

SYMPATHOADRENAL ACTIVITY AND LIPID PEROXIDATION IN ISCHEMIC HEART DISEASE: PATHOGENETIC SIGNIFICANCE OF MALONDIALDEHYDE

Kholmirezayev S.A., G'ulomov M.A.

Impulse Medical Institute

Teacher of the Department of Pathology and Microbiology

Impulse Medical Institute

Teacher of the Department of Pathology and Microbiology

Gmail: saidkamolkholmirezayev1@gmail.com

Gmail: boburjongulomov991@gmail.com

Abstract. This article analyzes the pathogenetic relationship between lipid peroxidation, malondialdehyde, and activation of the sympathoadrenal system in ischemic heart disease. Ischemic heart disease is currently considered not only as a consequence of coronary artery narrowing, but also as a complex pathological process associated with oxidative stress, endothelial dysfunction, microcirculatory disorders, neurohumoral activation, and metabolic imbalance. Myocardial ischemia activates the sympathoadrenal system and increases the secretion of adrenaline and noradrenaline. Catecholamines increase heart rate, myocardial contractility, and myocardial oxygen demand. At the same time, their excessive production contributes to mitochondrial dysfunction, generation of reactive oxygen species, and activation of lipid peroxidation. Malondialdehyde, one of the main end-products of lipid peroxidation, is an important biochemical marker associated with cell membrane damage, PZLP modification, endothelial dysfunction, and atherosclerotic plaque instability. The relationship between sympathoadrenal hyperactivity and increased MDA levels in ischemic heart disease is important for assessing myocardial injury, arrhythmogenicity, and cardiac remodeling risk.

Keywords: ischemic heart disease, sympathoadrenal system, catecholamines, lipid peroxidation, malondialdehyde, oxidative stress, endothelial dysfunction, atherosclerosis, myocardial ischemia.

Introduction. Ischemic heart disease (IHD) is one of the most important problems in modern cardiology. Coronary atherosclerosis, endothelial dysfunction, microcirculatory disorders, oxidative stress, and dysregulation of neurohumoral control play an important role in its pathogenesis. In traditional views, IHD was explained by atherosclerotic narrowing of the coronary artery lumen and reduced myocardial perfusion. However, according to modern scientific approaches, IHD is considered not only a mechanical stenosis but also a systemic pathological process associated with metabolic, inflammatory, oxidative, and autonomic mechanisms.

Myocardial ischemia is perceived by the body as a stress condition. In response, the sympathoadrenal system becomes activated, and the secretion of adrenaline and noradrenaline increases. Initially, this mechanism helps maintain cardiac output, sustain arterial blood pressure, and ensure perfusion of vital organs. However, prolonged activation of the sympathoadrenal system gradually loses its compensatory nature and becomes a maladaptive process. Excessive secretion of catecholamines promotes tachycardia, increases myocardial oxygen demand, reduces coronary perfusion, and enhances mitochondrial dysfunction, oxidative stress, and lipid peroxidation.

Lipid peroxidation is the oxidative process involving polyunsaturated fatty acids in biological membranes under the influence of reactive oxygen species. During this process, reactive products such as lipid hydroperoxides, diene conjugates, 4-hydroxynonenal, and malondialdehyde are formed. Malondialdehyde (MDA) is one of the most extensively studied end products of lipid peroxidation and is regarded as an important laboratory marker of oxidative stress and membrane damage. Increased MDA levels in ischemic heart disease may be associated with cellular membrane injury, endothelial dysfunction, LDL modification, atherosclerotic plaque instability, and myocardial damage.

In IHD, there is a mutually reinforcing pathological relationship between the sympathoadrenal system, oxidative stress, and lipid peroxidation. Ischemia increases sympathetic activity, while sympathetic hyperactivity enhances the formation of reactive oxygen species through catecholamines.

Reactive oxygen species activate lipid peroxidation, resulting in increased MDA levels. In turn, MDA modifies membrane proteins, phospholipids, and LDL particles, thereby aggravating endothelial dysfunction and atherogenesis. Thus, a pathological chain is formed: “ischemia → sympathoadrenal activation → oxidative stress → lipid peroxidation → MDA → endothelial dysfunction.”

Aim of the study. To analyze, based on modern scientific literature, the pathogenetic relationship between lipid peroxidation, malondialdehyde, and activation of the sympathoadrenal system in ischemic heart disease, and to highlight the significance of these processes in the development of endothelial dysfunction, myocardial injury, atherosclerotic plaque instability, and arrhythmogenicity.

