State of the art paper

Redox imbalance and oxidative stress in cardiovascular diseases: mechanisms, biomarkers, and therapeutic targets

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Submitted: 26 May 2025; **Accepted:** 10 September 2025
Online publication: 30 September 2025

Arch Med Sci Atheroscler Dis 2025; 10: e220–e227
DOI: https://doi.org/10.5114/amsad/210585

Abstract

Cardiovascular diseases (CVDs) are the leading cause of global morbidity and mortality, with oxidative stress and redox imbalance playing pivotal roles in their initiation and progression. In this comprehensive review, we explore the molecular mechanisms by which reactive oxygen and nitrogen species disrupt vascular homeostasis, promote endothelial dysfunction, and drive adverse cardiac remodeling. We highlight key redox-sensitive pathways, including NADPH oxidase activation, mitochondrial dysfunction, endothelial nitric oxide synthase uncoupling, and endoplasmic reticulum stress. Emerging oxidative stress biomarkers, such as 8-iso-prostaglandin F2α, oxidized low-density lipoprotein, and myeloperoxidase, are critically examined for their diagnostic and prognostic relevance. Additionally, we discuss therapeutic strategies targeting oxidative stress, ranging from conventional antioxidants to novel mitochondrial-directed and enzyme-specific interventions. Despite advances in understanding the redox landscape of CVDs, challenges remain in translating these insights into effective clinical therapies. Future research integrating omics technologies, precision medicine, and combined lifestyle-pharmacological approaches may offer new opportunities for redox-based cardiovascular interventions.

Key words: oxidative stress, redox imbalance, cardiovascular diseases, biomarkers, NADPH oxidase, mitochondrial dysfunction, endothelial dysfunction, antioxidant therapy.

Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide, accounting for nearly 18 million deaths annually according to the World Health Organization [1]. Despite remarkable advances in diagnostic techniques, pharmacological therapies, and pre-

ventive strategies, the global burden of CVDs continues to escalate, driven by aging populations, urbanization, sedentary lifestyles, unhealthy dietary patterns, and the growing prevalence of metabolic disorders such as diabetes and obesity [2]. This persistent rise not only underscores the limitations of current interventions but also highlights the urgent need for a deeper understanding of the underlying pathophysiological mechanisms.

Among the diverse molecular and cellular processes implicated in cardiovascular pathology, redox imbalance and oxidative stress have emerged as pivotal contributors to disease initiation, progression, and clinical outcomes [3]. Oxidative stress – an imbalance between the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the capacity of antioxidant defense systems – plays a dualistic role in human biology, both physiological and potentially pathological [4]. At physiological levels, ROS and RNS function as crucial signaling molecules regulating vascular tone, gene expression, cell proliferation, apoptosis, and host defense mechanisms [5]. Controlled redox signaling is essential for maintaining endothelial function, modulating inflammatory responses, and preserving vascular homeostasis [6]. However, an excess of ROS or RNS, or impaired antioxidant capacity, disrupts these finely tuned processes, leading to endothelial dysfunction, enhanced vascular permeability, pro-inflammatory gene activation, and ultimately structural and functional deterioration of the cardiovascular system [7]. Cumulative evidence from in vitro studies, animal models, and clinical investigations underscores the deleterious role of oxidative stress in various stages of cardiovascular disease [8]. For instance, oxidized low-density lipoprotein (oxLDL) is a key instigator of atherogenesis, triggering endothelial activation, monocyte recruitment, and foam cell formation [9]. In hypertension, ROS-mediated reductions in nitric oxide (NO) bioavailability contribute to increased vascular resistance and blood pressure elevation [10]. During myocardial ischemia-reperfusion events, abrupt ROS surges induce widespread tissue injury through mitochondrial dysfunction, calcium overload, and activation of cell death pathways [11]. Furthermore, chronic oxidative stress promotes maladaptive cardiac remodeling, myocardial fibrosis, and impaired contractile function, hallmarks of heart failure progression [12].

