IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 11 Ser.5 (November. 2023), PP 45-52
www.iosrjournals.org

"Oxidative-Nitrosative Stress"- Atherosclerotic Coronary Artery Disease Promoter

Reshma Gopan M[1], Deepika Chandrasekaran[2], Dinesh Roy[3]
[1]*Research Scholar, Meenakshi University, Chennai, India.*
[2]*Department of Physiology, Meenakshi Medical College Hospital and Research Institute, Kanchipuram, India.*
[3]*CEO & Senior Cytogeneticist, Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, India.*

Abstract
Coronary artery disease (CAD) is one of the most important cardiovascular diseases affecting people worldwide. Any species which contains unpaired electrons and is capable of independent existence is called a free radical. When the creation of oxygen- or nitrogen-containing free radicals or reaction products of these two moieties exceeds the antioxidant capacity to scavenge such species, Oxidative and Nitrosative stress occur. An increasing body of research has demonstrated that the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in pathophysiologic settings has a substantial impact on the onset and progression of CAD. P53 is a tumor suppressor protein that plays a role in regulating cell growth and has a well-established role in carcinogenesis. It may also play a role in CAD by modulating smooth muscle cell proliferation (a characteristic of atherogenesis). This review focuses on the mechanisms underlying ROS & RNS formation, the impact of p53 gene polymorphism, their contribution to endothelial dysfunction and atherosclerosis, methods for their detection, and therapeutic approaches for the management of CAD that target the sources of oxygen and nitrogen- derived free radicals. The information produced by this review seeks to enhance our knowledge of the mechanisms behind cardiovascular problems caused by free radicals. Identifying genetic variations that increase the risk of atherosclerosis can lead to more effective prevention, diagnosis, treatment, and genetic counseling in an important area of cardiology.

Keywords: *Atherosclerosis; Coronary Artery Disease; Nitrosative stress; Oxidative stress; p53 gene polymorphism*

Date of Submission: 13-11-2023 Date of Acceptance: 23-11-2023

I.INTRODUCTION

Coronary artery disease (CAD) is a complex multifactorial phenomenon caused due to the blockage in coronary arteries, resulting in inadequate supply of blood and oxygen to Myocardium. This disease has proven to be a leading cause of death in both developed and developing countries(1). This is a chronic, mostly progressive pathological process with predominant serious prognosis. Despite the development of pharmacological and nonpharmacological interventions, 33% of the men and 43% of the women die within 5 years after myocardial infarction (MI)(2).Therefore, a novel therapeutic approach against coronary heart disease is awaited.

Reactive Oxygen Species (ROS) are by- products of various oxidative physiological and biochemical processes, which plays significant role in both cardiac physiology and pathology. Recent studies have reported that overproduction of ROS can cause myocardial infarction, atherosclerosis, and diabetes(3).

Reactive Nitrogen Species (RNS) are generated by the enzymatic activity of inducible nitric oxide synthase (iNOS), which is upregulated in response to various stimuli, including inflammation and oxidative stress.RNS, in particular, have been shown to play a critical role in the pathogenesis of CAD.

The effects of ROS/RNS on cellular structures, such as mitochondria, increase the production of free radicals, and increase intracellular levels of oxidative stress. This vicious cycle induces functional and structural adaptations that promote a faster progression of heart failure(4). Mitochondrial dysfunction has been repeatedly detected in CAD and plays a pivotal role in the generation of ROS/RNS. The p53 gene, which is a tumor suppressor gene, is involved in the regulation of cell cycle arrest, DNA repair, and apoptosis in response to cellular stress, including oxidative stress. The p53 gene, also plays an important role in the pathogenesis of CAD.

Therefore, there is a need for further research to investigate the role of RNS, ROS, and p53 gene polymorphisms in the pathogenesis of CAD. Such research may help to identify new therapeutic targets for the prevention and treatment of this devastating disease.

In this review, we will first detail the physiological role of ROS/RNS production in the heart and the vessels. Then, we will investigate the impact of Oxidative-Nitrosative stress in CAD. In the last part of this review, we will detail the role of TP53 and analyse the association between p53 gene polymorphism and susceptibility to CAD. The information exposed in this review might be useful for the future proposal of anti-NSS therapies.

II.OXIDATIVE STRESS

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of Reactive Oxygen Species (ROS) in cells and tissues and the ability of a biological system (antioxidants) to detoxify these reactive products.