Literature review:

Activation of the sympathoadrenal system and oxidative stress.

In conditions of myocardial ischemia, the balance between cardiac contractility and coronary perfusion is disrupted. In response to this process, the sympathetic nervous system and the adrenal medulla become activated. As a result, the secretion of adrenaline, noradrenaline, and, to some extent, dopamine increases. Noradrenaline is mainly released from sympathetic nerve endings and exerts a direct effect on the heart. Adrenaline, in contrast, is mainly released from the adrenal glands and contributes to the formation of a systemic hemodynamic response. Catecholamines increase heart rate and myocardial contractility through β_1 -adrenoceptors. In the short term, this mechanism has compensatory significance. However, prolonged sympathoadrenal hyperactivity increases myocardial oxygen demand, shortens the duration of diastolic perfusion, and aggravates ischemia. In addition, excessive catecholamine levels enhance the formation of reactive oxygen species through mitochondria, the monoamine oxidase system, and NADPH oxidase.

During catecholamine oxidation, semiquinones, quinones, and other reactive metabolites may be formed. These metabolites damage cardiomyocyte membranes, mitochondrial DNA, ion channels, and contractile proteins. As a result, energy deficiency, impaired Ca^{2+} homeostasis, apoptosis, and electrical instability develop in cardiomyocytes. Therefore, chronic activation of the sympathoadrenal system is considered one of the major sources of oxidative stress in ischemic heart disease.

Mechanism of lipid peroxidation.

Lipid peroxidation is a chain biochemical process initiated by free radicals. This process mainly occurs in polyunsaturated fatty acids within cellular membranes. In the first stage, reactive oxygen species abstract a hydrogen atom from the fatty acid chain, leading to the formation of a lipid radical. In the next stage, the lipid radical reacts with oxygen and forms a lipid peroxy radical. This radical then affects other lipid molecules, generating new radicals and continuing the chain reaction. The main products of lipid peroxidation are lipid hydroperoxides, diene conjugates, 4-hydroxynonenal, and malondialdehyde. These products impair cell membrane fluidity, ion permeability, and receptor function. As a result, membrane stability decreases, mitochondrial membrane potential becomes disrupted, and intracellular signaling systems are damaged. In ischemic heart disease, lipid peroxidation is intensified by several sources, including myocardial ischemia, reperfusion, excessive catecholamine oxidation, RAAS activation, inflammatory mediators, and endothelial dysfunction. This process is especially pronounced during ischemia-reperfusion, when the re-entry of oxygen sharply increases the generation of reactive oxygen species. This, in turn, enhances lipid peroxidation and leads to an increase in MDA levels.

Biochemical and pathogenetic significance of malondialdehyde.

Malondialdehyde is one of the final reactive aldehyde products of lipid peroxidation. It is formed as a result of the oxidation of polyunsaturated fatty acids and is considered one of the widely used laboratory markers of oxidative stress. MDA is a biologically active molecule capable of reacting with proteins, phospholipids, and nucleic acids. One of the most important pathogenetic effects of MDA is the modification of LDL particles. The amino groups of apoprotein B-100 in LDL react with MDA, resulting in the formation of MDA-modified LDL. Such LDL particles are easily taken up by macrophages, thereby promoting foam cell formation. This process plays an important role in the formation and progression of atherosclerotic plaques.

MDA may also exert a negative effect on the endothelial glycocalyx. The endothelial glycocalyx is a protective layer of the vascular wall and participates in sensing shear stress, regulating nitric oxide production, and limiting platelet adhesion. When the glycocalyx is damaged under the influence of MDA, the endothelium cannot properly perceive mechanical signals, nitric oxide production decreases, and the vasodilatory response becomes impaired. As a result, coronary microcirculation and the regulation of vascular tone are disrupted. MDA may also directly damage cardiomyocytes. It modifies membrane phospholipids and proteins, thereby impairing ion channel function. This leads to disturbances in Ca^{2+} handling, sarcoplasmic reticulum function, and mitochondrial energetics. As a result, cardiomyocyte contractility decreases, diastolic relaxation is impaired, and arrhythmogenicity increases.

Interaction between MDA and the sympathoadrenal system.

