BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

NEUROIMMUNE PATHOGENETIC RELATIONSHIP BETWEEN THE SYMPATHOADRENAL SYSTEM AND INFLAMMATORY MEDIATORS IN ISCHEMIC HEART DISEASE

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https://doi.org/10.5281/zenodo.20521251

Abstract. This article analyzes the pathogenetic relationship between sympathoadrenal system activation and inflammatory mediators in ischemic heart disease. According to modern concepts, ischemic heart disease is not explained only by mechanical narrowing of the coronary arteries, but is considered a complex pathological process involving atherosclerotic plaque, endothelial dysfunction, impaired coronary microcirculation, oxidative stress, autonomic imbalance, and low-grade chronic inflammation. Myocardial ischemia activates the sympathoadrenal system and increases catecholamine secretion. As a result, heart rate, myocardial contractility, arterial blood pressure, and myocardial oxygen demand increase. At the same time, catecholamines may affect immune cells, the endothelium, and platelets, thereby enhancing the activity of inflammatory mediators such as IL-6, TNF-α, MCP-1, and CRP. Conversely, inflammatory mediators may impair autonomic regulation and contribute to prolonged sympathetic hyperactivity. Thus, a "neuroimmune vicious circle" is formed: ischemia activates the sympathoadrenal system, while sympathetic hyperactivity intensifies inflammation, oxidative stress, and endothelial dysfunction. These mechanisms play an important role in the progression of ischemic heart disease, atherosclerotic plaque instability, microvascular dysfunction, and adverse cardiovascular outcomes.

Keywords: ischemic heart disease, sympathoadrenal system, catecholamines, IL-6, TNF-α, MCP-1, CRP, inflammation, endothelial dysfunction, oxidative stress.

Introduction. Ischemic heart disease (IHD) is one of the most urgent problems in modern cardiology and is considered one of the leading causes of mortality and disability associated with cardiovascular diseases worldwide. Despite advances in the detection, treatment, and revascularization of coronary atherosclerosis, the risk of myocardial infarction, heart failure, arrhythmias, and sudden cardiac death related to IHD remains high. This requires the pathogenesis of the disease to be studied not only in terms of coronary artery stenosis, but also through neurohumoral, immune-inflammatory, oxidative, and microvascular mechanisms.

In the traditional approach, the main cause of IHD was considered to be atherosclerotic narrowing of the coronary artery lumen and reduced myocardial perfusion. However, in modern scientific concepts, IHD is regarded as a multicomponent pathological process. In this process, atherosclerotic plaque, endothelial dysfunction, impaired coronary microcirculation, autonomic nervous system imbalance, oxidative stress, and low-grade chronic inflammation interact with each other and determine the course of the disease.

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 from the adrenal medulla increases. In the short term, this response helps maintain cardiac output and arterial blood pressure. However, prolonged sympathetic hyperactivity increases myocardial oxygen demand, causes tachycardia and reduced coronary perfusion, and further aggravates ischemia. Inflammation plays an important role in the pathogenesis of IHD. Atherosclerosis is no longer regarded merely as the accumulation of lipids in the vascular wall, but rather as a chronic inflammatory process involving immune cells, cytokines, chemokines, oxidized lipoproteins, and endothelial activation. IL-6, TNF-α, MCP-1 (monocyte chemoattractant protein-1) and CRP are involved in atherosclerotic plaque formation, monocyte migration, endothelial dysfunction, platelet activation, and plaque instability.

There is a bidirectional relationship between the sympathoadrenal system and inflammatory mediators. Sympathetic hyperactivity enhances the production of inflammatory mediators through adrenergic receptors on immune cells. Conversely, IL-6, TNF-α, and other cytokines affect central autonomic regulation and baroreflex sensitivity, leading to the long-term maintenance of increased sympathetic tone. Thus, in ischemic heart disease, a vicious cycle is formed: "sympathoadrenal activation — inflammation — endothelial dysfunction — ischemia."

Aim of the study. To analyze, based on modern scientific literature, the pathogenetic relationship between sympathoadrenal system activation and inflammatory mediators in ischemic heart disease, as well as to highlight the association of IL-6, TNF-α, MCP-1, and CRP with endothelial dysfunction, oxidative stress, atherosclerotic plaque instability, and autonomic imbalance.

Literature review:

The role of sympathoadrenal system activation in ischemic heart disease.

As a result of myocardial ischemia, cardiomyocytes develop a deficiency of oxygen and energetic substrates. This may lead to reduced cardiac contractility, decreased cardiac output, and changes in arterial blood pressure. This condition is detected through baroreceptors and central autonomic centers, resulting in activation of the sympathetic nervous system as a compensatory response. The release of noradrenaline from sympathetic nerve endings and adrenaline from the adrenal medulla increases. Noradrenaline stimulates cardiac β1-adrenoceptors, increasing heart rate and myocardial contractility. Initially, this mechanism helps maintain cardiac output. However, when prolonged, it causes tachycardia, increased myocardial oxygen demand, shortening of diastolic coronary perfusion time, and aggravation of ischemia.

Catecholamines and inflammatory mediators.