Oxidative stress is now considered a new risk factor responsible for the development of CAD that affects the onset, prognosis, quality of life,and survival of patients[5].

Reactive Oxygen Species (ROS)

ROS are the products of the normal cellular aerobic metabolism generated during the reduction of oxygen[6]. ROS can be classified into two groups of compounds namely; radicals and non-radicals. The examples for the radicals include Superoxide ($^{\bullet}O^{-}$), Oxygen radical ($O^{\bullet\bullet}$), Hydroxyl ($OH^{\bullet}$), Alkoxyradical ($RO^{\bullet}$), Peroxyl radical ($ROO^{\bullet}$)[7]. The high reactivity of these radicals is due to the presence of one unpaired electron which tends to donate it or to obtain another electron to attain stability[8]. The non-radical species include hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hypobromous acid (HOBr), ozone (O_3), singlet oxygen ($^1O_2$) [9]. These non-radical species are not free radicals but can easily lead to free radical reactions in living organisms[10]. 2

2

Sources of ROS

The reactive oxygen species (ROS) comes from both endogenous and exogenous sources.

Endogenous sources of ROS

ROS production by cytosol: Several soluble cell components, including thiols, hydroquinones, catecholamines, and flavins, can contribute to intracellular ROS production as they are able to undergo redox reactions

ROS production by mitochondria: The primary ROS generated within mitochondria by univalent autooxidation of electron carriers is $O2^{\bullet-}$ [11], which is converted by mitochondrial SOD into H_2O_2, which can be turned into $^{\bullet}OH$ radical via the Fenton reaction:

$H_2O_2 + Fe^{2+} \rightarrow {}^{\bullet}OH + OH^{-} + Fe^{3+}$

The main sites involved in mitochondrial ROS production are localized at Complexes I and III (12)

ROS production by peroxisomes: During fatty acid β- and α-oxidation, amino acid and glyoxylate metabolism, and synthesis of lipidic compounds[13] and most enzymes catalyzing these processes produce ROS during their activity[14]

Table 1: ROS producing enzymes in peroxisomes

Enzyme	Substrate	ROS
Acyl CoA-oxidases (enzymes of β-oxidation)	Fatty acids	H_2O_2
D-amino acid oxidase	D-proline	H_2O_2
L-α-hydroxy oxidase	Glycolate	H_2O_2
Urate oxidase	Uric acid	H_2O_2
D-aspartate oxidase	D-aspartate	H_2O_2
Xanthine oxidase	Xanthine	$O_2^{\bullet-}$, H_2O_2

Note: Adapted from Free Radicals: Properties, Sources, Targets, and Their Implication in Various Diseases, by Alugoju Phaniendra. et al., 2015 "Ind J Clin Biochem", 30(1):11–26

ROS production by Endoplasmic Reticulum: Smooth endoplasmic reticulum presents a chain of electron transport, constituted by two systems devoted to xenobiotic metabolism and introduction of double bonds in fatty acids, which are also able to produce ROS. Another microsomal system, which shares this ability, provides oxidative protein folding[15]

ROS production by Plasma membrane: Plasma membrane is a key site of free radical reactions because it is generally exposed to an oxidizing environment. Free radicals can be produced during the conversion of arachidonic acid into products, such as prostaglandins, thromboxanes, and leukotrienes, by membrane associated

enzymes such as lipoxygenase and cyclooxygenase[16] . Such enzymes metabolize arachidonic acid released from membrane phospholipids via phospholipase A2 activity and generate ROS as by-products during arachidonic acid oxidation[15]

Other endogenous sources: include prostaglandin synthesis, auto-oxidation of adrenalin, phagocytic cells, reduced riboflavin, $FMNH_2$, $FADH_2$, immune cell activation, inflammation, mental stress, excessive exercise, infection, cancer, aging, ischemia etc (17).

Although all these sources contribute to the overall oxidative burden, the vast majority of cellular ROS (approximately 90%) come from mitochondria due to oxidativephosphorylation[18].

Exogenous sources of ROS

Includes alcohol, air and water pollution, tobacco, heavy metals (Fe, Cu, Co, Cr), transition metals (Cd, Hg, Pb, As), industrial solvents, pesticides, high temperature, ultraviolet light, cooking (smoked meat, used oil, fat), Drugs (Paracetamol, Ethanol, Halothene etc) [19].

