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SYMPATHOADRENAL SYSTEM ACTIVITY AND THE RISK OF ARRHYTHMIA DEVELOPMENT IN PATIENTS WITH ISCHEMIC HEART DISEASE

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Abstract. Ischemic heart disease (IHD) remains one of the leading causes of cardiovascular morbidity and mortality worldwide. Among its most dangerous complications are ventricular arrhythmias, sudden cardiac death, heart failure, and recurrent hospitalization. In recent years, it has become clear that arrhythmogenesis in IHD cannot be explained only by coronary stenosis, myocardial scarring, or reduced left ventricular ejection fraction. Myocardial ischemia activates the sympathoadrenal system, increases catecholamine release, enhances β-adrenergic signaling, disrupts intracellular calcium handling, and promotes oxidative stress. Calcium/calmodulin-dependent protein kinase II (CaMKII) is considered a key molecular mediator in this process. By modulating ryanodine receptors, L-type Ca^{2+} channels, the phospholamban/SERCA system, and $Na_v1.5$ sodium channels, CaMKII promotes diastolic Ca^{2+} leak, delayed afterdepolarization, action potential duration dispersion, and myocardial electrical instability. This review analyzes the relationship between sympathoadrenal activation and arrhythmia risk in patients with IHD through CaMKII-dependent mechanisms, delayed afterdepolarization, and electrical instability.

Keywords: sympathoadrenal system, catecholamines, CaMKII, delayed afterdepolarization, electrical instability, ventricular arrhythmia, heart rate variability, oxidative stress.

Introduction. Ischemic heart disease is a complex clinical and pathophysiological condition caused by a mismatch between myocardial oxygen demand and oxygen delivery through the coronary circulation. It develops as a result of atherosclerotic coronary artery disease, impaired epicardial or microvascular blood flow, endothelial dysfunction, and abnormalities in coronary vasomotor regulation. According to the 2024 ESC Guidelines for the management of chronic coronary syndromes, chronic coronary syndrome should not be interpreted only as a consequence of epicardial coronary stenosis. It also includes microvascular dysfunction, vasomotor disorders, endothelial dysfunction, and long-term cardiovascular risk stratification [1].

One of the most important determinants of clinical prognosis in ischemic heart disease is arrhythmia. Ventricular premature beats, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation are particularly important after myocardial infarction, as they increase the risk of sudden cardiac death. The 2022 ESC Guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death emphasize the need for comprehensive risk assessment in patients with coronary artery disease, including left ventricular ejection fraction, myocardial scar, Holter ECG findings, clinical symptoms, and additional risk markers [2].

However, arrhythmic risk cannot be explained only by an anatomical substrate, such as myocardial scar or slowed conduction. In ischemic heart disease, myocardial ischemia acts as a strong stress signal for the body and activates the sympathetic nervous system and the adrenal medulla. As a result, secretion of adrenaline, noradrenaline, and dopamine increases. Initially, this

response serves as a compensatory mechanism that maintains myocardial contractility, heart rate, and arterial blood pressure. However, prolonged or excessive sympathoadrenal activation increases myocardial oxygen demand, promotes tachycardia, causes intracellular Ca^{2+} overload, enhances oxidative stress, and contributes to the formation of an arrhythmogenic environment [3,4].

In recent years, CaMKII has attracted increasing attention in the pathogenesis of arrhythmias. CaMKII is an important enzyme involved in cardiac Ca^{2+} signaling, excitation-contraction coupling, ion channel regulation, oxidative stress response, and the maintenance of electrical stability in cardiomyocytes. Ischemia, reperfusion, increased catecholamines, and reactive oxygen species can activate CaMKII. Activated CaMKII enhances diastolic Ca^{2+} leak through ryanodine receptors, modifies L-type Ca^{2+} channel activity, increases sarcoplasmic reticulum Ca^{2+} loading through the phospholamban/SERCA system, and enhances late sodium current through $Na_v1.5$ channels [5,6].

These processes lead to delayed afterdepolarization (DAD), action potential duration dispersion, heterogeneous refractoriness, and electrical instability. As a result, favorable conditions are created for triggered activity and re-entry mechanisms in the myocardium. Therefore, modern assessment of arrhythmic risk in patients with IHD should include not only LVEF and myocardial scar, but also sympathoadrenal activity, heart rate variability, oxidative stress, CaMKII-related mechanisms, and disturbances of calcium homeostasis.