The intricate network of oxidative stress-induced molecular alterations encompasses not only direct macromolecular damage but also dysregulation of redox-sensitive transcription factors such as NF-κB, AP-1, and Nrf2, which govern the expression of genes involved in inflammation, antioxidant defenses, and cell survival [13]. Additionally, oxidative post-translational modifications of proteins, including S-glutathionylation and carbonylation, further impair cellular functions and exacerbate disease pathology [14]. Given the central involvement of oxidative stress in cardiovascular diseases, significant efforts have been directed toward the identification of reliable oxidative biomarkers and the development of redox-modulating therapies [15]. Biomarkers such as 8-iso-prostaglandin F2α, malondialdehyde (MDA), myeloperoxidase (MPO), and advanced glycation end products (AGEs) have demonstrated potential in reflecting oxidative burden and predicting clinical outcomes [16]. On the therapeutic front, interventions ranging from dietary antioxidants to targeted enzyme inhibitors and mitochondrial-directed therapies are under exploration, though translating experimental success into clinical efficacy remains a formidable challenge [17].

In this comprehensive review, we aim to elucidate the mechanistic basis of redox imbalance in cardiovascular diseases, investigate the clinical significance of emerging oxidative biomarkers, and critically evaluate current and potential antioxidant therapeutic strategies. To ensure methodological transparency and reproducibility, we identified comprehensive searches of PubMed, Scopus, and Web of Science databases up to June 2025. Search terms included keyword and Medical Subject Headings (MeSH) combinations such as oxidative stress, redox imbalance, reactive oxygen species, cardiovascular diseases, biomarkers, NADPH oxidase, mitochondrial dysfunction, and antioxidant therapy.

Redox biology in cardiovascular homeostasis

In healthy cardiovascular systems, a delicate balance between the production of ROS and the activity of antioxidant defense mechanisms is essential for maintaining vascular tone, endothelial integrity, and normal cardiac physiology [6]. Low to moderate levels of ROS, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and nitric oxide (NO), act as secondary messengers in intracellular signaling cascades, regulating processes such as angiogenesis, vascular remodeling, and cardiomyocyte contraction [4]. Under physiological conditions, the primary sources of ROS include mitochondrial electron transport chains (particularly complexes I and III), membrane-bound NADPH oxidases (NOX family enzymes), xanthine oxidase, and uncoupled endothelial nitric oxide synthase (eNOS) [8, 18]. Mitochondria, although mainly responsible for ATP production through oxidative phosphorylation, generate small amounts of ROS as by-products [1]. NADPH oxidases, especially NOX2 and NOX4 isoforms, are tightly regulated to modulate ROS production in response to mechanical and biochemical stimuli [20].

Antioxidant defenses act synergistically to neutralize excess ROS and prevent oxidative damage.

Enzymatic antioxidants include superoxide dismutases (SOD1, SOD2, and SOD3), which catalyze the dismutation of superoxide into hydrogen peroxide; catalase, which decomposes hydrogen peroxide into water and oxygen; and glutathione peroxidases (GPxs), which reduce hydrogen peroxide and lipid hydroperoxides [21]. Non-enzymatic antioxidants, such as ascorbic acid (vitamin C), tocopherol (vitamin E), glutathione (GSH), and coenzyme Q10, further reinforce cellular protection against oxidative insults [22]. Redox signaling is intricately involved in the regulation of cardiovascular homeostasis. Controlled ROS generation modulates the activity of critical transcription factors, including nuclear factor kappa B (NF-κB), nuclear factor erythroid 2–related factor 2 (Nrf2), and hypoxia-inducible factor-1α (HIF-1α) [13]. NF-κB is activated by low levels of ROS and regulates the expression of inflammatory cytokines and adhesion molecules, while Nrf2 governs the expression of antioxidant response element (ARE)-driven genes to bolster cellular defenses. HIF-1α stabilization under redox-modulated hypoxic conditions promotes angiogenesis and metabolic adaptation [23, 24].

Disruption of this delicate redox balance – whether through excessive ROS production, impaired antioxidant responses, or persistent environmental stressors – initiates a cascade of deleterious processes. Endothelial dysfunction, characterized by reduced NO bioavailability and increased vascular permeability, is a hallmark of early atherogenesis [25]. Redox-sensitive modifications of proteins, lipids, and DNA compromise cellular viability and accelerate vascular aging, laying the foundation for the development of hypertension, atherosclerosis, myocardial ischemia, and heart failure [26]. Thus, the maintenance of redox homeostasis is fundamental not only to cardiovascular health but also to the prevention of disease progression. Understanding the sources, regulation, and functional consequences of ROS and the antioxidant systems is crucial for identifying novel therapeutic targets aimed at restoring vascular and myocardial redox balance.