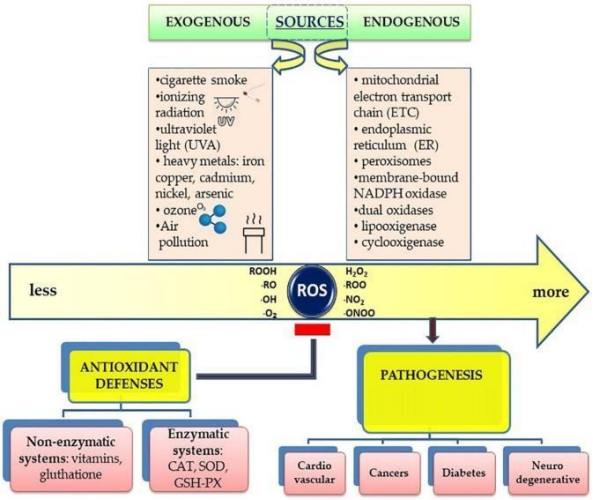


Figure 1: Schematic presentation of ROS sources. Adapted from –Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Disease", by Mehdi Sharifi-Rad, et al., 2020, Frontiers in Physiology"

Physiological roles of ROS

ROS are renowned for their capacity to be both destructive and beneficial. At moderate or low levels ROS have beneficial effects and are involved in various physiological functions like immune function, in a number of cellular signaling pathways, in mitogenic response and in redox regulation[20,21].

At physiological level, besides their role destructing pathogens in the immune defense against external insults[22]. or the synthesis of cellular structures like protein complexes, [23]. ROS function as redox messengers (second messengers). Cells can generate ROS constitutively and exogenously, and use them for intracellular signaling and for stimulating redox-sensitive signaling pathways to modify the cellular content of the cytoprotective regulatory proteins.[24,25]. Thus, ROS control pro-inflammatory signaling, pro-fibrotic signaling, cell proliferation, apoptosis and a range of other biological processes without triggering a requirement for macromolecular damage [26]. In fact, the ROS-mediated redox messenger activity is thought to be larger than the ROS-mediated macromolecular damage activity [27].

ROS plays a key role in cell proliferation and survival in response to growth factor, hormone, and cytokine stimulation[28]. Otherfunctions of ROS include their role in mitoptosis[29] and autophagy[30]. Moreover,

there is a cross-talk between ROS and Ca^{2+}[24]. Multiple evidences show that intracellular Ca^{2+} modulates ROS generation and clearance processes and thereby shift the redox state from oxidized to reduced, and vice versa[31,32].

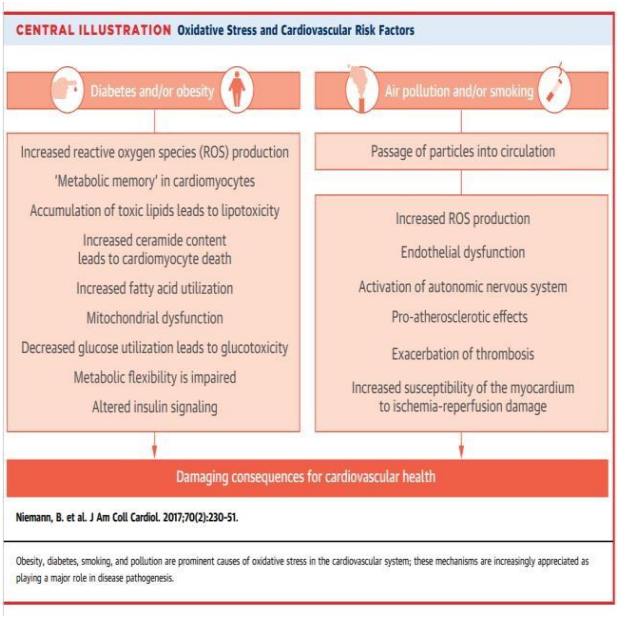
Pathological Roles of ROS in cardiactissue

Increased production of ROS that exceeds endogenous antioxidant defense mechanisms causes oxidizing of DNA, proteins, carbohydrates, lipids, and other biological macromolecules, leading to oxidative stress[33]. Conditions of excessive cell stress, secondary to neurohormonal stimulation and/or a systemic pro-inflammatory state, concur to alter the redox intracellular balance, increasing production of oxidant species and hampering antioxidant defences[34]. This produces detrimental effects on the cellular functions that might

contribute to CAD.

