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Chapter

The Shear Stress/KLF2/Nrf2/ARE Pathway: A Hemodynamic Defense against Oxidative Stress

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Abstract

Many diseases have oxidative stress and inflammation as underlying pathological features, including metabolic and inflammatory/autoimmune disorders, diseases of the lung, liver, kidney, gastrointestinal tract, cardiovascular and nervous systems. A leading physiological mechanism for oxidative stress is the nuclear erythroid-related factor 2-like 2/antioxidant response element (Nrf2/ARE) signaling pathway. It maintains intracellular homeostasis and protects cells from oxidative damage by inducing phase II detoxifying and oxidative-stress responsive genes. Nrf2 transcription factor functions as the key controller of the redox homeostatic gene regulatory network, and is tightly controlled by the repressor protein, Kelch-like ECH-associated protein 1 (Keap1). Pharmacological agents to inhibit Keap1 and boost effectiveness of the Nrf2/ARE pathway have been developed and more are in development. This chapter elucidates the importance of hemodynamic laminar shear stress in oxidative homeostasis and examines hemodynamic induction of the shear stress (SS)/Krupple-like factor2 (KLF2)/Nrf2/ARE pathway as a means to combat oxidative stress through hemodynamics.

Keywords: shear stress, mechanotransduction, Nrf2, KLF2, oxidative stress, hemodynamics, homeostasis

1. Introduction

In the mid-nineteenth century, Claude Bernard introduced the idea of the “inner world” when he theorized that bodily systems function to maintain a constant internal environment—what he called the milieu intérieur. A half century later, Walter Cannon popularized the concept in his book, Spirit of the Body, wherein he coined the word homeostasis, which, “...does not imply something set and immobile, a stagnation. It means a condition—a condition which may vary, but is relatively constant.” Homeostasis is achieved by constant rebalancing within the body of competing mechanisms such as vasodilation vs. vasoconstriction, coagulation vs. anti-coagulation, and inflammatory vs. anti-inflammatory elements [1]. This balance of control is usually attained by negative feedback mechanisms [2].

All imbalances of these antagonistic mechanisms lead to heterostasis or disease, which are deleterious to the body in some respect. None perhaps is more harmful to the body and more likely to lead to morbidity and mortality than excess oxidative stress with inadequate antioxidant response. Oxidative stress-based diseases affect all parts of the body and manifest themselves through some of the worst diseases.
which afflict mankind. To compound the problem, these diseases currently have only symptomatic relief (Figure 1).

Hemodynamics play a key role in the SS/KLF2/Nrf2/ARE antioxidant pathway since its resulting shear stress upregulates both KLF2 and Nrf2 along with other antioxidants such as catalase, superoxide dismutase, glutathione peroxidase, sirtuin, bilirubin, and others [3, 4]. Each of these substances add to the collective antioxidant production generated through this pathway. The SS/KLF2/Nrf2/ARE pathway is only a part of a broad biochemical cascade induced by shear stress that creates a complex, multifaceted, overlapping and interacting response to oxidative stress which contributes to oxidation/reduction (Redox) homeostasis.

2. The endothelium

Endothelial cells (EC) comprise the endothelium, lining the lumen of all blood vessels. The endothelium is the largest organ in the human body with a total weight comparable to other vital organs and possessing a surface area larger than six tennis courts [5]. Once thought of as a passive barrier, now viewed as an organ crucial to maintaining vascular health, endothelial dysfunction is an important factor in the initiation, progression and clinical complication of vascular disease. EC are an integral part of tissues and organs. A unique cellular system lining the inside of blood vessels, the EC form an interface between circulating blood and the parenchymal cells. EC
are regulators of hemostasis, vasomotor control, immunological and platelet functions, inflammatory responses, vascular smooth muscle cell growth and migration. EC fundamentally control vascular tone by sensing and reacting through secretion of transcellular and intracellular signaling molecules. Additionally, the endothelium forms an essential vascular barrier for solute transport and osmotic balance [6, 7].

