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A Narrative Review to Explore Serpina3n, Nppa, and Anxa1 Proteins: Promising Cardiac Biomarkers for Myocadiac Infarction

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Structural proteins are essential for preserving the shape and functionality of the heart muscle because of their fibrous nature and repeating amino acid sequence, forming stable structures. The sarcomere is the fundamental unit of muscle contraction, primarily composed of structural proteins like troponin, myosin, actin, and titin. An intracellular cascade that upsets calcium homeostasis and activates proteolytic enzymes, which break down these vital structural proteins, is set off by an oxygen shortage during a myocardial infarction. Ischemia, or low blood flow to the heart, is a condition that compromises oxygen and nutrition-dependent cellular functions. Emerging cardiac biomarkers for myocardial infarction MI, include proteins viz, serpina3n, Nppa, and Anxa1. Therefore, this review explores their roles for clinical use and advantages over common cardiac biomarkers for MI.

Traditional biomarkers like troponins and creatine kinase-MB are widely used but have limitations, due to delayed elevation or specificity issues. Recent reports have identified Serpina3n as a valuable biomarker for MI. Anxa1 is known for its anti-inflammatory properties, and Nppa is a peptide hormone primarily secreted in response to atrial stretch and increased blood volume. Further research is needed to explore the roles of these structural proteins in the diagnosis of cardiac injuries.

Keywords: Cardiac biomarkers; serpina3n; Nppa; Anxa1; myocardial infarction.

1. INTRODUCTION

Myocardial infarction (MI), commonly referred to as “heart attack,” is caused by decreased or complete cessation of blood flow to a portion of the myocardium. It may be “silent” and go undetected, or it could be a catastrophic event leading to hemodynamic deterioration and sudden death. As the most severe manifestation of coronary artery disease, myocardial infarction (MI) is a complex and multifactorial pathophysiologic process. However, the pathogenesis that underlies MI remains unclear [1].

To sustain its operations, the heart needs a substantial energy source, which is supplied by adenosine triphosphate (ATP), primarily generated via oxidative phosphorylation [2]. Cardiomyocytes are strictly dependent on oxygen to meet their metabolic demands. An interruption of coronary blood flow rapidly stresses cardiomyocytes, ultimately leading to apoptosis and necrosis [2]. Acute myocardial infarction can occur when one or more big epicardial coronary arteries are acutely blocked for longer than 20 to 40 minutes. Because of the occlusion, there is less oxygen in the myocardium, which causes myofibril relaxation and sarcolemmal disruption [3]. These changes are one of the first ultrastructural changes in the process of MI, which are followed by mitochondrial alterations. The prolonged ischemia ultimately results in liquefaction necrosis of myocardial tissue. The necrosis spreads from the sub-endocardium to the sub-epicardium. The subepicardium is believed to have increased collateral circulation, which delays its death [3].

Risk factors such as smoking and abnormal apolipoprotein ratio showed the strongest association with acute myocardial infarction. The increased risk associated with diabetes and hypertension was found to be higher in women, and the protective effect of exercise and alcohol was also found as well [3]. Other risk factors include a moderately high level of plasma homocysteine, which is an independent risk factor of MI and can be treated with folic acid, vitamin B6, and vitamin B12. Some non-modifiable risk factors for myocardial infarction include advanced age, male gender and genetics. The role of genetic loci that increase the risk for MI is under active investigation [3].

In addition to being utilized for prognosis and management in patients with acute heart failure, pulmonary embolism, and other disease states, cardiac markers are also employed for the diagnosis and risk classification of patients with chest discomfort and suspected acute coronary syndrome (ACS). Cardiac markers are categorized into four groups: those that indicate myocardial ischemia (ischemia-modified albumin), those that indicate myocardial necrosis (myoglobin, cardiac troponins, and creatine kinase-MB [CK-MB] fraction), those that suggest

myocardial stress (natriuretic peptides), and those that indicate inflammation and prognosis (C-reactive protein [CRP], soluble CD40 ligand [sCD40L], and homocysteine) [4].

However, new cardiac biomarkers are evolving such serpina3n, NPPA and Anxa1 proteins as predictive tools in earlier diagnosis of MI. Therefore, this review explores their roles for clinical use and advantages over common cardiac biomarkers for MI.

2. OVERVIEW OF COMMON CARDIAC BIOMARKERS

Initially, the CK-MB isoenzyme was the preferred biochemical diagnostic for identifying acute MI. CK-MB is found in skeletal muscle as well, despite being more concentrated in the myocardium. False-positive increases can arise in a variety of clinical contexts, such as myopathy, trauma, and intense exercise.