Mitochondrial dysfunction is a hallmark of CAD, and markers of both oxidative stress and inflammation are enhanced in CAD, with prognostic significance[35]. The excessive release of ROS from the mitochondria into the cytosol may trigger further ROS generation by several mechanisms. Reactive oxygen species (ROS) negatively affect myocardial calcium handling, cause arrhythmias, and contribute to cardiac remodeling by inducing hypertrophic signaling, apoptosis, and necrosis[34]. Neurohumoral activation via the renin- angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), combined with increased pre- and after-load, impose additional myocardial oxidativestress[36].

The current therapeutic approach for atherosclerotic vascular plaque stabilization and disease includes RAAS inhibitors, statins, and acetylsalicylic acid, because of their pleiotropic antioxidative effects [37-39]. There is a need to elucidate oxidative stress physiology and pathophysiology, to identify novel therapeutic modalities for selective oxidative stress targeting in atherosclerosis[40].



III. NITROSATIVE STRESS

RNS falls under oxidative stress in the traditional category. However, in recent years, a growing body of knowledge has revealed that Nitrosative stress, as an independent special biochemical phenomenon in the process of cell death, has unique pathophysiological characteristics[41] that differ from those of oxidative stress in a general sense.

Reactive Nitrogen Species (RNS)

RNS include peroxynitrite ($ONOO^-$), nitrogen dioxide ($^{\bullet}NO_2$), peroxynitrous acid (HNO_3), dinitrogen trioxide (N_2O_3), nitroxyl (HNO), peroxynitrous acid (ONOOH), peroxynitrate (O_2NOO^-), peroxynitric acid (O_2NOOH), nitrosonium cation (NO^+), nitrate (NO^-), nitrite (NO^-) and nitroxyl anion (NO^-) and can lead to nitrosative stress (NSS) [42,43].

Sources of RNS production

$NO^{\bullet}$ is the main precursor of RNS. $NO^{\bullet}$ is produced from the metabolism of the amino acid, L-arginine. The enzymes catalyzing this process, known as nitric oxide synthases (NOS), convert L-arginine into L-citrulline and $NO^{\bullet}$ by a 5-electron oxidation of aguanidine nitrogen of L-arginine[44].

The presence of high concentrations of superoxide anions (O^-) is also essential for their formation. $O^{\bullet}$, in the presence of O^-, can form all of the RNS, but the predominant molecule formed is $ONOO^-$, which is the mostcytotoxic[45] [$O2^{\bullet-} + NO^{\bullet} = ONOO^-$ (Peroxynitrite)]

Isoforms of Nitric Oxide Synthase

Until now, three isoforms of nitric oxide synthase have been distinguished. Two isoforms, neuronal NOS (nNOS; type I NOS) and endothelial NOS (eNOS; type III NOS), are expressed constitutively and regulated by the interaction of Ca^{2+} with calmodulin[45]. The other isoform, inducible-NOS (iNOS; type II NOS), is induced in response to infection, inflammation, or trauma and is not regulated by Ca^{2+} because it

forms a complex with calmodulin at very low concentrations of $_{Ca}2+$(46).

Physiological Roles of RNS in CardiacTissues

NO• generated by nNOS in neurons serves in communication between nerve cells, whereas the free radical generated by iNOS in macrophages and smooth muscle cells contributes to their killing mechanism[47], and NO• generated by eNOS in endothelium, brain, peripheral neurons and heart relaxes blood vessels and maintains normal blood pressure[48].

RNS form part of the immune responses serving as nonspecific defenses, and they participate as second messengers in signal transduction pathways.

Under physiological conditions, NO• is a cytoprotective molecule with a vasodilator action. NO• inhibits the activation and adhesion of platelets and neutrophils and has protective effects against ischemia reperfusion and heart failure[48,49].

Pathological Roles of RNS

NSS represents a pathological condition that contributes to the deterioration of organs and systems[42]. It is associated to several cardiometabolic pathologies that include atherosclerosis, hypertension, endothelial dysfunction and diabetes, among others [50,51]. RNS respond multiple times quicker than O2− with different particles and have a more extended mean half. NSS can cause severe damage since RNS are stable chemicals that rapidly permeate into intracellular organelles and react at extremely fast rates[50].