In ischemic heart disease, the relationship between MDA and the sympathoadrenal system manifests in two directions. The first direction is that sympathoadrenal hyperactivity enhances MDA formation. Excessive catecholamine secretion increases the metabolic load on the heart, intensifies mitochondrial oxygen consumption, and increases the generation of reactive oxygen species. Reactive oxygen species, in turn, activate lipid peroxidation and lead to MDA formation.

The second direction is that MDA formation aggravates the consequences of sympathoadrenal activation. MDA damages membrane receptors, ion channels, and endothelial structures, thereby increasing the sensitivity of the myocardium and vascular wall to stress. When endothelial dysfunction develops, coronary blood flow cannot adequately adapt under conditions of sympathetic stimulation. As a result, myocardial ischemia becomes more severe against the background of tachycardia and increased arterial blood pressure.

Thus, a pathological vicious circle forms between the sympathoadrenal system and MDA. Myocardial ischemia activates the sympathoadrenal system; catecholamines enhance oxidative stress and lipid peroxidation; MDA levels increase; and MDA, in turn, aggravates endothelial dysfunction and myocardial injury, further intensifying ischemia. The endothelium is an important biological system that regulates vascular tone, platelet activity, inflammatory responses, and microcirculation. In ischemic heart disease, endothelial cell function is disrupted under the influence of oxidative stress and MDA. Reactive oxygen species combine with nitric oxide to form peroxynitrite, resulting in reduced nitric oxide bioavailability. A decrease in nitric oxide weakens the vasodilatory response of blood vessels and worsens coronary microcirculation. In the setting of sympathoadrenal activation, microcirculatory dysfunction becomes even more clinically significant because myocardial oxygen demand increases.

Myocardial injury, arrhythmogenicity, and remodeling.

An increase in MDA levels reflects membrane damage and mitochondrial dysfunction in myocardial cells. Lipid peroxidation in the cardiomyocyte membrane disrupts ion channel function, impairs Ca^{2+} homeostasis, and increases electrical instability. This creates conditions for the development of delayed afterdepolarizations, ectopic impulses, and ventricular arrhythmias.

Mitochondrial dysfunction reduces ATP production. Under conditions of energy deficiency, the activity of ion pumps such as $\text{Na}^+/\text{K}^+-\text{ATPase}$ and $\text{Ca}^{2+}-\text{ATPase}$ decreases. As a result, intracellular Na^+ and Ca^{2+} levels increase, spontaneous Ca^{2+} release from the sarcoplasmic reticulum is enhanced, and arrhythmogenicity increases. Sympathoadrenal hyperactivity further aggravates this process by increasing Ca^{2+} influx through β -adrenoceptor stimulation. Prolonged oxidative stress and increased MDA levels may contribute to fibroblast activation, collagen synthesis, and the development of interstitial fibrosis. In myocardial fibrosis, the propagation of electrical impulses becomes heterogeneous, a substrate for re-entry mechanisms is formed, and cardiac remodeling becomes more pronounced. Therefore, MDA is considered not only a marker of oxidative stress but also an important indicator associated with structural and functional changes in the myocardium.

Diagnostic significance of MDA assessment.

In clinical and scientific studies, MDA is most commonly determined using the thiobarbituric acid-reactive substances method. In this method, MDA forms a colored complex with thiobarbituric acid, and its intensity is assessed spectrophotometrically. An increase in MDA levels indicates activation of lipid peroxidation and enhanced oxidative stress in the body. In ischemic heart disease, the assessment of MDA together with catecholamines, heart rate variability, ECG, and echocardiographic parameters has scientific and practical significance. For example, in patients with high MDA levels, elevated catecholamines, and reduced HRV, sympathoadrenal hyperactivity and oxidative stress may be simultaneously active. Such a condition may increase the risk of myocardial injury, arrhythmias, and unfavorable outcomes after revascularization.

In addition, assessment of MDA levels before and after treatment may be useful for monitoring therapeutic effectiveness. A decrease in MDA levels during revascularization, β -blocker therapy, RAAS inhibitors, statins, and approaches with antioxidant properties may indicate a reduction in oxidative stress. However, in clinical practice, MDA should not be interpreted as an independent marker for decision-making, but rather in combination with other clinical, instrumental, and laboratory parameters.

Modern therapeutic approaches.