After the appearance of symptoms, CK-MB first occurs 4-6 hours later, peaks at 24 hours, and then returns to normal in 48–72 hours. It has limited use in both early (before 72 hours) and late (beyond 72 hours) acute MI diagnosis. But if its levels increase after first falling after an acute MI, its release kinetics can help diagnose reinfarction. The tissue CK-MB1 isoform usually predominates, hence the ratio of CK-MB2/CK-MB1 is usually less than 1. If the ratio is more than 1.7 and the CK-MB2 is increased, the outcome is positive. CK-MB2 can be detected in serum within 2-4 hours after infarction onset and peaks at 6-9 hours, making it an early marker for acute MI. Two large studies evaluating its use revealed a sensitivity of 92% at 6 hours after symptom onset, compared with 66% for CK-MB and 79% for myoglobin [5].

Myoglobin is a heme protein found in skeletal and cardiac muscle that has attracted considerable interest as an early marker of MI. Its early release profile is explained by its low molecular weight: After an infarction, myoglobin usually increases 2-4 hours later, peaks 6–12 hours later, and returns to normal in 24-36 hours. While there are rapid myoglobin assays available, they are not cardio-specific [5].

The troponins are regulatory proteins found in skeletal and cardiac muscle. In addition to being used in the diagnosis of MI, an elevated troponin level can identify patients at high risk for major adverse cardiac events (MACE). Three subunits of troponin have been identified: troponin I (TnI), troponin T (TnT), and troponin C (TnC). The genes that encode for the skeletal and cardiac isoforms of TnC are identical, meaning that there is no structural difference between them [6]. Other studies revealed that an elevated troponin level at baseline was an independent predictor of mortality, even in patients with chest pain and acute MI with ST-segment elevation (STEMI) who were eligible for reperfusion therapy [7].

Ischemia-modified albumin (IMA) is a novel marker of ischemia that is produced when circulating serum albumin contacts ischemic heart tissues [8]. After a brief period of myocardial ischemia, IMA levels increase, peaking within 6 hours, and can last up to 12 hours. But individuals with advanced cancer, certain infections, and cirrhosis also have elevated IMA levels, which lowers the assay's specificity [8].

3. MOLECULAR CARDIAC PROTEINS

3.1 Changes of Cardiac Structural Proteins in Myocardial Infarction

Structural proteins are essential components of cells and tissues for stability, strength, and shape. Due to their fibrous nature and repeating amino acid sequence, these proteins can form stable structures and play a crucial role in maintaining the architecture and function of the heart muscle. Structural proteins such as titin, myosin, actin, and troponin are essential components of the sarcomere, the basic unit responsible for muscle contraction. The significant alterations in these proteins contribute to the changes observed in cardiac muscle in MI, particularly in terms of contractile function and overall structural integrity [9].

During a myocardial infarction, the reduced blood supply to the heart causes ischemia, leading to a breakdown in cellular processes that rely on oxygen and nutrients. The oxygen deficit triggers an intracellular cascade that disrupts calcium homeostasis and activates proteolytic enzymes like calpains. These enzymes degrade key structural proteins such as titin and myosin, which are responsible for maintaining the elasticity and contractile strength of the heart muscle [10]. As these proteins degrade, the structural integrity of the sarcomere is compromised, weakening the muscle’s ability to contract, thus reducing cardiac output [10]. This

structural disintegration is a key factor contributing to heart failure post-MI.

Additionally, the loss of dystrophin and other cytoskeletal proteins further compromises the stability of cardiac cells, leading to cell death and weakening of the heart wall [11]. The heart muscle heals by fibrosis, resulting in stiffness. This alters the geometry of the heart, leading to ventricular remodeling and loss of contractile efficiency [11].

The changes in structural proteins not only affect the mechanical function of the heart but also have implications for cellular signaling and the regulation of cardiac muscle contraction. Proteins like troponin, responsible for regulating calcium binding during muscle contraction, are degraded during MI, leading to an impairment in the excitation-contraction coupling mechanism. This results in diminished contractile force and contributes to worsening cardiac function after the infarction [12].

4. PROMISING DIAGNOSTIC CARDIAC BIOMARKERS

4.1 Serpina3n

This is a serine protease inhibitor released into the circulation during muscle atrophy [1]. Serpina3n, also called α-1-antichymotrypsin is a member of the serine protease inhibitor family and plays a role in inflammatory processes and tissue remodeling, which are integral to cardiac pathology.