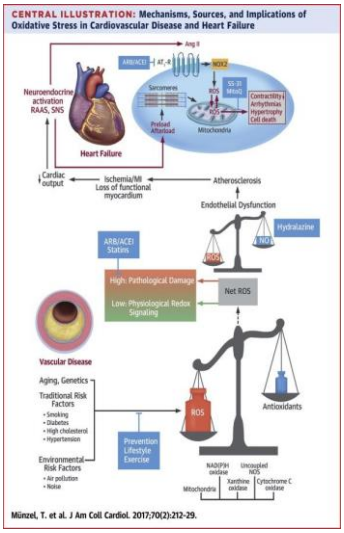
Nitric oxide synthases (NOSs), and in particular endothelial NOS (eNOS), can be potential sources of O_2 under certain pathophysiologic conditions[51].The excessive release of ROS from the mitochondria into the cytosol may trigger further ROS generation by several mechanisms, including nitric oxide synthase (NOS) uncoupling or conversion of xanthine dehydrogenase[34] to its ROS- producing form, xanthine oxidase[52]. When the NOS mitochondrial isoform is uncoupled, peroxynitrite is produced. These are highly reactive oxidative species that, together with superoxide anions (O^-), can damage the function and structure of all cellular macromolecules (such as nucleic acids, proteins and lipids), leading to: 1) an altered Ca^{2+} regulation and activated pathways associated with electrical remodelling, 2) a stimulation of cardiomyocyte hypertrophy, 3) the induction of apoptosis, 4) the promotion of fibrosis and 5) the activation or hampering of the inflammatory response[34]. All these alterations are recognized as key elements in the development of heart failure[53]. Hemoglobin is the largest reservoir of O_2 and NO in the human. Thus, sustained or excessive desaturation of hemoglobin, characteristic of chronic heart failure (CHF), would increase ROS production[54]. It was recently reported that CHF is characterized by accumulation of heme-NO (compared to controls) and venous desaturation [55].

Also, there is an increase in 3-nitrotyrosine formation in subjects with cardiovascular diseases. Therefore, 3-nitrotyrosine can be considered as a biomarker of RNS in cardiovascular diseases[56].

IV. OXIDATIVE/NITROSATIVE STRESSIN CAD

Previously considered a disease of cholesterol, we now consider atherosclerosis (the major underlying cause for CAD), to be an inflammatory disease. The atherosclerosis is started with the damage of vascular endothelial cells, and smooth muscle cells play an important role in the stability of plaque, while macrophages exist an important function in the stability of mature plaque and the formation of thrombosis[57]. Oxidative-Nitrosative stress is a key player in the pathogenesis of atherosclerotic CAD. Numerous studies have shown impaired balance of prooxidants and antioxidants in patients with CAD [58-61]. Oxidative stress is today considered a new risk factor responsible for the development of CAD that affects the onset, prognosis, quality of life,and survival of patients[5].

Figure 2: Pathophysiological role of ROS in cardiactissue



ROS and RNS can activate pro-inflammatory pathways in endothelial cells and immune cells. This leads to the recruitment of immune cells into the arterial wall and the formation of fatty streaks, a precursor to advanced atherosclerotic plaques. High levels of ROS and RNS can weaken the fibrous cap of the plaque, making it more likely to rupture. Plaque rupture is a critical event that can lead to thrombosis and acute cardiovascular events like heart attacks or strokes. In the vessel wall, endothelial cells, smooth muscle cells (SMCs) and macrophages are sources of free radicals[62]. A substantial data has been shown that ROS are involved in endothelial injury,dysfunction, and lesion progression[63]. Endothelial dysfunction leads to increased endothelial permeability, up regulation of endothelial adhesion molecules, and inflammatory cell infiltration into the arterial wall[60]. Endothelial dysfunction induces RNS production from sources other than eNOS,such as NAD(P)H oxidase andmitochondria[64].

In normal cardiac tissue, inducible nitric oxide (NO) synthase (iNOS) is expressed at low levels. However, upon stress, such as inflammation and hypoxia large quantities of NO are generated as a result of iNOS activation[65]. Although NO is a crucial mediator for maintaining vascular tone and preventing platelet aggregation and adhesion, imbalanced NO production induces inflammation and cytotoxic injury[65]. A variety of mediators, including ROS and RNS, trigger iNOS expression during the inflammatory process. iNOS modulates acute and chronic inflammatory conditions, and NO accumulates in inflamed tissues[66].

