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Review Article

Role of Free Radical-induced Oxidative Stress in the Pathogenesis of Coronary Artery Disease

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Abstract
Oxidative stress is associated with various pathophysiological events such as cancer, kidney diseases, and diabetes. Studies have shown that reactive oxygen species (ROS) also play a key role in the development of vasculopathies and can cause disorders such as atherosclerosis, hypertension, and coronary stenosis. Atherosclerosis, due to endothelial cell damage, results in at least impaired endothelial function and consequently macrophage infiltration and impaired smooth muscle function. Since then, many researchers have focused on low-density lipoprotein (LDL) oxidation and its interaction with the endothelium as the primary injury that leads to the formation of fatty streaks and eventually to atherogenesis. It has now become clear that different types of ROS are not only produced in the vessel wall but also contribute to the pathogenesis of a range of cardiovascular disorders individually and collectively.
Keywords: Oxidative stress, Coronary artery disease, Reactive oxygen species, Atherosclerosis

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Coronary Artery Disease

Coronary artery disease (CAD) is a common heart disease. The disease has many victims, especially in advanced societies and old ages. Coronary arteries disease develops when the coronary arteries become too narrow that limit blood supply to the heart. In the advanced case, if blood supply to a coronary artery is completely blocked, the blood supply to the part of the heart muscle will stop that results in myocardial infarction (1-2).

Prevalence of Coronary Artery Disease

According to the World Health Organization (WHO), the number of global CAD-related deaths is 17.9 million people. During the period from 2006 to 2010, approximately 117 2000 deaths were reported in Iran, of which 46% (n = 539 679 cases) occurred due to CAD. There was a decreasing trend in CAD-related deaths during 2006 to 2008, but the above-mentioned rate increased during 2009 and 2010. The highest number of CAD-related deaths was reported in 2001 (n = 110 985 cases) and the lowest rate in 2008 (n = 106 129 cases) (3). In general, the prevalence of CAD is 13.1% in Iran. The prevalence of CAD in patients with chest pain is higher than in patients without chest pain (22.3% vs. 8.2%). The prevalence of CAD is higher in patients with CAD-related risk factors than in patients without risk factors (22.5 vs. 9.5%) (4).

Risk Factors for Coronary Artery Disease

Many risk factors, including hyperlipidemia, diabetes, hypertension, smoking, and obesity, are important contributors to CAD. However, approximately 2% of cardiovascular events occur in people who do not have any of these risk factors (2). Many recent studies have suggested a link between increased production of ROS and CAD. High ROS concentrations can cause membrane lipid peroxidation, protein alteration, DNA breakage, activation of neutrophils, disruption of signal transduction pathways and impairment of the regulation of vascular cells and cardiac myocyte (5, 6). The body is equipped with antioxidant systems to defend against oxidant agents that improve vascular function and inhibit atherogenesis by clearing free radicals (7). In this regard, fat-soluble vitamins, especially vitamin E and aqueous phase antioxidants, including glutathione and vitamin C play a very prominent role. Vitamin E, found

in low-density lipoprotein (LDL) particles, inhibits lipid peroxidation (8). Previous studies have shown increased LDL oxidation, altered levels of antioxidant enzymes including glutathione peroxidase, superoxide dismutase and catalase, as well as a decrease in vitamins C, A and E in CAD patients (9-20).

The Mechanism of Plaque Formation in Vessels and Subsequent Damage to coronary Cells

The primary event following the development of atherosclerosis is endothelial damage, which leads to the penetration and accumulation of LDL in the subendothelial space. LDL accumulated in pathological states during the oxidation process is converted to oxidized LDL (ox-LDL). These modified lipoproteins increase the expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) on endothelial cells, leading to the recruitment of leukocytes in the subendothelial space. These inflammatory cells migrate into intima by the interaction of chemotaxis factors such as monocyte chemoattractant protein-1 (MCP-1), eotaxin, and INF-γ. The monocytes that enter this space swallow deformed lipoproteins. These fat-laden macrophages are called foam cells and the appearance of these foam cells in the arterial wall is characteristic of the primary atherosclerotic lesion. Lymphocytes and monocytes migrated to intima, together with foam cells, release a variety of cytokines that lead to inflammation and ROS production. Growth factors released by these cells, as well as stimulation of smooth muscle cell migration by oxygen free radicals and collagen deposition, lead to the development of atheromatous plaque. The important thing in this process is that oxygen free radicals make smooth muscle cells express scavenger receptors and be converted into foam cells. ROSs also release matrix metalloproteinases (MMPs), which destroys the wall of fibers in atheromatous plaque and the endothelial basement membrane, leading to the physical breakdown of the plaque and in turn vascular obstruction (21).

