ADENOSINE IN CARDIOVASCULAR PHYSIOLOGY: MULTIFACETED ROLES IN CORONARY VASODILATION, ATHEROPROTECTION, AND PLATELET REGULATION

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Received on : xx-xx-xxxx
Accepted on : xx-xx-xxxx

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ABSTRACT

This review delves into various aspects of acute coronary syndrome (ACS), emphasizing recent advancements. Despite progress, ACS remains a major global health concern. The classical view linking coronary stenoses to chronic syndrome is challenged, with optimal medical therapy often showing better outcomes. Diverse ACS mechanisms include plaque rupture, calcified nodules, spontaneous dissection of the coronary arteries, and coronary artery spasm. Immune factors, particularly neutrophils and their extracellular traps, play a dual role in both inflammation and tissue healing. The adaptive immune response involving T and B lymphocytes adds complexity. Metabolic and lipid-related factors like adenosine pathways, vitamin D, and lipoprotein-associated phospholipase A2 impact atherothrombotic processes. Non-coding RNAs, including circular, long, and microRNAs contribute to ACS. Genic therapies like Olpasiran and Inclisiran show promise in targeting specific molecular pathways to reduce cardiovascular risk factors. Overall, this review offers a comprehensive understanding of ACS, incorporating recent molecular, immunological, and therapeutic advances, highlighting the need for ongoing research to improve diagnostic and treatment strategies.

KEYWORDS: Acute coronary syndrome (ACS), Coronary artery disease (CAD), Plaque rupture, Plaque erosion, Calcified nodules, Spontaneous coronary artery dissection, Coronary spasm, Immune response, Neutrophils.

INTRODUCTION

Advances in acute coronary syndrome (ACS) diagnosis and treatment have been significant over recent decades, especially concerning procedures like percutaneous intervention and the development of antithrombotic medications (1). Despite these improvements, Ischemic heart disease contributes significantly to mortality rates, and cardiovascular illnesses continue to be the world's leading cause of death. Identification of atherosclerotic lesions through angiograms is crucial in diagnosing coronary artery disease (CAD). Coronary stenoses development has been linked to acute cardiac events such unstable angina, and cardiac death, which greatly hinder blood flow and were thought to be the main lesions causing chronic coronary syndrome (CCS) (2). Revascularizing significant coronary artery stenoses has shown to relieve symptoms as well as improve quality of life. However, as compared to the best medical care alone, certain trials have not demonstrated statistically significant prognostic benefits from interventional techniques (3). Optimal It has been demonstrated that medical therapy lowers the rates of cardiac mortality as well as myocardial infarction (MI). Despite implementing therapies based on guidelines, a portion of patients with chronic coronary syndrome (CCS) still experiences progression to acute events, which adversely affects overall patient outcomes (4). Consequently, there has been a shift in research towards identifying unique features of atherosclerotic plaques to enhance the categorization of patient risk. Moreover, advancements in understanding the genetic elements and pathogenic pathways have demonstrated fresh understanding of the atherothrombotic mechanism (5).

Clinical Acute Coronary Syndrome Presentation

ACS encompasses a range of clinical conditions, such as unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI). Such circumstances are differentiated based on the severity and urgency of

required treatment (6). Unstable angina, the mildest form of angina, is characterized by symptoms suggestive of sudden myocardial damage but lacks supporting biochemical evidence. MI, as defined by the Fourth Universal Definition, both NSTEMI as well as STEMI are categorized as type 1 myocardial infarctions, requiring not only clinical symptoms of ischemia but also evident increases in troponin levels (7). Due to improved management of established risk factors, STEMI within ACS is becoming less common in Western nations, although in-hospital death and morbidity rates are still significant (8). Additionally, there has been a shift from the traditional understanding of non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Intravascular ultrasonography (IVUS) as well as optical coherence tomography (OCT) has permitted the examination of the plaque content, morphology, and characteristics in vivo (9). While thrombus formation and ruptured lipid-rich plaques are the main contributors to ACS, research suggests that a significant number of patients also experience plaque erosion, spontaneous coronary artery dissection (10).

Physiopathology of Acute Coronary Syndrome

The pathophysiology of ACS involves two primary mechanisms: plaque rupture and plaque erosion. Plaque rupture, An event that frequently results in the abrupt development of coronary atherosclerosis, involves the luminal rupture of a "vulnerable" plaque (11). The characteristics of these plaques include a significant lipid core, foam cells, macrophages, covered by a thin tissue that is fibrotic cap (12). Rupture releases prothrombotic substances, initiating the coagulation cascade and leading to thrombus formation. Inflammatory mediators hinder extracellular matrix production and prompt release of proteases, contributing to cap degradation (13). The production of plasminogen activator inhibitor-1 and fibrin, two prothrombotic components, increases the risk of clot formation. Core elements revealed during rupture activate circulating platelets, enhancing the coagulation process and causing swift thrombus formation (14).