The endothelium is easily overlooked in clinical practice since it does not lend itself to evaluation. Compounding the problem is that many physicians are not trained in endothelial health. Few textbooks focus on EC and medical school curricula generally lack courses on the endothelium. Additionally, while diseases of other organs are associated with measurable biomarkers, endothelial dysfunction has no reliable markers. Like other organs in the body, the endothelium is highly complex with physiological, biochemical and biomechanical parameters. The endothelium, more than most tissues in the body, is adaptive and flexible, responding to the ever-changing milieu of the local microenvironment.

Unsurprisingly, the EC have a broad potential as therapeutic targets. Since EC are strategically located between the blood and tissue, they are rapidly exposed to biomolecules, injected pharmacological agents, as well as hemodynamic physical forces. Also, the endothelium is highly changeable in size and elasticity in response to intrinsic or extrinsic physiological controllers, and thus is amenable to therapeutic intervention while supplying a direct line of communication with every organ in the body [8].

3. Hemodynamics, shear stress and mechanotransduction

Mechanical forces guide the form and function of the cardiovascular system, whose main role of transporting blood to every tissue in the body is essentially physico-mechanical. The stroke volume generates hemodynamic forces on the arterial vasculature: wall shear stress, hydrostatic pressures and cyclic stretch [9]. Laminar SS, the more important of these forces, is a tangential force arising due to the dragging friction of blood elements with the vessel wall. SS will vary from a low of ~1 dyne/cm² in veins up to >50 dyne/cm² in arterial vessels [10].

Hemodynamically driven blood flow and SS produce EC mechanotransduction, a group of events whereby a cell can actively sense, integrate, and convert a physical stimulus into electrical and biochemical signals [11]. These forces are sensed and interpreted by EC in the luminal vessel wall to: a) guide development during embryogenesis and remodeling during postnatal and adult life; b) optimize blood flow to the tissues and; c) ensure mechanical integrity of the vessel walls. These SS signals bring about intracellular changes, such as activation of signaling pathways and transcriptional regulation that modify gene and protein expressions as well as endothelial phenotype and function [12]. Shear stress-induced mechanotransduction influences key molecules and signaling pathways that lead to the changes in cell functions and behavior.

EC are exposed to fluid forces of greater magnitude than those experienced by other tissues. The mechanically related responses controlled by the endothelium are most important in the control of vascular tone in regulating blood flow. The principal functions of endothelium include: a) maintenance of anticoagulant properties; b) regulation of vascular permeability; c) control of vessel diameter; and d) responses to pathological consequences associated with inflammation, wound healing, and cardiovascular disorders.

Hemodynamic factors in these processes can influence endothelial anatomy and function either by the direct action of shear stress and other stretch forces on the endothelium or by indirect modification of the local concentrations of chemicals.
and agonists at the endothelial surface (Figure 2). The mechanisms may have overlapping actions such as direct forces acting on surface enzymes while receptors concurrently modify enzyme-substrate and agonist-receptor interactions while one or both can be influenced by convective or diffusive transport [13].

It has been shown that EC-induced gene expression is important in hemostasis, thrombosis, growth regulation and proinflammatory activation and is transcriptionally regulated by mechanotransduction [4]. Many of these activated regulatory genes are directly involved in EC adhesion (e.g., ICAM-1). These observations suggest a novel paradigm linking biomechanical stimulation with endothelial activation. Studies have revealed the existence of shear stress response elements (SSRE) in the promoters of physiologically relevant genes such as the platelet-derived growth factor (PDGF), endothelial nitric oxide synthase (eNOS) and vascular cellular adhesion molecule (VCAM-1), that act to up- or down-regulate gene transcription.

One of the key shear stress-generated endothelial molecules is eNOS. This enzyme generates nitric oxide (NO) from L-arginine and O2. NO regulates EC survival, vascular tone (vasodilation), angiogenesis and possesses anti-inflammatory and antioxidant properties [14].

Figure 2.
The hemodynamic oxidation regulation pathway. Hemodynamic shear stress and mechanotransduction create a cascade of complex, interacting events which induce dozens of physiologically active substances. Some are brought about through the SS/KLF2/Nrf2/ARE pathway, others are through direct autocrine and paracrine pathways.
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To date, few have attempted to use hemodynamics, to counter excess oxidative stress. This is in part due to a shortage of methods with which to engage the body hemodynamically. Existing therapeutic methods of increasing blood flow sufficiently to generate therapeutic levels of shear stress include: exercise, electrical stimulation, external counter pulsation (ECP), periodic acceleration, and simulated (passive) skeletal muscle exercise.