Reactive Oxygen Species

There are many ROSs that are produced by different reactions in the body (Figure 1) and play central roles in vascular physiology (Figure 2) and pathophysiology, the most important of which include nitric oxide (NO), superoxide (O^-_2), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$). NO is usually produced by endothelial nitric oxide synthase (eNOS) in the vascular endothelium, but inducible nitric oxide synthase (iNOS) is expressed in macrophages and smooth muscle cells under inflammatory conditions. NO is a critical mediator of endothelium-dependent vasodilation and may also play a role in plaque aggregation and maintain balance between smooth muscle cell growth and differentiation. Superoxide is produced by the reduction of an oxygen electron by various types of oxidases. When O^-_2 is produced along

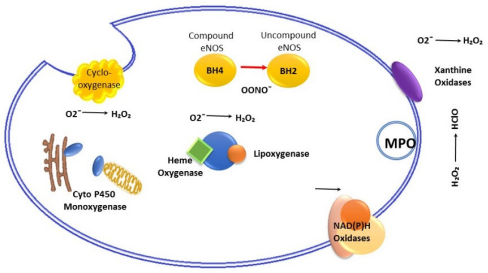

Figure 1. Potential Sources of ROS.

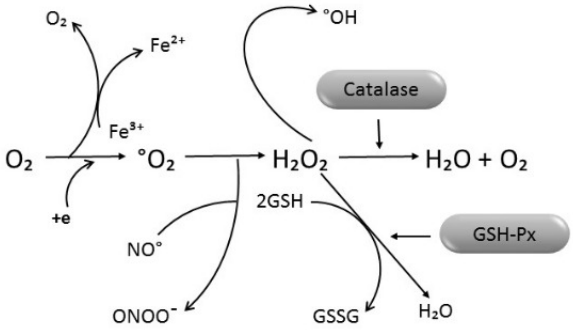

Figure 2. ROS Which Play Central Roles in Vascular Physiology.

with NO, they react rapidly and form a highly reactive molecule ($ONOO^-$). $ONOO^-$ is an important mediator for lipid peroxidation and protein nitration, including LDL oxidation. It has significant proatherogenic effects. In the absence of NO, O^-_2 is rapidly converted to ROS and more stable H_2O_2 by the superoxide dismutase enzyme, which is then converted to H_2O by catalase or glutathione peroxidase. The effects of O^-_2 and H_2O_2 on vascular function are critically dependent on their production rate. When formed in small amounts intracellularly, they can act as secondary intracellular messengers and pathways that result in the growth of vascular smooth muscle cells (VSMCs) and fibroblasts. High ROS concentrations can cause DNA damage, significant toxicity, or even apoptosis, which has been proved in endothelial cells and smooth muscle cells (22, 23).

Cellular and Enzymatic Sources of ROS in the Vessel Wall

Oxidative stress reflects the imbalance between ROS production and the ability of a biological system to neutralize and inhibit its toxic mediators or repair damage. Any disturbance and disruption of the normal state of oxidation-reduction through the production of

peroxides and free radicals results in toxic effects and damage to all intracellular components and structures, including proteins, lipids, and DNA (24-27).

Various ROSs are produced by enzymatic or chemical reactions. NO is produced in endothelial cells by activating eNOS during normal vascular function. Vasodilator hormones increase intracellular Ca^{2+}, which leads to increased eNOS activity and NO release. Physical forces, such as shear stress, activate eNOS through protein kinase A or Akt-dependent phosphorylation. The pathophysiological expression of iNOS in macrophages and VSMCs increases the level of cytokines and consequently local inflammation. This, in turn, results in NO production in the absence of further stimuli. In addition, eNOS is deactivated and O^-_2 is produced more than NO_3 under some conditions. Therefore, depending on the surrounding environment, NOS enzymes are potentially important sources of NO and O^-_2 (28).