However, plaque erosion is relatively recent conceptual framework in ACS, involving the superficial erosion of an atherosclerotic plaque. Although historically reported at around 20% prevalence, recent research suggest an raised prevalence of approximately 40% (15). Plaque erosion is typically identified in vivo using OCT as well as it is associated with younger patients, With an average age of 53.8 years, plaque rupture occurs at 65.1 years (16). Vascular risk factors are distributed unevenly in plaque erosion, with greater hemoglobin concentration, lower rates of diabetes and hypertension, and lower levels of LDL cholesterol and C-reactive protein. Compared to plaque rupture, plaque erosion has less complexity and severity in CAD (17). Molecular mechanisms involve local shear stress, leading to thrombus formation in high endothelial shear stress areas, as well as basement membrane degradation, endothelial cell desquamation, and death due to fluid dynamic impact (18). Toll-like receptor (TLR)-2 activation sustains inflammation and promotes granulocyte recruitment, with recruited granulocytes, mainly neutrophils, forming neutrophil extracellular traps (NETs) linked to plaque erosion and thrombus formation (19).

Lipid and Metabolic Factors in the Process of Atherothrombosis

Adenosine, initially recognized by Berne for its role in coronary vasodilation within the cardiovascular system, influences various pathways associated with coronary blood flow and atherothrombotic events. The A2a subtype, found widely in smooth muscle and endothelial cells and functioning via four G protein-coupled receptors, significantly impacts cardiovascular functions. Adenosine exhibits a protective effect against atherosclerosis by stimulating endothelial cell growth during angiogenesis and suppressing pro-inflammatory cytokine reactions (20). Adenosine plays a crucial role in promoting collateral circulation and mitigating damage caused by ischemia, particularly in hypoxic conditions where elevated levels of A2a receptors enhance its effects. This increased expression effectively balances inflammatory responses mediated by pathways such as HIF-1α and NF-kB. Another significant aspect of adenosine's function is its role in regulating platelet aggregation. Studies demonstrate that elevating intracellular cAMP concentration in platelets promotes increased aggregation while reducing internal calcium mobilization. These experiments often involve mice lacking the A2a receptor. The genetic variations of adenosine and its interactions with drugs like ticagrelor underscore its importance, particularly in influencing platelet reactivity. Therefore, caution should be exercised when using adenosine during procedures such as fractional flow reserve measurement (21).

Lipoprotein (a)

Similar to low-density lipoprotein (LDL), lipoprotein (a) or Lp(a) contains apolipoprotein B (apoB), which binds to the surface of apolipoprotein (a) (apo(a)). Apo(a), highly resembling plasminogen and encoded by the gene for lipoprotein(a), is crucial in Lp(a) function. Lp(a) serves several clinical and

physiological functions, such as affecting blood coagulation, interacting with immune cells, as well as participating in adhesion molecule activities. Additionally, It is an important factor in transporting human plasma's oxidized phospholipids, which have pro-inflammatory and pro-atherogenic properties. Lp(a) aids in the onset and advancement of atherosclerotic plaques in disease settings, elevates the risk of blood clot formation leading to conditions like myocardial infarction (MI) or ischemic stroke, as well as it triggers inflammation. Similar to LDL, lipoprotein (a) or Lp(a) contains apolipoprotein B (apoB), which binds to the surface of apolipoprotein (a) (apo(a)) (22). Apo (a), highly resembling plasminogen and lipoprotein(a) gene encodes, is crucial in Lp(a) function. Lp(a) serves various physiological as well as pathological roles, including influencing blood coagulation, interacting with immune cells, promoting the growth of vascular smooth muscle, and participating in adhesion molecule activities (23). For instance, in large-scale studies like the REVEAL trial, which observed a decrease in major coronary events with anacetrapib, both the cost-effectiveness ratio and the overall benefits presented challenges for its widespread adoption in routine clinical practice.