Catecholamines not only regulate the hemodynamic response but also influence immune-inflammatory processes. Adrenergic receptors are present on immune cells, endothelial cells, and platelets. Chronic sympathetic hyperactivity may activate inflammatory signaling pathways such as NF-κB and MAPK through these cells, thereby increasing the secretion of IL-6, TNF-α, and MCP-1. IL-6 is an important pro-inflammatory cytokine in ischemic heart disease; it stimulates the synthesis of CRP and fibrinogen and enhances endothelial activation and the procoagulant state. TNF-α aggravates endothelial dysfunction, oxidative stress, and myocardial dysfunction. It reduces nitric oxide bioavailability and weakens the vasodilatory response of blood vessels. MCP-1 attracts monocytes to the subendothelial space and plays an important role in atherosclerotic plaque formation by promoting macrophage accumulation and foam cell formation. CRP is an important biomarker reflecting low-grade chronic inflammation and residual cardiovascular risk.

Oxidative stress and endothelial dysfunction.

In ischemic heart disease, activation of the sympathoadrenal system and inflammatory mediators mutually reinforce each other through oxidative stress. The production of reactive oxygen species increases as a result of catecholamines, IL-6, TNF-α, and RAAS activation. Reactive oxygen species combine with nitric oxide to form peroxynitrite, resulting in reduced nitric oxide bioavailability and the development of endothelial dysfunction.

Endothelial dysfunction leads to impaired coronary microcirculation, vasoconstriction, platelet activation, and microvascular ischemia. Therefore, oxidative stress is considered one of the main linking mechanisms between the sympathoadrenal system, inflammation, and impaired coronary perfusion in ischemic heart disease.

Atherosclerotic plaque instability and thrombosis.

Inflammatory mediators contribute to the destabilization of atherosclerotic plaques. IL-6 and TNF-α enhance endothelial inflammation, MCP-1 stimulates monocyte migration, and macrophages produce metalloproteinases that weaken the fibrous cap. As a result, the risk of plaque rupture and coronary thrombosis increases.

Activation of the sympathoadrenal system further intensifies this process. Tachycardia, elevated arterial blood pressure, and the effects of catecholamines on platelets create favorable conditions for plaque rupture and thrombosis. Therefore, stress and sympathetic hyperactivity may act as triggering factors for acute coronary events.

Heart rate variability and neuroimmune imbalance.

Heart rate variability is an important indicator for assessing autonomic regulation. SDNN is used to evaluate overall autonomic regulation, RMSSD mainly reflects parasympathetic activity, and LF/HF is used to assess the balance between the sympathetic and parasympathetic systems. In ischemic heart disease, reduced HRV may indicate sympathetic predominance and weakened parasympathetic protection.

When parasympathetic activity decreases, the anti-inflammatory cholinergic mechanism becomes weakened. This may contribute to the persistently elevated levels of mediators such as IL-6, TNF-α, and CRP. Therefore, the combined assessment of HRV parameters and inflammatory biomarkers is considered a promising approach for identifying the neuroimmune risk profile in patients with ischemic heart disease.

Modern therapeutic approaches.

The modern approach to the treatment of ischemic heart disease is not limited only to the restoration of coronary blood flow. The main goals are to reduce myocardial ischemia, slow the atherosclerotic process, decrease thrombotic risk, and control neurohumoral hyperactivity and residual inflammatory risk.

β-blockers reduce the adverse effects of the sympathoadrenal system on the heart, lower heart rate, and decrease myocardial oxygen demand. Statins, in addition to reducing LDL cholesterol, exert anti-inflammatory effects and improve endothelial function. RAAS inhibitors reduce the vasoconstrictive, pro-oxidant, and pro-inflammatory effects of angiotensin II. In recent years, anti-inflammatory approaches, including low-dose colchicine, have attracted scientific interest in terms of reducing atherosclerotic inflammation. However, such therapy should be selected based on individual risk, potential adverse effects, and the patient's clinical condition.

Conclusion

In ischemic heart disease, the relationship between sympathoadrenal system activation and inflammatory mediators represents an important neuroimmune component of disease pathogenesis. Myocardial ischemia activates the sympathoadrenal system, increases catecholamine secretion, and

enhances myocardial oxygen demand. Prolonged sympathetic hyperactivity, in turn, intensifies inflammation, oxidative stress, endothelial dysfunction, and platelet activation.

IL-6, TNF-α, MCP-1, and CRP are important mediators reflecting inflammatory activity, atherosclerotic plaque instability, and residual cardiovascular risk in ischemic heart disease. These mediators may also influence autonomic regulation and contribute to the maintenance of increased sympathetic tone. As a result, a vicious cycle is formed: "sympathoadrenal activation — inflammation — oxidative stress — endothelial dysfunction — ischemia."

Therefore, in the assessment of ischemic heart disease, it is important to consider not only the degree of coronary stenosis but also sympathoadrenal activity, heart rate variability parameters, and inflammatory biomarkers. Such an approach represents a promising scientific and practical direction for identifying the individual risk profile of patients, individualizing therapy, and reducing residual risk.

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