Almost all types of vascular cells produce O^-_2 and H_2O_2 (29). In addition to mitochondrial sources of ROS, O^-_2 or H_2O_2 can be produced by many enzymes (Figure 2). Cytochrome P450 and membrane-associated NADPH oxidases are thought to be two important sources of ROS in normal vessels (30, 31). The homologous cytochrome P450 isoenzyme with CYP 2C9 has been identified in coronary arteries and shown to produce O^-_2 in response to bradykinin (32). NADPH oxidases, which are structurally similar to neutrophil NADPH oxidases but produce less O^-_2 over a longer period of time, have been identified in vascular cells. Endothelial enzymes, VSMCs, and fibroblasts are not the same but have subunits and unique regulatory mechanisms. One important aspect of ROS generation by VSMC (Vascular smooth muscle cells) NADPH oxidase is that it occurs mainly intracellularly and makes it ideally suited for modifying signal transduction pathways and gene expression (29).

The activity of NADPH oxidases can be modulated by vasodilator hormones affecting the vascular wall and G-protein 1-rac (33). Angiotensin II (Ang II), tumor necrosis factor-α (TNF)-α, thrombin, and platelet-derived growth factor all enhance oxidase activity and elevate intracellular O^-_2 and H_2O_2 levels in VSMCs. Ang II and ceramide lactoside activate endothelial cells, whereas fibroblasts increase O^-_2 production in response to Ang II, TNF-α, interleukin-1, and platelet-activating factor. Physical pressures such as cellular stretching, laminar shear stress, and oscillatory flow distribution occurring at the branch points are also potent activators of O^-_2 production in endothelial cells. There are two major mechanisms by which the hormones and physical forces activate NADPH oxidase: 1. Rapid mechanism by which the expression of the enzyme is activated by phosphorylation, GTPase activity, and the production of related second messengers (34) and 2. long-term mechanism which works when enzyme rate-limiting subunits are overexpressed and consequently higher levels of the enzyme are likely to be activated (35).

Macrophages may be the major source of vascular O^-_2 in the case of diseases. They oxidize LDL by activating various enzymes. Neutrophils and monocytes may also secrete myeloperoxidase, which seems to initiate lipid peroxidation (36). Two potential candidates for the initiation of myeloperoxidase-dependent lipid peroxidation include tyrosyl radical and nitrogen dioxide (NO_2). The removal of myeloperoxidase markedly reduces the formation of F2-isoprostanes (F2iPs), indicators of in vivo lipid peroxidation in an experimental model of peritonitis (37).

Biochemical Consequences of ROS Production in the Vessel Wall

As noted above, ROS participates in some of the most basic functions of the vessel wall. NO is a critical mediator for endothelium-dependent vasodilation, whereas O^-_2 and H_2O_2 mediate VSMC growth, differentiation, and apoptosis. $ONOO^-$ –induced lipid peroxidation and protein nitration are some of the earliest atherogenic events. Since macrophages induce extracellular ROS release, they activate MMP-2 and MMP-9 (38, 39). Once activated, MMPs can degrade collagen-based extracellular matrix and help attenuate fibrous cap and plaque breakdown (38). In VSMCs, ROS exerts its effects by activating specific intracellular signaling pathways and can severely affect normal physiology and the course of vascular disease. In addition, it is evident that stable ROSs may also affect cell function by acting on messenger molecules or by acting as random ligands for membrane and nuclear receptors in vascular cells.

Since only NO is involved in vasodilation by activating VSMC guanylate cyclase, O^-_2 and H_2O_2 can alter the activity of selected intracellular proteins. Unlike NO, no specific target has been identified for this ROS and there is no clear identity for the actual reactive species although laboratory studies show that O^-_2 and H_2O_2 are capable of inhibiting protein phosphatases (40-42). ROS regulates several general classes of genes, including adhesion molecules and chemotactic factors, antioxidant enzymes, and vasoactive substances. Some of these are clearly considered adaptive responses, such as the induction of superoxide dismutase and catalase by H_2O_2. There is a specific relationship between severe regulation of adhesion molecules (VCAM-1, ICAMs) and chemotactic molecules (MCP-1) by oxidant-sensitive mechanisms with vascular pathology. These molecules reinforce adhesion and migration of monocytes into the vessel wall. In contrast, transcriptional induction of adhesion molecules by cytokines is inhibited by NO independently through cyclic guanosine monophosphate. These mechanisms are incorporated into the normal vascular wall by suppressing the expression of the adhesion molecule and stimulate its expression in vasculopathies or vessels (43, 44).