Materials and Methods. This article was prepared as a narrative clinical and pathogenetic review. Scientific sources published in PubMed, PMC, European Heart Journal, Nature Reviews Cardiology, American Journal of Physiology-Heart and Circulatory Physiology, Journal of Molecular and Cellular Cardiology, and ESC clinical guidelines were analyzed. The literature search was performed using the following keywords: “ischemic heart disease”, “chronic coronary syndrome”, “sympathetic activation”, “sympathoadrenal system”, “catecholamines”, “ventricular arrhythmia”, “sudden cardiac death”, “CaMKII”, “delayed afterdepolarization”, “electrical instability”, “ischemia-reperfusion arrhythmia”, “heart rate variability”, and “baroreflex sensitivity”. The inclusion criteria were as follows: clinical guidelines, experimental studies, clinical studies, and review articles related to ischemic heart disease, myocardial infarction, ischemia-reperfusion injury, sympathetic activation, CaMKII, delayed afterdepolarization, heart rate variability, and ventricular arrhythmias. Priority was given to modern sources published during the last 7-10 years. However, several fundamental publications on heart rate variability and post-infarction risk stratification were also included [8,9].

The exclusion criteria included studies focused only on congenital channelopathies, articles not directly related to ischemic heart disease, pediatric studies, and publications that did not discuss CaMKII, DAD, or electrical instability mechanisms.This article is not based on a real clinical cohort. It summarizes existing scientific evidence. Therefore, no artificial patient numbers, p-values, or correlation coefficients were included in the Results section. The findings were generalized as a pathogenetic model based on available literature.

Results. The literature analysis showed that there are several key pathogenetic links between sympathoadrenal system activity and arrhythmia development in ischemic heart disease.

The first key link is myocardial ischemia and sympathoadrenal activation. During ischemia, oxygen deficiency, accumulation of metabolites, pain impulses, hemodynamic stress, and psychoemotional strain activate the sympathetic nervous system. Noradrenaline is released mainly from sympathetic nerve endings, while adrenaline is secreted primarily from the adrenal medulla. This response increases heart rate, myocardial contractility, atrioventricular conduction, and peripheral vascular tone. Initially, it helps maintain cardiac output. However, in the presence of coronary stenosis or microvascular dysfunction, increased heart rate and contractility further

elevate myocardial oxygen demand. This aggravates ischemia and increases arrhythmogenic risk [1,3].

The second link is β-adrenergic signaling and Ca^{2+} overload. When catecholamines activate β_1-adrenergic receptors, the adenylate cyclase - cAMP - protein kinase A pathway is enhanced. As a result, Ca^{2+} influx through L-type Ca^{2+} channels increases, the sarcoplasmic reticulum becomes more loaded with Ca^{2+}, and myocardial contractility increases. However, when this process becomes excessive, cardiomyocytes cannot adequately control Ca^{2+} during diastole. Spontaneous Ca^{2+} release from the sarcoplasmic reticulum through ryanodine receptors occurs. This spontaneous Ca^{2+} release activates inward depolarizing current through the Na^+/Ca^{2+} exchanger and contributes to the development of delayed afterdepolarization [4,5].

The third link is CaMKII activation. Under physiological conditions, CaMKII participates in the fine regulation of cardiac contraction and relaxation. However, increased intracellular Ca^{2+}, catecholamines, angiotensin II, oxidative stress, and ischemia-reperfusion injury can pathologically activate CaMKII. Bell et al. showed that CaMKII is activated early during ischemia-reperfusion and may be associated with arrhythmias, especially during the first minutes of reperfusion [5].

The fourth link is CaMKII-mediated electrical dispersion through $Na_v1.5$. In an experimental study by Howard et al., CaMKII-dependent phosphorylation of the $Na_v1.5$ channel at Ser571 increased late Na^+ current, prolonged action potential duration, enhanced APD dispersion, and increased susceptibility to arrhythmia [6]. In the ischemia-reperfusion model, CaMKII activation and $Na_v1.5$ phosphorylation increased, APD heterogeneity became more pronounced, and spontaneous arrhythmic events became more frequent. Mexiletine reduced late Na^+ current and decreased APD dispersion and arrhythmia susceptibility [6].