V.CAD & TP53 GENE

Apoptosis of cardiomyocytes is accompanied with acute coronary occlusion [67]. Because apoptotic loss of cardiomyocytes causes heart failure,[68] inhibition of apoptosis has been suggested as an additional therapeutic approach to coronary heart disease [69]. Increased oxidative- nitrosative stress as well as somatic DNA damage could be important pathogenic factors that act as additional prognostic predictors and potential targets for therapeutic strategies in CAD for early management and prevention of the disease[70].

The tumor suppressor p53 is an important transcription factor that regulates cell cycle progression, cellular senescence, and apoptosis[71]. p53 is not only an important gene of inhibiting tumor, but also closely associated with apoptosis. Loss of p53 activity causes unrestrained growth while increased levels of p53 arrest cells in the G1 phase of the cell cycle[72]. Protein level of p53 is generally kept low in the heart but it is elevated when cardiac cells are exposed to hypoxia[73-75].

P53 gene be subdivided into two types: mutant type and wild type[76,77]**.** In particular, the mutant type p53 gene is used to promote the growth of the cells and to participate in the occurrence of tumors.

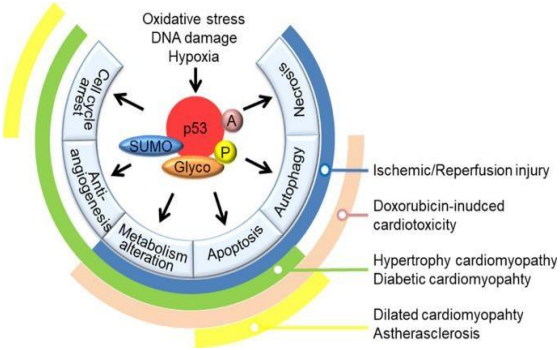


Figure 3: Regulatory roles of p53 gene in cardiovascular health. Adapted from "Men, H., Cai, H., Cheng, Q. et al. The regulatory roles of p53 in cardiovascular health and disease. Cell. Mol. Life Sci. 78, 2001–2018 (2021)‖

The major function of wild-type p53 gene is to involve in the negative modulation of cell growth and the expression of apoptotic regulation[78-80]. Further studies have shown that wild-type p53 gene can promote the release of cytochrome C and other apoptosis inducing factors by affecting cell cycle and the change of mitochondrial Bcl-2/Bax ratio, start Caspase protease-cascaded reaction and activate the occurrence of myocardial cell apoptosis, so as to promote the apoptosis of cardiovascular system, and play an important role in the pathogenesis of myocardial infarction, heart failure, atherosclerosis and other cardiovascular disease [81]**.** When myocardial cells express completely functional wild-type p53, they can recover from physiological apoptosis, while inhibiting wild- type p53 can delay the progress of cardiovascular diseases[57].

As far as Nitrosative stress is concerned, high concentrations of peroxynitrite leads to rapid cell death, associated with rapid energetic derangements and PARP activation, while lower concentrations of peroxynitrite, after several hours, can result in cytochrome *c* release from

mitochondria and caspase 3-, 2-, 8- and 9- dependent apoptotic cell death[82]. Specifically, the p53 gene polymorphism may lead to a reduction in DNA repair activity, increase inflammation, and an increased susceptibility to oxidative stress, all of which can contribute to the development of CAD.

Table 2: Summary of experimental & clinical studies investigating the role of ROS/RNS in cardiacdiseases