Exercise is an excellent therapy to combat oxidative stress even though it generates reactive oxygen species (ROS). Unfortunately, most patients in need of this therapy either cannot, or will not, comply with prescriptive exercise needed to reach therapeutic levels of SS. Electrical stimulation has been used for years to simulate exercise with good success, but the field suffers from confusing heterogeneity. There is an overwhelming number of electrical stimulators in the market with differences in voltage, current, waveform, protocol, size and number of electrodes employed. Also, there are not many randomized clinical trials of electrical stimulation with statistically validated results. Other alternatives to exercise include a simulated jogging device that provides passive cycles of leg movement resulting in an increased level of blood flow and shear stress in the legs. There are also external counter pulsation (ECP) devices that produce SS. Their use, however, is currently limited to treating angina pectoris and heart failure. ECP consists of pneumatic cuffs placed on legs and lower torso with cyclic inflations and deflations that are timed to the patient’s heartbeat such that cuffs inflate at the beginning of diastole and deflate at the beginning of systole. In theory, this action increases the number of pulses in the circulation thereby producing additional SS. Lastly, SS has been increased through a motorized bed that has a reciprocating motion, creating back-and-forth movement of blood flow. This therapy, known as whole-body periodic acceleration, does not increase blood circulation, however it does increase levels of shear stress [15]. The use of hemodynamics as a therapy, despite today’s lack of strong evidence, appears to hold promise, with Fledderus and colleagues [16] finding that, “Physiological levels of shear stress will induce activation and nuclear translocation of Nrf2, and Nrf2-dependent cytoprotective gene expression.” They also found that “SS generated KLF2 primes the activation of the Nrf2 pathway by inducing nuclear localization of Nrf2”.

4. Oxidative stress and homeostasis

Excessive, chronic oxidative stress has been implicated in the development and exacerbation of diseases affecting most of the body’s major organs, including cancer, diabetes, autoimmune, cutaneous, neurodegenerative, pulmonary and cardiovascular diseases, infection, inflammation, and aging (Figure 1). Endogenous oxidative stressors normally result from metabolic processes involving mitochondria. Chronic exposure to excess reactive oxygen species causes cellular and macromolecular damage [17]. Oxidative stress is the result of an imbalance of pro-oxidant and antioxidant substances that lead to the generation of toxic ROS, such as hydrogen peroxide, nitric oxide, superoxide, hydroxyl radicals and others [18]. The production of ROS is usually in balance with homeostatic antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (Gpx). In vivo studies have found that most oxidative damage occurs from reduced levels of antioxidants rather than increased ROS production [19]. Adequate levels of both are considered to be essential for normal cell function. Mitochondria create their own antioxidants to balance their generation of ROS, such as manganese SOD (Mn-SOD) which converts O2•- to H2O2 which is further reduced by CAT and Gpx to harmless H2O and O2. Importantly, CAT, Gpx, and SOD are essential antioxidants that are hemodynamically upregulated.
Hemodynamics

in response to physiological levels of endothelial SS [20, 21]. The Copper/zinc-SOD (Cu/Zn-SOD) antioxidant, which is also upregulated in response to shear stress, plays a role in stabilizing O2•- and contributes to the homeostatic redox state. Antioxidant defenses are extremely important as they eliminate free radicals, thereby providing biological protection. These systems not only defend against the problems of oxidative damage but are essential for disease prevention [22].

Oxidant and antioxidant signaling are both features of oxidative homeostasis, which is the maintenance of nucleophilic tone and a healthy physiological steady state. Redox imbalance is rapidly reversed by feedback reactions, maintained by continuous signaling for production and elimination of electrophiles and nucleophiles, thus maintaining homeostasis [23]. The production of oxygen free radicals sometimes exceeds the capacity of the endogenous antioxidant system and oxidative stress occurs as well as cellular injury. Oxygen free radicals can cause cellular membrane lipid peroxidation and protein oxidation which leads to disruption of cellular integrity. In addition, apoptosis and autophagy, resulting from oxidative stress, represent important mechanisms that can lead to the destruction of cells in many systems [24].