Redox imbalance and pathogenesis of cardiovascular diseases

The disruption of redox homeostasis, characterized by excessive production of ROS and impaired antioxidant defenses, is a fundamental pathogenic mechanism underlying the initiation and progression of CVDs [3]. Mounting evidence has elucidated how oxidative stress not only contributes to molecular and cellular injury but also actively drives complex pathophysiological processes such as endothelial dysfunction, vascular inflammation, thrombogenesis, myocardial remodeling, and electrophysiological disturbances [7, 27–29].

Atherosclerosis

Oxidative stress is a key early player in atherogenesis. Excess ROS promotes oxidation of low-density lipoprotein (LDL) particles within the subendothelial space. Oxidized LDL (oxLDL) is highly atherogenic, stimulating endothelial cell activation, upregulation of adhesion molecules (e.g., VCAM-1, ICAM-1), and recruitment of circulating monocytes [9]. Internalized oxLDL by macrophages leads to foam cell formation, a hallmark of the early fatty streak lesion [9]. Moreover, ROS amplify local inflammation by activating nuclear factor-κB (NF-κB) signaling, perpetuating cytokine release and leukocyte recruitment [13].

Hypertension

Oxidative stress contributes to the pathogenesis of hypertension through multiple mechanisms. ROS reduce nitric oxide (NO) bioavailability by reacting with NO to form peroxynitrite, a potent oxidant, resulting in impaired endothelium-dependent vasodilation [30]. NADPH oxidase-derived superoxide has been identified as a major source of vascular oxidative stress in experimental models of hypertension [20]. Additionally, redox-sensitive pathways promote vascular smooth muscle cell proliferation and extracellular matrix remodeling, contributing to increased arterial stiffness and elevated systemic vascular resistance [31].

Myocardial infarction and ischemia-reperfusion injury

During myocardial ischemia, oxygen deprivation leads to metabolic disturbances, mitochondrial dysfunction, and accumulation of reduced electron carriers. Upon reperfusion, the sudden restoration of oxygen triggers an overwhelming burst of ROS generation, predominantly from mitochondria and xanthine oxidase [32]. This "oxidative burst" exacerbates cardiomyocyte apoptosis, necrosis, and inflammation, amplifying infarct size and impairing functional recovery [32]. Strategies targeting oxidative stress during reperfusion, such as mitochondrial-targeted antioxidants, are under active investigation [33].

Heart failure

Chronic oxidative stress is intimately involved in the progression of heart failure (HF). Persistent ROS overproduction induces mitochondrial DNA damage, disrupts ATP production, impairs calcium handling, and promotes cardiomyocyte apoptosis [34]. Redox-mediated activation of matrix metalloproteinases (MMPs) and fibrotic pathways leads to maladaptive extracellular matrix remodeling, chamber dilation, and contractile dysfunction

[12]. Importantly, oxidative stress acts in concert with neurohormonal activation (e.g., angiotensin II, aldosterone) to drive HF progression [12].

Arrhythmias

ROS directly affect ion channel function and electrophysiological properties of cardiomyocytes, creating a substrate for arrhythmogenesis. Oxidative modifications of sodium, potassium, and calcium channels alter action potential duration and conduction velocity [35]. Additionally, ROS-induced Ca^{2+} leakage from the sarcoplasmic reticulum via ryanodine receptors contributes to triggered activity and ventricular arrhythmias, particularly in the setting of ischemia, heart failure, or inherited channelopathies [35]. Overall, oxidative stress orchestrates a multifaceted and dynamic contribution to cardiovascular disease development and progression. Targeting redox imbalance thus represents a promising therapeutic avenue across a spectrum of CVDs.

Molecular pathways of oxidative damage

The molecular mechanisms underlying oxidative damage in cardiovascular diseases are complex and multifactorial, involving multiple cellular sources and intricate signaling networks. Understanding these pathways is crucial for identifying therapeutic targets aimed at mitigating oxidative injury and restoring redox homeostasis [36].