The fifth link is oxidative stress and CaMKII. During ischemia and reperfusion, production of reactive oxygen species increases. ROS can activate CaMKII through oxidative modification. Hansen et al. demonstrated that CaMKII and reactive oxygen species contribute to early reperfusion arrhythmias, although oxidation of CaMKIIδ at methionines 281/282 was not shown to be the only determining mechanism [7]. This is an important point: CaMKII is involved in arrhythmogenesis, but its role as a clinically established biomarker or therapeutic target has not yet been fully translated into routine practice [7].

The sixth link is delayed afterdepolarization and triggered activity. DAD is a pathological depolarizing oscillation that occurs during diastole after completion of repolarization. If the amplitude of DAD reaches the threshold level, a new action potential is generated. This can initiate premature ventricular complexes, couplets, short runs of nonsustained ventricular tachycardia, or polymorphic ventricular tachycardia. In ischemic myocardium, such triggers can interact with scarred or slowly conducting areas and initiate re-entry. Thus, DAD acts as a trigger, while myocardial scar serves as the substrate [3,4].

The seventh link is heart rate variability and autonomic imbalance. Reduced HRV reflects decreased parasympathetic protection and increased sympathetic predominance. In the ATRAMI study, SDNN <70 ms and baroreflex sensitivity <3.0 ms/mmHg after myocardial infarction were independently associated with cardiac mortality. Patients with both reduced SDNN and reduced BRS had higher two-year mortality, indicating that autonomic markers may have prognostic value independent of LVEF and ventricular arrhythmias [8].

Discussion. Arrhythmia development in ischemic heart disease is a multistage process. In the classical approach, the main focus is placed on coronary artery stenosis, infarct area, myocardial scarring, and left ventricular systolic dysfunction. This approach remains clinically important because reduced LVEF, post-infarction scar, and nonsustained ventricular tachycardia are key

criteria for assessing the risk of sudden cardiac death [2]. However, according to modern concepts, myocardial electrical stability depends not only on the anatomical substrate, but also on neurohumoral, metabolic, oxidative, and intracellular ion-related mechanisms. The sympathoadrenal system acts as a functional amplifier in this process. If a patient has myocardial scar or conduction heterogeneity, sympathetic activation makes this substrate more dangerous. Noradrenaline increases heart rate, modifies repolarization duration, enhances Ca^{2+} influx, and disrupts intracellular ionic balance. Under these conditions, even a single premature ventricular impulse may initiate re-entry or fibrillatory activity [3,4]. CaMKII is located at the molecular center of this process. Its importance lies in the fact that it affects several arrhythmogenic pathways simultaneously. First, it enhances diastolic Ca^{2+} leak through RyR2 phosphorylation. Second, it modifies the activity of L-type Ca^{2+} channels and increases Ca^{2+} influx. Third, it affects the phospholamban/SERCA system and alters sarcoplasmic reticulum Ca^{2+} loading. Fourth, it increases late Na^+ current through $Na_v1.5$ channels. The combination of these changes promotes DAD, early afterdepolarization, APD dispersion, heterogeneous refractoriness, and triggered activity [5,6].

Delayed afterdepolarization is particularly important from a clinical perspective. DAD is usually associated with Ca^{2+} overload and becomes more pronounced during sympathetic activation. When β-adrenergic stimulation increases heart rate, diastole shortens and cardiomyocytes have less time to remove Ca^{2+}. The sarcoplasmic reticulum becomes overloaded with Ca^{2+}. As a result, spontaneous Ca^{2+} release occurs during diastole. The Na^+/Ca^{2+} exchanger removes this Ca^{2+} from the cell in exchange for Na^+ entry, producing an inward depolarizing current. If this current is strong enough, a new action potential is generated. Therefore, DAD is often the initiating mechanism for ventricular premature beats and triggered tachyarrhythmias.

Electrical instability is a broader concept than DAD. It means that the electrical properties of the myocardium become spatially and temporally heterogeneous. In ischemic areas, the membrane potential decreases, ATP deficiency weakens ion pump function, extracellular K^+ accumulation changes excitability, and intracellular Na^+ and Ca^{2+} increase. During reperfusion, ROS production, pH recovery, Ca^{2+} overload, and modification of membrane channels further increase arrhythmogenicity. Thus, electrical instability reflects the simultaneous formation of both trigger and substrate.