Hemodynamic SS is a key modulator of the body’s response to oxidative stress. Physiological levels of laminar SS, ~12 to 15 dynes/cm^2, as in laminar arterial flow, promote EC survival and quiescence, alignment of EC in the direction of flow, and secretion of substances that reduce oxidation and coagulation while allowing

Figure 3.
Effects of shear stress on endothelium. Biochemical changes brought about through hemodynamics, shear stress and mechanotransduction can have both beneficial and destructive consequences throughout the body. Generally, low or disturbed flow and SS lead to endothelial dysfunction and disease, while normal physiological flow helps maintain endothelial homeostasis.
vasodilation to increase flow. In contrast, low SS, or turbulent flow and other atypical flow patterns that involve changes in direction and magnitude of flow with shear stress $<5$ dynes/cm$^2$, promote ROS generation, adhesive and inflammatory molecules, vasoconstrictors, endothelial proliferation and apoptosis (Figure 3) [24–26].

5. Shear stress induced Nrf2

Nrf2, a basic leucine zipper (bZIP) transcription factor is widely expressed and can be found in many organs and tissues such as the kidney, muscle, lung, heart, liver and brain [25]. The CNC family of proteins regulates gene expression, tissue differentiation and development in a variety of organs. Nrf2, perhaps the most studied of the CNC family, is responsible for the expression of phase II enzymes and a number of endogenous antioxidants including ARE-mediated processes that induce the activation of antioxidative enzymes and detoxifying enzymes, including heme oxygenase 1 (HO-1), quinone oxidoreductase (NQO1), nicotinamide adenine dinucleotide phosphate (NAD(P)H), and glutathione-S-transferase (GST) [26, 27].

Under basal conditions, the amount of Nrf2 is low due to its continuous sequestration by KEAP1 and subsequent proteasomal degradation. In this homeostatic state, Nrf2 is continuously ubiquitinated and targeted for proteasomal degradation by Kelch-like (ECH)-associated protein 1 (KEAP1). Electrophiles from endogenous and exogenous sources or other small molecules which can activate Nrf2 are thus able to do so by inactivating KEAP1 or by disrupting the KEAP1-Nrf2 binding interface [17]. Shear stress generated KLF2 induces nuclear translocation of the Nrf2 which leads to more Nrf2-ARE interactions and production of antioxidant agents (Figure 4).

The transcription factor that functions as the key controller of the redox homeostatic gene network, Nrf2 has roles in metabolic reprogramming, proteostasis, autophagy, unfolded protein response, mitochondrial biogenesis. Inflammation, and immunity. Through this complex regulatory network, Nrf2 appears to function as a truly pleiotropic transcription factor [28, 29].

Together, more than 500 Nrf2 target genes have varying roles in mounting cellular defenses through encoding a large network of proteins, some of which catalyze phase I, II and III cytoprotective detoxification, while others are antioxidant and anti-inflammatory agents [30]. Nrf2 plays a large role in controlling cellular redox homeostasis through the regulation of key enzymes and proteins involved in synthesis, utilization and regeneration of glutathione (GSH), thioredoxin (TXN), peroxiredoxin and NADPH [31]. The activities of Nrf2 are a major determinant of the cellular redox state.

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Exposure to toxicants or ROS from oncogenic signaling, genetic mutations, chronic wounds, autophagy disruption, or metabolic alterations disrupt the KEAP1-Nrf2 complex leading to proteasomal degradation of Keap1 and the translocation and activation of Nrf2. KLF2 substantially enhances antioxidant activity of Nrf2 by inducing its nuclear localization and activation [16]. Nrf2 translocates into the nucleus where it heterodimerizes with a small musculoaponeurotic fibrosarcoma (sMAF) protein and binds to the antioxidant response elements (ARE), transcription
Figure 4. The SS/KLF2/Nrf2/ARE pathway. Shear stress upregulates KLF2 which induces the nuclear translocation and activation of Nrf2, while, concurrently, free radicals break Keap1-Nrf2 binding and lead to its degradation. Nrf2 interacts with ARE to upregulate a broad array of antioxidant elements.

Figure 5. The SS/KLF2/Nrf2/ARE cardioprotective pathway. Showing the effects of the SS/Nrf2/KLF2/ARE pathway in cardiovascular health. The chart will be very similar for all diseases of oxidative stress.
factors and cofactors to regulate its target genes, encoding proteins involved in antioxidants, detoxification, metabolism, and inflammation (Figure 5) [8, 17].