Author	Experimental model	Focus of study	Results	Clinical implications
Shih *et al.* (83)	Animal model(rat)	ROS on Ang II-induced (*β- MyHC*) gene expression	a) ↑ β-MyHC promoter activity b) ↑ Intracellular ROS	Ang II increases *β-MyHC* gene expression. Catalase or N-acetyl-cysteinedecreased hypertrophy
Li *et al.* [84]	Animal model (guinea pig)	NADPH	NADPH-dependent ROS generation during progression of LVH	Hypertrophy and/or transition to heartfailure
Higuchi *et al.* (85)	Animal model(rat)	*Rac1* gene	Activation of Rac1 results in stimulation ofNF-κB activity	Hypertrophy
Infanger *et al.* (86)	Animal model (murine)	Nox4	a) Sympatheticoveractivation b) Decline in cardiacfunction	Targeted inhibitioncould provide a novel treatment forMI-induced heart failure
Silberman *et al.* (87)	Animal model (murine)	NO and diastolic dysfunction	a) Cardiac oxidation b) NOS uncoupling c) Diastolic dysfunction	BH4 may representa possible treatmentfor diastolic dysfunction
Thuc *et al.* (88)	Animal model(rat)	Pravastatin	a) Suppressed H2O2-induced cell death b) ↑ Left ventricular functional recovery c) ↓ Infarct size	Cardioprotection
Chang *et al.* (89)	Human Adults	Nox2 and atrial fibrillation	a) ↑ NADPH-stimulated superoxide release b) ↑ Membrane-bound Nox2 containing NADPHoxidase mRNA expression	Atrial remodeling

			c) Moderate-to-severe myolysis and hypertrophy	
Li *et al.* [90]	Human Adults	Oxidative stressand atrial fibrillation	↑ IL-6, IL-8, IL-10, TNF-alpha, MCP1, VEGF, and NTpBNP concentrations	Inflammation is associated with atrial fibrillation independent of co-morbidities

VI.CONCLUDING REMARKS

Research over the past few decades has led to identification of multiple ROS generating systems that could potentially be modulated in CAD. Given the critical role of Oxidative - Nitrosative stress, and p53 gene polymorphism in the pathogenesis of CAD, understanding the underlying mechanisms involved in the regulation of these processes could lead to the development of novel therapeutic strategies for the prevention and treatment of CAD. For instance, targeting the iNOS-derived RNS pathway or developing antioxidants that can scavenge ROS and RNS may represent promising therapeutic approaches to mitigate oxidative stress-induced damage in CAD. Similarly, targeting the p53 pathway or developing drugs that can modulate p53 activity may represent potential therapeutic strategies for the treatment of CAD.

REFERENCES

[1]. Naghavi. M, Abajobir, A.A, Abbafati, C, Abbas, K.M, Abd-Allah, F, Abera, S.F, Et Al. 2015. Global, Regional, And National Age-Sex Specific Mortality For 264 Causes Of Death, 1980–2016: A Systematic Analysis For The Global Burden Of Disease Study 2016. The Lancet, 390(10100), Pp.1151-1210.

[2]. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Et Al. Heart Disease And Stroke Statistics–2007 Update: A Report From The American Heart Association Statistics Committee And Stroke Statistics Subcommittee. Circulation. 2007;115:E69 – E171

[3]. Ray PD, Huang PW, Tsuji Y. Reactive Oxygen Species (ROS) Homeostasis And Redox Regulation In Cellular Signaling. Cell Signal 2012;24:981-90.

[4]. Tsutsui H, Kinugawa S And Matsushima S. Oxidative Stress And Heart Failure. Am J Physiol Heart Circ Physiol 2011; 301: H2181–H2190

[5]. X. Yang, T. He, S. Han Et Al., ―The Role Of Traditional Chinese Medicine In The Regulation Of Xidative Stress In Treating Coronary Heart Disease,‖ Oxidative Medicine And CellularLongevity, Vol. 2019, Article ID 3231424, 13 Pages, 2019.

[6]. H. Cai And D. G. Harrison, ―Endothelial Dysfunction In Cardiovascular Diseases: The Role Of Oxidant Stress,‖ Circulation Research, Vol. 87, No. 10, Pp. 840–844, 2000

[7]. Halliwell B. Free Radicals And Other Reactive Species In Disease. Nature Encyclopedia Of Life Sciences. 2001. P. 1–7.

[8]. Phaniendra A, Jestadi DB, Periyasamy L. Free Radicals: Properties, Sources, Targets, And Their Implication In Various Diseases. Indian J Clin Biochem. 2015 Jan;30(1):11-26. Epub 2014 Jul 15.

[9]. Kohen R, Nyska A. Invited Review Oxidation Of Biological Systems: Oxidative Stress Phenomena, Antioxidants, Redox Reactions, And Methods For Their Quantification. ToxicolPathol. 2002;30(6):620–650.

[10]. Genestra M. Oxyl Radicals, Redox-Sensitive Signalling Cascades And Antioxidants. Review Cell Signal. 2007;19(9):1807–1819.