NADPH oxidases (NOX enzymes)

NADPH oxidases (NOXs) are a family of membrane-bound enzyme complexes whose primary function is the generation of ROS. Unlike other ROS sources where ROS production is a byproduct, NOXs purposefully produce superoxide (O_2^-) by transferring electrons from NADPH to molecular oxygen [20]. Among the NOX isoforms, NOX1, NOX2, NOX4, and NOX5 are prominently expressed in the cardiovascular system [37]. NOX2 is predominantly found in endothelial cells, vascular smooth muscle cells (VSMCs), and cardiomyocytes, playing a central role in oxidative stress associated with hypertension, atherosclerosis, and heart failure [37]. NOX4, which primarily produces hydrogen peroxide (H_2O_2), has a more complex role, contributing to both physiological and pathological processes depending on the context and level of activation [37].

Mitochondrial dysfunction

Mitochondria are critical regulators of cellular energy metabolism and ROS homeostasis. Under physiological conditions, the mitochondrial electron transport chain (ETC) leaks small amounts of electrons, primarily at complexes I and III, leading to the formation of superoxide [19]. However, under stress conditions such as ischemia-reperfusion, hyperglycemia, or hypertrophy, mitochondrial dysfunction amplifies ROS production, resulting in mitochondrial DNA (mtDNA) damage, impaired oxidative phosphorylation, and initiation of cell death pathways including apoptosis and necrosis [38]. The accumulation of dysfunctional mitochondria further exacerbates ROS generation, establishing a vicious cycle of oxidative injury and energetic failure in cardiomyocytes [38].

Uncoupled endothelial nitric oxide synthase

Endothelial nitric oxide synthase (eNOS) is pivotal for maintaining vascular homeostasis through the production of nitric oxide (NO), a potent vasodilator and anti-inflammatory molecule [6]. In pathological states, deficiency of essential cofactors such as tetrahydrobiopterin (BH4) or increased oxidative stress can lead to eNOS uncoupling. Uncoupled eNOS shifts from producing NO to generating superoxide, thereby exacerbating oxidative stress and impairing endothelial function. This phenomenon significantly contributes to endothelial dysfunction observed in hypertension, diabetes, and atherosclerosis [39].

Endoplasmic reticulum stress

The endoplasmic reticulum (ER) plays a central role in protein folding, calcium homeostasis, and lipid synthesis. ER stress, triggered by the accumulation of misfolded or unfolded proteins, activates the unfolded protein response (UPR) to restore homeostasis. However, prolonged or severe ER stress leads to oxidative stress through enhanced ROS production, primarily via ERO1 and NOX4 pathways [40]. In the cardiovascular system, ER stress-induced oxidative stress has been implicated in the pathogenesis of atherosclerosis, heart failure, and diabetic cardiomyopathy [40, 41]. Collectively, these molecular pathways highlight the multifaceted origins of oxidative stress in cardiovascular diseases. Targeting specific components within these pathways offers promising therapeutic strategies to mitigate oxidative damage and improve clinical outcomes.

Emerging oxidative stress biomarkers in cardiovascular diseases

The identification and validation of biomarkers reflecting oxidative stress are of great significance for improving the early diagnosis, risk stratification, prognosis, and therapeutic monitoring of CVDs. Biomarkers of oxidative stress provide crit-

ical insights into disease activity and may serve as surrogate endpoints in clinical trials targeting redox imbalances [42].

8-iso-prostaglandin F2α (8-iso-PGF2α)

8-iso-PGF2α, a member of the isoprostane family, is a stable product of non-enzymatic peroxidation of arachidonic acid. Elevated levels of 8-iso-PGF2α have been consistently associated with increased oxidative stress in patients with atherosclerosis, hypertension, and acute coronary syndromes [43, 44]. Measurement of urinary or plasma 8-iso-PGF2α serves as a reliable and specific indicator of lipid peroxidation and oxidative injury.

Malondialdehyde

Malondialdehyde is a widely studied marker of lipid peroxidation, formed as a byproduct of the oxidation of polyunsaturated fatty acids. Increased MDA levels have been observed in patients with coronary artery disease, heart failure, and stroke. Although easy to measure, concerns remain regarding the specificity and reproducibility of MDA assays [45].