Conclusion

Free radical-induced oxidative stress plays a key role in the pathogenesis of cardiovascular diseases. Modulation of free radical production is an important modality in the reduction or treatment of cardiovascular diseases.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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Ethical Statement

Not applicable.

Authors' Contribution

RA wrote the manuscript. MM, HA, and EE collected the data, revised the literature and contributed to conception and design of the study. All authors contributed to critical revision, edition, and final approval of the manuscript.

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Informed Consent

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References

1. Chand R. Coronary artery disease. In: Eltorai A, Hyman C, Healey T, eds. Essential Radiology Review. Cham: Springer; 2019. p. 263-5. doi: 10.1007/978-3-030-26044-6_75.
2. Boulanger CM, Loyer X, Rautou PE, Amabile N. Extracellular vesicles in coronary artery disease. Nat Rev Cardiol. 2017;14(5):259-72. doi: 10.1038/nrcardio.2017.7.
3. Koohi F, Salehinia H, Mohammadian-Hafshejani A. Trends in mortality from cardiovascular disease in Iran from 2006-2010. Journal of Sabzevar University of Medical Sciences. 2015;22(4):630-8. [Persian].
4. Babapour Saatlou B, Kazemi Khaledi A. Prevalence of coronary artery disease among the candidate patients for cardiac valve's surgery in Tehran-Imam Khomeini hospital (1999-2003). Journal of Ardabil University of Medical Sciences. 2007;7(3):254-8. [Persian].
5. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol. 2004;29(8):439-93.
6. Ambrosio G, Tritto I. Reperfusion injury: experimental evidence and clinical implications. Am Heart J. 1999;138(2 Pt 2):S69-75. doi: 10.1016/s0002-8703(99)70323-6.
7. Griendling KK, Sorescu D, Lassègue B, Ushio-Fukai M. Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology. Arterioscler Thromb Vasc Biol. 2000;20(10):2175-83. doi: 10.1161/01.atv.20.10.2175.
8. Schwenke DC. Antioxidants and atherogenesis. J Nutr Biochem. 1998;9(8):424-45. doi: 10.1016/S0955-2863(98)00046-1.
9. Princen HM, van Poppel G, Vogelezang C, Buytenhek R, Kok FJ. Supplementation with vitamin E but not beta-carotene in vivo protects low density lipoprotein from lipid peroxidation in vitro. Effect of cigarette smoking. Arterioscler Thromb. 1992;12(5):554-62. doi: 10.1161/01.atv.12.5.554.
10. Pastore A, Federici G, Bertini E, Piemonte F. Analysis of glutathione: implication in redox and detoxification. Clin Chim Acta. 2003;333(1):19-39. doi: 10.1016/s0009-8981(03)00200-6.
11. Sen CK. Redox signaling and the emerging therapeutic potential of thiol antioxidants. Biochem Pharmacol. 1998;55(11):1747-58. doi: 10.1016/s0006-2952(97)00672-2.
12. Arrigo AP. Gene expression and the thiol redox state. Free Radic Biol Med. 1999;27(9-10):936-44. doi: 10.1016/s0891-5849(99)00175-6.