Regulation of Vitamin D and Calcium Balance

Vitamin D is essential for several organs, such as the cardiovascular system, and is vital for maintaining the balance of Ca^{+}, P, as well as bone tissue. It is synthesized by the skin or obtained from dietary sources and undergoes modifications to produce calcitriol, its active form. The vitamin D receptor, commonly found in the cardiovascular system, initiates cascades of signals with anti-inflammatory and antioxidative properties, thus safeguarding cardiovascular health. Approximately 9 percent of individuals with ACS exhibit a deficiency in calcitriol, which is distinct from their 25(OH) vitamin D levels and it has potential for predicting cardiovascular risk (24). The idea of the vascular-bone axis highlights the relationship between abnormal calcium deposition in vessel walls and accelerated bone resorption, leading to vascular calcification. Numerous mediators connect vascular calcification with bone homeostasis, underscoring the importance of calcium deposition in coronary arteries during acute events. Clinical trials investigating vitamin D treatment, particularly in individuals deficient in vitamin D, have yielded conflicting outcomes. Despite the lack of definitive results in large trials and meta-analyses, More investigation is required to fully understand the intricate interplay between vitamin D, calcium homeostasis, and cardiovascular health (25).

Phospholipase A2 Associated with Lipoproteins

Phospholipase A2 (PLA2), an enzyme superfamily, plays a vital role in hydrolyzing phospholipids to release essential fatty acids involved in signaling inflammation and energy production. Lipoprotein-associated PLA2 (Lp-PLA2), a member of Group VII of the PLA2 superfamily, is associated with both LDL and HDL in the bloodstream. While initially identified as platelet-activating factor acetyl-hydrolase, Lp-PLA2 is implicated in plaque development, accelerating atherosclerosis, and forming necrotic cores. Elevated levels of Lp-PLA2 have been independently linked to increased risks of stroke and coronary artery disease (CAD). Studies utilizing mouse models suggest that reducing the expression of Group VII PLA2 genes decreases atherosclerosis burden and inflammation, indicating that Lp-PLA2 could be a potential therapeutic target (25). However, clinical studies investigating the use of darapladib, the most advanced Lp-PLA2 inhibitor, did not demonstrate significant benefits for patients with stable CAD or ACS. Despite challenges in translating preclinical potential into successful clinical trials, the role of Lp-PLA2 as a cardiovascular risk marker remains significant (26).

ACS Genetics: The Various RNAs

The biology of the heart relies significantly on microRNAs (miRNAs), the dysregulation of which has been linked to several illnesses, such as CAD. Certain cardiac miRNAs, such as miR-133a and miR-499, hold promise as biomarkers for myocardial infarction (MI), enhancing diagnostic accuracy. MiRNAs exhibit a complex interplay with atherosclerosis, impacting processes such as inflammation, smooth muscle cell homeostasis, and endothelial senescence. Conversely, miRNAs associated with inflammation, like miR-181c and miR-362, may heighten plaque susceptibility. However, caution is warranted in interpreting miRNA research due to potential biases in sample processing, platform selection, and a lack of standardization (27). Cellular functions are significantly influenced by long non-coding RNAs (lncRNAs) in cardiovascular disorders, with dysregulated lncRNAs detected in patient plasma samples and cardiac tissue following myocardial infarction (MI), suggesting potential diagnostic utility. Nevertheless, comprehensive research and standardization efforts are necessary to establish lncRNAs as reliable diagnostic biomarkers (28). Certain circRNAs, such as circ-tetratricopeptide

repeat domain 3 (circ-Ttc3) and Cdr1as (CiRS-7), play regulatory roles in myocardial infarction (MI), influencing processes like cell death, mitosis, and apoptosis. However, due to the limited understanding of circRNA production and function, their clinical application remains challenging, necessitating further research. Nonetheless, emerging evidence suggests that circRNAs could serve as promising therapeutic targets by aiding in myocardial recovery post-MI (29).

CONCLUSION

In conclusion, the landscape of research in acute coronary syndrome (ACS) has witnessed significant strides in understanding the complex interplay of various factors contributing to its pathogenesis and progression. The field is still developing, with new actors like long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) replacing more established indicators like cholesterol and plaque composition. Despite advancements in therapeutic interventions and diagnostic tools, challenges persist in translating promising pre-clinical findings into consistent clinical benefits. The intricate web of genetic, metabolic, and inflammatory pathways involved in ACS underscores the need for comprehensive and personalized approaches to patient care. As we delve deeper into the molecular intricacies of ACS, the pursuit of innovative strategies and a deeper understanding of the multifaceted nature of this cardiovascular condition will be critical for improving patient outcomes and addressing the global burden of cardiovascular diseases.

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How to cite this article:

Waly M., Srivastava S., Nag R., Fatima K., Eba A. Adenosine In Cardiovascular Physiology: Multifaceted Roles In Coronary Vasodilation, Atheroprotection, And Platelet Regulation. Era J. Med. Res. 2024; 11(2): X-X.