like angina pectoris.

The ROS group includes superoxide anion, hydroxyl radical and peroxynitrite, so interaction with NO leads to the production of peroxynitrite, a substance less effective for the activation of guanylyl cyclase. Therefore decomposition of NO from ROS is increased. NO directly inhibits cell proliferation or LDL oxidation. As NO production decreases, therefore, it is expected that vasoconstriction will occur and leads to atherosclerosis and hypertension. NADPH oxidase family of enzymes plays a central role in generation of reactive oxygen species (ROS) in cardiac arrthymia by catalyzing the formation of superoxide anion ($O^{2\bullet-}$) which cause synchronized changes in action potential duration, a process which potentially contributes to arrhythmias. Thus, mitochondrial ROS could potentially be a contributing factor to persistent cardiovascular disorders. Thus, attenuation of oxidative stress can be a potential mechanism in management of cardiovascular disorders and antioxidant therapy may prove beneficial in combating cardiovascular disorders.

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