13. Ashfaq S, Abramson JL, Jones DP, Rhodes SD, Weintraub WS, Hooper WC, et al. The relationship between plasma levels of oxidized and reduced thiols and early atherosclerosis in healthy adults. J Am Coll Cardiol. 2006;47(5):1005-11. doi: 10.1016/j.jacc.2005.09.063.
14. Kugiyama K, Ohgushi M, Motoyama T, Hirashima O, Soejima H, Misumi K, et al. Intracoronary infusion of reduced glutathione improves endothelial vasomotor response to acetylcholine in human coronary circulation. Circulation. 1998;97(23):2299-301. doi: 10.1161/01.cir.97.23.2299.
15. Weinbrenner T, Cladellas M, Isabel Covas M, Fitó M, Tomás M, Sentí M, et al. High oxidative stress in patients with stable coronary heart disease. Atherosclerosis. 2003;168(1):99-106. doi: 10.1016/s0021-9150(03)00053-4.
16. Azarsiz E, Kayikcioglu M, Payzin S, Yildirim Sözmen E. PON1 activities and oxidative markers of LDL in patients with angiographically proven coronary artery disease. Int J Cardiol. 2003;91(1):43-51. doi: 10.1016/s0167-5273(02)00595-8.
17. Yegin A, Yegin H, Alicigüzel Y, Deger N, Semiz E. Erythrocyte selenium-glutathione peroxidase activity is lower in patients with coronary atherosclerosis. Jpn Heart J. 1997;38(6):793-8. doi: 10.1536/ihj.38.793.
18. Delport R, Ubbink JB, Human JA, Becker PJ, Myburgh DP, Vermaak WJ. Antioxidant vitamins and coronary artery disease risk in South African males. Clin Chim Acta. 1998;278(1):55-60. doi: 10.1016/s0009-8981(98)00131-4.
19. Serdar Z, Aslan K, Dirican M, Sarandöl E, Yeşilbursa D, Serdar A. Lipid and protein oxidation and antioxidant status in patients with angiographically proven coronary artery disease. Clin Biochem. 2006;39(8):794-803. doi: 10.1016/j.clinbiochem.2006.02.004.
20. Nojiri S, Daida H, Mokuno H, Iwama Y, Mae K, Ushio F, et al. Association of serum antioxidant capacity with coronary artery disease in middle-aged men. Jpn Heart J. 2001;42(6):677-90. doi: 10.1536/jhj.42.677.
21. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. Curr Atheroscler Rep. 2017;19(11):42. doi: 10.1007/s11883-017-0678-6.
22. Niwa K, Inanami O, Yamamori T, Ohta T, Hamasu T, Karino T, et al. Roles of protein kinase C delta in the accumulation of P53 and the induction of apoptosis in H2O2-treated bovine endothelial cells. Free Radic Res. 2002;36(11):1147-53. doi: 10.1080/1071576021000016409.
23. Deshpande NN, Sorescu D, Seshiah P, Ushio-Fukai M, Akers M, Yin Q, et al. Mechanism of hydrogen peroxide-induced cell cycle arrest in vascular smooth muscle. Antioxid Redox Signal. 2002;4(5):845-54. doi: 10.1089/152308602760599007.
24. Nourooz- Zadeh J, Eftekhar E, Haghparast F, Khademwatan, Ekhlasmand M. Evaluation of measures of oxidative stress in patients with proven coronary artery disease (CAD) compared with normal persons. J Adv Med Biomed Res. 2007; 15 (60) :47-56.
25. Hajizadeh MR, Eftekhar E, Zal F, Jafarian A, Mostafavi-Pour Z. Mulberry leaf extract attenuates oxidative stress-mediated testosterone depletion in streptozotocin-induced diabetic rats. Iranian Journal of Medical Sciences. 2014 Mar; 39(2):123.
26. Nourooz-Zadeh J, Eftekhar E. Physiological importance of