Since Nrf2 helps protect cells from oxidative damage, it aids in preventing major diseases. Several reports have shown the importance of the Keap1–Nrf2 system as a therapeutic target for many neurodegenerative diseases and even cancer. As a consequence, academia and the pharmaceutical industry have been investigating the Keap1–Nrf2 system attempting to increase Nrf2. Several pharmacological inhibitors of Keap1 have been developed to boost the effectiveness of the Nrf2/ARE pathway.

Several studies have documented the age-related decline of Nrf2. On the other hand, Narashimhan and Rajasekaran, [33] as well as Grounder and colleagues [34] found that simulated exercise in murine examples using electrical stimulation resulted in significant improvement in Nrf2 levels. In the case of Grounder’s group, after six weeks of simulated moderate exercise, the aged group improved their Nrf2 levels to nearly equal those of the young group. It would seem, in light of this, that age is not the problem: lack of hemodynamic flow is the problem.

6. Shear stress generated KLF2

KLF2 is induced by SS and for more than twenty years SS importance in endothelial medicine has been steadily growing. Initially, there were investigations into whether KLF2 was an essential regulator of endothelial and organ system survival. Investigators demonstrated that KLF2 expression is increased during laminar flow in homeostasis and is reduced because of low or turbulent flow or cytokine storm. KLF2 promotes EC health through a profile of >1,000 target genes and suppresses inflammation in part through its competition with NFkB for critical transcriptional co-factors (Figure 6). KLF2 also promotes transcription of anti-thrombotic
genes, further lending to its vasoprotective role. Endothelial KLF2 acts as a master controller promoting EC quiescence and integrity through its effects in multiple transcriptional networks [36]. In physiological conditions, the vascular endothelium is largely maintained in a quiescent and impermeable state by the constitutive activity of KLFs and the mechanosensory proteins VE-cadherin and platelet endothelial cell adhesion molecule-1 (PECAM-1). Upregulation of KLF2 results in the upregulation of Nrf-2 and eNOS together with concomitant inhibition of mitochondrial ROS production while inhibiting the transcriptional activity of NF-κB.

C-type natriuretic peptide (CNP), an autocrine and paracrine mediator is potently induced by KLF2 in cardiomyocytes and fibroblasts. It regulates a number of vital physiological functions in the cardiovascular system [37]. Circulating biomarkers of healthy endothelial function would be useful to detect the earliest deficiencies in endothelial function. CNP is an endothelial paracrine factor that has been implicated in endothelial-dependent vasodilation in certain vascular beds, in addition to suppressing neointimal hyperplasia. CNP acts on adjacent vascular smooth muscle cells by impinging on the cyclic guanosine monophosphate (cGMP) pathway that is also responsive to NO. Parmar and colleagues demonstrated that CNP is induced by statins in a KLF2-dependent manner which indicates that this molecule could be a possible biomarker of EC [38].

7. Other shear stress-generated antioxidants

The role of hemodynamics in oxidative homeostasis is of major importance. The SS/KLF2/Nrf2/ARE pathway is powerful and important, but hemodynamically driven SS produces additional synergistically acting and interacting antioxidants that can help restore redox balance. The body’s endogenous antioxidant defense system relies on a complex group of enzymatic and nonenzymatic antioxidants that act against free radicals to blunt or block their pathological effects. The hemodynamically regulated antioxidants discussed below, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), heme oxygenase-1 (HO1), thioredoxin (TRX), and sirtuin (SIRT1), are indispensable in the defense against oxidative stress. These antioxidants are in continuous action to balance against ROS which are continuously generated in normal body metabolism, in particular through the mitochondrial energy production pathway.

7.1 Superoxide dismutase (SOD)

The first detoxification enzyme and the most powerful antioxidant in the body is SOD. It is an antioxidant enzyme that acts as the body’s first line of defense against ROS. SOD catalyzes the dismutation of two molecules of superoxide anion to hydrogen peroxide (H2O2) and molecular oxygen (O2), rendering the superoxide anion less toxic (the H2O2 is further reduced by CAT and GPx). SOD is a metalloenzyme and has a metal cofactor for its activity. Three isoforms of the enzyme are identified as 1. copper/zinc (Cu/Zn SOD), 2. manganese (Mn SOD), and 3. iron (Fe/SOD) also known as extracellular (EC/SOD) [39, 40].