Approaches aimed at reducing lipid peroxidation and sympathoadrenal hyperactivity in ischemic heart disease should be comprehensive. β -blockers reduce the excessive effects of catecholamines on the heart, lower heart rate, and decrease myocardial oxygen demand. Through these mechanisms, ischemia, metabolic load, and oxidative stress may be reduced.

Statins, in addition to lowering LDL cholesterol, exert pleiotropic antioxidant and anti-inflammatory effects. They help reduce oxidized LDL levels, improve endothelial function, and increase the stability of atherosclerotic plaques.

RAAS inhibitors reduce the vasoconstrictive, pro-oxidant, and profibrotic effects of angiotensin II. As a result, NADPH oxidase activity, ROS formation, and myocardial remodeling processes are attenuated.

Although antioxidant approaches are theoretically important, their clinical use requires caution. Some meta-analyses have shown that supplements such as coenzyme Q10 may reduce MDA levels and increase the activity of antioxidant enzymes; however, these agents do not replace standard treatment for ischemic heart disease. Therefore, the main focus should remain on evidence-based therapies, including antithrombotic treatment, lipid control, β -blockers, RAAS inhibitors, appropriate determination of indications for revascularization, and lifestyle modification.

Conclusion

In ischemic heart disease, there is an important pathogenetic relationship between lipid peroxidation, malondialdehyde, and activation of the sympathoadrenal system. Myocardial ischemia activates the sympathoadrenal system, increases catecholamine secretion, and enhances myocardial oxygen demand. Prolonged sympathoadrenal hyperactivity promotes mitochondrial dysfunction, the generation of reactive oxygen species, and lipid peroxidation.

Malondialdehyde is an important final product of lipid peroxidation and reflects oxidative stress, membrane damage, LDL modification, endothelial dysfunction, and atherosclerotic plaque instability. Increased MDA levels in ischemic heart disease may be associated with myocardial injury, microvascular dysfunction, arrhythmogenicity, and remodeling processes.

Therefore, the assessment of MDA in patients with ischemic heart disease, together with catecholamines, ECG, echocardiography, heart rate variability, and other laboratory parameters, may help to better understand the pathogenetic activity of the disease. This approach represents a promising scientific and practical direction for risk stratification before and after revascularization, assessment of oxidative stress, and improvement of individualized monitoring strategies.

References

1. Byrne R.A., Rossello X., Coughlan J.J., Barbato E., et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *European Heart Journal*. 2023;44(38):3720–3826. doi:10.1093/eurheartj/ehad191.
2. Simantiris S., Papastamos C., Antonopoulos A.S., et al. Oxidative Stress Biomarkers in Coronary Artery Disease. *Current Topics in Medicinal Chemistry*. 2023;23(22):2158–2171. doi:10.2174/1568026623666230502140614.
3. Lankin V.Z., Tikhaze A.K., Melkumyants A.M. Malondialdehyde as an Important Key Factor of Molecular Mechanisms of Vascular Wall Damage under Heart Diseases Development. *International Journal of Molecular Sciences*. 2022;24(1):128. doi:10.3390/ijms24010128.
4. Kibel A., Lukinac A.M., Dambic V., et al. Oxidative Stress in Ischemic Heart Disease. *Oxidative Medicine and Cellular Longevity*. 2020;2020:6627144. doi:10.1155/2020/6627144.
5. Singal P.K., Kapur N., Dhillon K.S., Beamish R.E., Dhalla N.S. Potential oxidative pathways of catecholamines in the formation of lipid peroxides and genesis of heart disease. *Advances in Experimental Medicine and Biology*. 1983;161:391–401.
6. Dhalla N.S., Temsah R.M., Netticadan T. Role of oxidative stress in cardiovascular diseases. *Journal of Hypertension*. 2000;18(6):655–673.
7. Del Rio D., Stewart A.J., Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. *Nutrition, Metabolism and Cardiovascular Diseases*. 2005;15(4):316–328. doi:10.1016/j.numecd.2005.05.003.
8. Jorat M.V., Tabrizi R., Kolahdooz F., et al. The effects of coenzyme Q10 supplementation on biomarkers of inflammation and oxidative stress among coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. *Inflammopharmacology*. 2019;27(2):233–248. doi:10.1007/s10787-019-00572-x.
9. Kong A.S.Y., et al. Oxidative Stress Parameters as Biomarkers of Cardiovascular Disease: Toward a Standardized Approach. *Antioxidants*. 2022;11(6):1175. doi:10.3390/antiox11061175.