glutathione in health and disease. Journal of Birjand University of Medical Sciences. 2007 Sep 10;14(3):9-15.
27. KhademVatan K, Haghparast F, Eftekhar E, NorozZadeh J. Pro oxidant and antioxidant status in patients with coronary artery disease proven angiographic ally. Hormozgan Medical Journal. 2009; 12(4):231-6.
28. Vásquez-Vivar J, Kalyanaraman B, Martásek P, Hogg N, Masters BS, Karoui H, et al. Superoxide generation by endothelial nitric oxide synthase: the influence of cofactors. Proc Natl Acad Sci U S A. 1998;95(16):9220-5. doi: 10.1073/pnas.95.16.9220.
29. Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. Circ Res. 2000;86(5):494-501. doi: 10.1161/01.res.86.5.494.
30. Rajagopalan S, Kurz S, Münzel T, Tarpey M, Freeman BA, Griendling KK, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest. 1996;97(8):1916-23. doi: 10.1172/jci118623.
31. Fleming I, Michaelis UR, Bredenkötter D, Fisslthaler B, Dehghani F, Brandes RP, et al. Endothelium-derived hyperpolarizing factor synthase (Cytochrome P450 2C9) is a functionally significant source of reactive oxygen species in coronary arteries. Circ Res. 2001;88(1):44-51. doi: 10.1161/01.res.88.1.44.
32. Buttery LD, Springall DR, Chester AH, Evans TJ, Standfield EN, Parums DV, et al. Inducible nitric oxide synthase is present within human atherosclerotic lesions and promotes the formation and activity of peroxynitrite. Lab Invest. 1996;75(1):77-85.
33. Griendling KK, Sorescu D, Lassègue B, Ushio-Fukai M. Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology. Arterioscler Thromb Vasc Biol. 2000;20(10):2175-83. doi: 10.1161/01.atv.20.10.2175.
34. Zafari AM, Ushio-Fukai M, Minieri CA, Akers M, Lassègue B, Griendling KK. Arachidonic acid metabolites mediate angiotensin II-induced NADH/NADPH oxidase activity and hypertrophy in vascular smooth muscle cells. Antioxid Redox Signal. 1999;1(2):167-79. doi: 10.1089/ars.1999.1.2-167.
35. Lassègue B, Sorescu D, Szöcs K, Yin Q, Akers M, Zhang Y, et al. Novel gp91(phox) homologues in vascular smooth muscle cells: nox1 mediates angiotensin II-induced superoxide formation and redox-sensitive signaling pathways. Circ Res. 2001;88(9):888-94. doi: 10.1161/hh0901.090299.
36. Brennan ML, Wu W, Fu X, Shen Z, Song W, Frost H, et al. A tale of two controversies: defining both the role of peroxidases in nitrotyrosine formation in vivo using eosinophil peroxidase and myeloperoxidase-deficient mice, and the nature of peroxidase-generated reactive nitrogen species. J Biol Chem. 2002;277(20):17415-27. doi: 10.1074/jbc.M112400200.
37. Zhang R, Brennan ML, Shen Z, MacPherson JC, Schmitt D, Molenda CE, et al. Myeloperoxidase functions as a major enzymatic catalyst for initiation of lipid peroxidation at sites of inflammation. J Biol Chem. 2002;277(48):46116-22. doi: 10.1074/jbc.M209124200.
38. Galis ZS, Muszynski M, Sukhova GK, Simon-Morrissey E, Libby P. Enhanced expression of vascular matrix metalloproteinases induced in vitro by cytokines and in regions of human atherosclerotic lesions. Ann N Y Acad Sci. 1995;748:501-7. doi: 10.1111/j.1749-6632.1994.tb17348.x.
39. Rajagopalan S, Meng XP, Ramasamy S, Harrison DG, Galis ZS. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J Clin Invest. 1996;98(11):2572-9. doi: 10.1172/jci119076.
40. Görlach A, Brandes RP, Bassus S, Kronemann N, Kirchmaier CM, Busse R, et al. Oxidative stress and expression of p22phox are involved in the up-regulation of tissue factor in vascular smooth muscle cells in response to activated platelets. Faseb j. 2000;14(11):1518-28.
41. Ushio-Fukai M, Zafari AM, Fukui T, Ishizaka N, Griendling KK. p22phox is a critical component of the superoxide-generating NADH/NADPH oxidase system and regulates angiotensin II-induced hypertrophy in vascular smooth muscle cells. J Biol Chem. 1996;271(38):23317-21. doi: 10.1074/jbc.271.38.23317.
42. Suh YA, Arnold RS, Lassegue B, Shi J, Xu X, Sorescu D, et al. Cell transformation by the superoxide-generating oxidase Mox1. Nature. 1999;401(6748):79-82. doi: 10.1038/43459.
43. Lu D, Maulik N, Moraru II, Kreutzer DL, Das DK. Molecular adaptation of vascular endothelial cells to oxidative stress. Am J Physiol. 1993;264(3 Pt 1):C715-22. doi: 10.1152/ajpcell.1993.264.3.C715.
44. Spiecker M, Darius H, Kaboth K, Hübner F, Liao JK. Differential regulation of endothelial cell adhesion molecule expression by nitric oxide donors and antioxidants. J Leukoc Biol. 1998;63(6):732-9.