Oxidized low-density lipoprotein (oxLDL)

OxLDL is a central player in the development of atherosclerosis, triggering endothelial dysfunction and foam cell formation [9]. Circulating oxLDL levels correlate with the extent of coronary artery disease and are predictive of adverse cardiovascular events. OxLDL also promotes a pro-inflammatory state by activating scavenger receptors and innate immune responses [46].

Myeloperoxidase (MPO)

MPO, a heme-containing peroxidase released by activated neutrophils and monocytes, catalyzes the production of reactive oxidants such as hypochlorous acid. Elevated plasma MPO levels are associated with endothelial dysfunction, plaque instability, and increased risk of myocardial infarction and heart failure. MPO serves both as a biomarker and as a potential therapeutic target in CVDs [47].

Advanced glycation end products (AGEs)

AGEs are formed through non-enzymatic glycation and oxidation of proteins and lipids. Accumulation of AGEs contributes to vascular stiffening, endothelial dysfunction, and chronic inflammation. Serum levels of AGEs and their soluble receptors (sRAGE) have been linked to adverse cardiovascular outcomes, particularly in diabetic and aging populations [48].

Therapeutic strategies targeting oxidative stress

Given the central role of oxidative stress in CVD pathophysiology, considerable efforts have been directed toward developing therapeutic interventions aimed at restoring redox balance [17]. These strategies can be broadly categorized into pharmacological antioxidant therapies, enzyme modulators targeting ROS production, mitochondrial-targeted treatments, and lifestyle interventions [49].

Pharmacological antioxidant therapies

Despite the strong preclinical rationale, conventional antioxidants such as vitamins C and E have consistently failed to demonstrate significant cardiovascular benefits in large-scale randomized controlled trials, including the HOPE study and the Heart Protection Study [50, 51]. Several factors likely contributed to these disappointing outcomes, including poor bioavailability, lack of target specificity, inappropriate timing of administration relative to disease stage, and the inability to reach critical intracellular sites of ROS generation, such as mitochondria. These limitations have underscored the complexity of redox biology in vivo and have prompted a paradigm shift toward more selective, mechanism-based interventions. In this context, the development of targeted therapies such as NADPH oxidase inhibitors, mitochondrial-directed antioxidants, and Nrf2 pathway activators represents a promising next-generation approach designed to overcome the shortcomings of broad-spectrum antioxidant supplementation.

Enzyme modulators

More specific approaches target enzymatic sources of ROS production. NADPH oxidase inhibitors, such as GKT137831, have demonstrated promise in preclinical models by reducing vascular inflammation and fibrosis [52]. Other emerging agents aim to enhance endogenous antioxidant defenses, such as activators of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which upregulates a battery of antioxidant and cytoprotective genes [53]. Bardoxolone methyl and other Nrf2 activators are under investigation for their potential cardiovascular benefits.

Mitochondrial-targeted antioxidants

Because mitochondria are a major source and target of oxidative stress, therapies aimed specifically at mitochondrial ROS have gained significant interest. Compounds such as MitoQ, SkQ1, and SS-31 selectively accumulate within mitochondria

and neutralize ROS at their source, protecting mitochondrial DNA, proteins, and membranes from oxidative damage. Preclinical studies suggest that mitochondrial antioxidants may attenuate cardiac ischemia-reperfusion injury, heart failure progression, and vascular dysfunction [54].

Lifestyle and dietary interventions

Lifestyle modifications remain a cornerstone in the management of oxidative stress. Diets rich in fruits, vegetables, and polyphenol-containing foods (e.g., Mediterranean diet) have been associated with reduced oxidative markers and improved endothelial function [55]. Regular aerobic exercise enhances endogenous antioxidant capacity and improves mitochondrial efficiency. Conversely, smoking cessation, weight loss, and glycemic control in diabetic patients reduce the systemic oxidative burden and favorably impact cardiovascular outcomes [55]. Despite promising preclinical findings, translating antioxidant strategies into clinical success remains challenging. Factors such as poor bioavailability, lack of target specificity, and disease stage at intervention may influence therapeutic efficacy [56]. Future studies should focus on precision medicine approaches, selecting appropriate patient subgroups, and combining antioxidant therapies with conventional treatments to maximize clinical benefit.