7.2 Catalase (CAT)

Catalases are enzymes that can neutralize hydrogen peroxide, a ubiquitous oxidant. The enzyme catalyzes the dismutation of two molecules of hydrogen peroxide into one molecule of oxygen and one molecule of water. CAT has a very
high turnover rate: one catalase enzyme can convert 40 million molecules of hydrogen peroxide to oxygen and water per second. This enzyme is necessary for survival as it prevents hydrogen peroxide from accumulating to dangerous levels. Hydrogen peroxide at high levels in the body can induce cellular damage [41, 42].

7.3 Heme oxygenase-1 (HO1)

The antioxidant effects of HO-1 consist of its ability to increase glutathione levels and to degrade heme, as well as to induce biliverdin and bilirubin, both of which have potent antioxidant properties. Biliverdin is a tetrapyrrolic, water-soluble compound formed when heme is broken down into biliverdin, carbon monoxide and iron by heme oxygenase. Biliverdin is anti-mutagenic, antioxidant, anti-inflammatory, and immunosuppressant [43, 44].

7.4 Glutathione peroxidase (GPx)

Hemodynamic shear stress strongly upregulates the GPx family of extracellular antioxidant proteins that catalyze the reduction of hydrogen peroxide and lipid hydroperoxides into water and alcohols. Sometimes, its activity depends on selenium as a cofactor, and for this reason, it is often referred to as a selenocysteine peroxidase. GPx fills a crucial role by inhibiting the lipid peroxidation process to protect cells from oxidative stress [45, 46].

7.5 Thioredoxin (TRX)

The Trx system, which includes NADPH, thioredoxin reductase (TrxR), and TRX, is an important system defending against oxidative stress through its disulfide reductase activity regulating protein dithiol/disulfide balance. The cytosolic and mitochondrial Trx systems, in which TrxRs are high molecular weight selenoenzymes, in concert with the glutathione-glutaredoxin (Grx) system (NADPH, glutathione reductase, GSH, and Grx) control cellular redox [47, 48].

7.6 Sirtuin (SIRT1)

SIRTs are a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases with the ability to deacetylate histone and nonhistone targets and is linked to cellular metabolism, the redox state and survival pathways. SIRT1 deficiency in endothelial cells (ECs), vascular smooth muscle cells and monocytes/macrophages contributes to increased oxidative stress, inflammation, foam cell formation, senescence and impaired nitric oxide production. It is well established that endogenous NO generated from eNOS plays a crucial role in maintaining vascular function and homeostasis, which facilitates vascular tone, leukocyte adhesion, smooth muscle cell proliferation and migration, and platelet aggregation. Previous studies have shown that endogenous NO serves as an anti-atherosclerotic and anti-aging factor and that SIRT1 in endothelial cells regulates NO production. SIRT1 may play a crucial role in reducing inflammation and oxidative stress. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) deacetylation by SIRT1 reduces oxidative stress through expression of antioxidant enzymes, including Mn-SOD. Additionally, Forkhead box protein O3a (FOXO3a) is deacetylated by SIRT1 and translocates to the nucleus, resulting in the upregulation of other antioxidant enzymes and catalases, thereby providing protection against oxidative stress [49–51].
8. Conclusions and further perspectives

The restoration of normal hemodynamics can provide a viable solution for the debilitating diseases that result from oxidative stress (Figure 1). While it may seem unlikely, the body has a large, complex, and robust antioxidant system with overlapping and synergistic actions. All those systems, however, are contingent upon hemodynamic activation of endocrine, autocrine and paracrine systems to restore the enzymes, proteins, genes, and other antioxidants essential for redox homeostasis. Numerous in vivo studies indicate that oxidative damage occurs from reduced levels of antioxidant enzymes rather than increased production of ROS. The utilization of hemodynamic forces and shear stress-initiated endothelial mechanotransduction to increase antioxidant enzymes is evident in the literature and warrants further investigation. The development of means and methods that enhance normal hemodynamics is also needed.
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