In clinical practice, these mechanisms can be assessed indirectly using several markers. For example, frequent ventricular premature beats, couplets, nonsustained ventricular tachycardia, QT dispersion, or ST-T changes on Holter ECG may indicate electrical instability. Among HRV parameters, reduced SDNN reflects decreased overall autonomic variability, reduced RMSSD indicates weakened parasympathetic activity, and an increased LF/HF ratio may suggest sympathovagal imbalance [8,9]. International standards for HRV emphasize that time-domain and frequency-domain indices should be evaluated under standardized conditions [9].

The scientific novelty of this topic is that it connects arrhythmic risk in patients with IHD not only with ECG or echocardiographic findings, but also with sympathoadrenal activity and molecular electrophysiology. The inclusion of CaMKII, DAD, and electrical instability makes the topic more modern. This approach explains arrhythmias in IHD at three levels: the clinical level - angina, infarction, reduced LVEF, and arrhythmias on Holter ECG; the neurohumoral level - catecholamines, HRV, and baroreflex dysfunction; and the molecular-electrophysiological level - CaMKII, Ca^{2+} overload, DAD, APD dispersion, and $Na_v1.5$-mediated electrical instability.

However, there is an important limitation. Evidence regarding CaMKII is strong mainly in experimental and translational studies. Direct measurement of CaMKII or the use of CaMKII inhibitors as standard therapy in patients with IHD has not yet been introduced into routine clinical

practice. Therefore, CaMKII should not be described as a clinically ready biomarker. It is more accurate to describe it as a promising pathogenetic and translational target.

Sympathoadrenal system activity also should not be assessed using only one marker. Conclusions based solely on adrenaline or noradrenaline levels are insufficient. These markers should be interpreted together with HRV, Holter ECG, LVEF, MDA, clinical symptoms, medication use, and comorbid diseases. For example, in a patient receiving β-blocker therapy, catecholamine levels may be high, but the clinical arrhythmic response may be lower. Conversely, in a patient with reduced LVEF, decreased HRV, elevated MDA, and NSVT on Holter ECG, sympathoadrenal activation may have much greater prognostic significance.

On this basis, a comprehensive model can be proposed for assessing arrhythmic risk in patients with IHD: 24-hour Holter ECG, HRV, echocardiography, catecholamines, oxidative stress markers, clinical risk factors, and, if necessary, cardiac magnetic resonance imaging to assess scar and fibrosis. This approach may improve individualized risk stratification and allows clinicians to evaluate the patient beyond the simplified criterion of "reduced or preserved LVEF".

Conclusion. In patients with ischemic heart disease, sympathoadrenal system activity is an important pathogenetic factor that increases the risk of arrhythmia development. Myocardial ischemia activates the sympathetic nervous system and the adrenal medulla. As a result, catecholamine secretion increases, β-adrenergic signaling is enhanced, heart rate and myocardial oxygen demand rise, and intracellular Ca^{2+} handling becomes impaired.

CaMKII acts as a central molecular mediator in this process. Through RyR2, L-type Ca^{2+} channels, the phospholamban/SERCA system, and $Na_v1.5$ sodium channels, CaMKII reduces myocardial electrical stability. CaMKII activation promotes diastolic Ca^{2+} leak, delayed afterdepolarization, late Na^+ current, action potential duration dispersion, and electrical instability. These changes create a pathogenetic basis for ventricular premature beats, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation.

Assessment of arrhythmic risk in patients with IHD should not be limited to LVEF, coronary stenosis, or ECG changes alone. Sympathoadrenal system activity, HRV, catecholamines, oxidative stress markers, arrhythmias detected by Holter ECG, and the structural and functional state of the myocardium should be evaluated together. The CaMKII-DAD-electrical instability model provides a deeper understanding of arrhythmia development in ischemic heart disease and may serve as an important scientific basis for future individualized risk stratification and the development of new therapeutic targets.

Practical Significance. This topic is promising for a PhD dissertation or scientific article because it integrates clinical cardiology, neurohumoral regulation, oxidative stress, and molecular electrophysiology into a single pathogenetic model. In future research, the combined assessment of 24-hour Holter ECG, HRV, catecholamines, MDA, echocardiographic parameters, and clinical risk factors in patients with IHD may help develop the concept of "residual sympathoadrenal-arrhythmogenic risk". This approach may allow the stratification of patients into low-, moderate-, and high-risk groups, individualization of post-revascularization monitoring, and improvement of preventive strategies.

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