Challenges and future directions

Although targeting oxidative stress represents a promising therapeutic strategy for CVDs, significant challenges remain. One of the major hurdles is the complexity and redundancy of redox signaling pathways. ROS are not merely damaging byproducts but are integral to physiological cellular signaling. Thus, indiscriminate suppression of ROS can potentially disrupt essential biological functions, leading to unintended consequences [2]. Another critical challenge is the timing and specificity of antioxidant therapies. Oxidative stress is a dynamic process that varies with disease stage and severity [17]. Intervening too late in the disease course may render antioxidant therapies ineffective, while early intervention requires reliable biomarkers for risk stratification [41]. Furthermore, many traditional antioxidants lack sufficient bioavailability, cellular targeting, or ability to penetrate critical compartments such as mitochondria, limiting their therapeutic potential [54].

Clinical translation has been further hampered by heterogeneity among patient populations and variability in oxidative stress burden [56]. Precision medicine approaches are needed to identify patient subgroups most likely to benefit from redox-modulating therapies. Advances in omics technologies, including redox proteomics, metabolomics, and transcriptomics, offer new opportunities for patient phenotyping and biomarker discovery, which could facilitate personalized interventions [57]. For example, redox proteomics could identify specific oxidative post-translational modifications linked to heart failure progression, enabling targeted interventions. Metabolomics profiling may reveal patient-specific oxidative stress signatures that predict response to NADPH oxidase inhibitors. Integrating these omics approaches with wearable health monitoring could optimize timing and dosing of antioxidant therapies in personalized treatment plans. Emerging strategies such as selective NOX inhibitors, Nrf2 activators, and mitochondrial-targeted antioxidants hold promise but require validation in large, well-designed clinical trials [53, 54]. Combination therapies targeting multiple sources or downstream effects of oxidative stress may offer synergistic benefits [58].

Future research should also focus on refining animal models to better recapitulate human CVD pathophysiology and on developing more sophisticated imaging techniques to assess oxidative stress *in vivo* [59]. Additionally, integrating lifestyle interventions with pharmacological treatments may yield more sustainable benefits by addressing both the causes and consequences of oxidative imbalance [57]. In summary, while the therapeutic targeting of oxidative stress in cardiovascular diseases remains an evolving field with many challenges, it also offers exciting opportunities. Continued interdisciplinary research efforts are essential to overcome current barriers and translate mechanistic insights into effective clinical therapies that can reduce the global burden of CVDs.

Conclusions

Oxidative stress and redox imbalance are fundamental contributors to the development and progression of cardiovascular diseases [1, 2]. Through mechanisms involving endothelial dysfunction, mitochondrial impairment, inflammatory activation, and structural remodeling, excess reactive oxygen and nitrogen species disrupt cardiovascular homeostasis and promote disease pathology [9, 19, 26]. While significant advances have been made in understanding the complex roles of redox biology in health and disease, translating this knowledge into effective clinical interventions remains a formidable challenge [56]. Emerging biomarkers of oxidative stress offer promising avenues for early diagnosis, risk stratification, and therapeutic monitoring, though further validation in diverse clinical settings is needed [41, 57]. Similarly, targeted therapeutic strategies, including NADPH oxidase inhibitors, mitochondrial antiox-

idants, and Nrf2 activators, hold great potential but require rigorous evaluation through well-designed clinical trials [52–54].

A future-oriented approach must embrace the integration of molecular insights, omics technologies, personalized medicine, and lifestyle interventions to comprehensively address the multifaceted nature of oxidative stress in cardiovascular disease [55–57].

Interdisciplinary collaboration between basic scientists, clinical researchers, and healthcare providers will be essential to overcome existing barriers and harness the full therapeutic potential of redox modulation [58, 59]. By continuing to unravel the intricate interplay between oxidative stress and cardiovascular health, we can pave the way toward innovative and effective strategies that not only treat but also prevent cardiovascular diseases, ultimately reducing the global burden of this leading cause of death and disability [1].

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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