The protein's ability to inhibit proteases such as neutrophil elastase and proteinase 3 suggests its role in modulating inflammatory responses and tiSSue damage [13].

In acute myocardial infarction (AMI) traditional biomarkers like troponins and creatine kinase-MB are widely used but have limitations, such as delayed elevation or specificity issues. Recent reports have identified Serpina3n as a valuable biomarker for AMI [14]. Elevated Serpina3n levels were found to correlate with the severity of myocardial injury, providing a potential adjunct to traditional biomarkers in diagnosing AMI.

Inflammation plays a crucial role in atherosclerosis, a precursor to many cardiovascular events such as AMI and Serpina3n's role as an inflammatory mediator makes it a candidate for evaluating atherosclerotic disease [14]. Serpina3n levels were elevated in patients with significant atherosclerosis, suggesting its potential role in assessing disease progression and therapeutic response. The biomarker's ability to reflect inflammatory processes may provide insights into the pathogenesis of atherosclerosis [14].

Serpina3n has emerged as a potential additional marker for heart failure HF. Studies have shown that its levels are elevated in HF patients and correlate with disease severity [15]. This suggests that Serpina3n could provide supplementary information on cardiac stress and inflammation, improving diagnostic accuracy and patient management. A good biomarker's sensitivity and specificity for the relevant disease are among its most important characteristics. Serpina3n has demonstrated encouraging outcomes in terms of cardiac disease sensitivity and specificity. According to reports, myocardial damage and inflammation cause Serpina3n levels to rise dramatically, giving it a sensitive marker for identifying both acute and chronic heart problems [16].

4.2 Anxa1

Anxa1 is a calcium-dependent phospholipid-binding protein that acts in immune system modulation and cell membrane organization [17] highly relevant in the context of myocardial infarction. It is a 37-kDa protein involved in various physiological processes, including inflammation, cell differentiation, and apoptosis. It is characterized by its ability to bind phospholipids in a calcium-dependent manner, which plays a crucial role in cellular membrane dynamics and signal transduction [18].

Anxa1 is known for its anti-inflammatory properties. It regulates inflammation by inhibiting the recruitment and activation of leukocytes and modulating the release of pro-inflammatory cytokines [19]. Li et al. [15] demonstrated that serum levels of Anxa1 were significantly elevated in patients with acute myocardial infarction compared to healthy controls and patients with non-cardiac conditions. The study found that Anxa1 levels correlated with myocardial injury markers, indicating its potential as a sensitive indicator of myocardial damage [15].

Compared to troponins, which specifically indicate myocardial cell damage, Anxa1 provides

complementary information related to inflammatory responses and tissue remodeling. A study compared Anxa1 with troponins and B-type natriuretic peptide BNP, in patients with acute myocardial infarction and found that Anxa1 levels offered additional diagnostic value, particularly in cases where troponin levels were inconclusive [20]. Although BNP is used primarily to assess heart failure and fluid overload, anxa1, while providing different information related to inflammation and tissue repair, could be used alongside BNP to offer a more comprehensive assessment of cardiac conditions. Maisel et al. [21] suggested that combining Anxa1 with BNP might improve diagnostic accuracy, particularly in patients with complex presentations.

4.3 Nppa

Nppa is a peptide hormone primarily secreted by the heart atria in response to atrial stretch and increased blood volume. It is synthesized as a prohormone, and cleaved to produce its active form, atria natriuretic peptide ANP. The peptide exerts its physiological effects by binding to specific receptors, leading to the production of cyclic guanosine monophosphate (cGMP). This signaling pathway promotes natriuresis, diuresis, and vasodilation, which collectively help in regulating blood pressure and fluid balance [22].

In myocardial infarction, the heart's hemodynamic stress and ischemic conditions can lead to elevated levels of Nppa. This elevation reflects the increased atrial pressure and myocardial stress associated with ischemic events [23]. Given its role in modulating cardiovascular homeostasis, Nppa is a relevant marker for assessing myocardial injury and cardiac function during an MI.

5. CONCLUSION

Structural proteins are essential for preserving cardiac function. When they are altered or degraded during myocardial infarction (MI), the heart's capacity to sustain efficient contractions is significantly altered, which increases the risk of heart failure, infarction, and other complications following the MI. It's interesting to note that all three of the proteins are readily identifiable in plasma as they are secreted. As a result, these proteins show promise as MI biomarkers for either diagnosis or therapy. Additional clinical research is required to investigate the connections between these proteins and MI and to identify important biomarkers.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPEOVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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