The Biochemical Aspects of a Non–ST-Segment Elevation Acute Coronary Syndrome

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The clinical course of an acute coronary syndrome can vary from relatively benign to potentially fatal. The biomarkers of myocardial necrosis relate to the amount of myocardial damage and are closely linked to a patient's prognosis. They are measured to help guide management decisions. Recent interest in myocardial neurohumoral mechanisms has identified the natriuretic peptides as strong prognostic biomarkers following an ischemic event. During an acute event they provide information regarding the area of myocardium at risk. The biomarkers of inflammation, such as C-reactive protein, are related to both the development of atherosclerosis and the risk of acute ischemic events. The mechanism characterizing the pathophysiology of the syndrome is represented by these cardiac biomarkers. Assessing combinations of pathobiologically diverse biomarkers may provide a better risk evaluation method and further dictate subsequent therapy.

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KEY WORDS

Acute coronary syndrome • C-reactive protein • Biomarker • Cardiac troponin • Natriuretic peptide

The assessment of biomarkers is considered as increasingly important with regard to all patients with chest pain. Historically, biomarkers were used for the retrospective verification of an acute myocardial infarction (MI). However, with the availability of more specific and sensitive biomarkers, the focus has shifted toward an earlier diagnosis of myocardial damage, assessment of risk, and treatment strategy.

Myocardial underperfusion is the principal pathophysiologic mechanism responsible for the symptoms of an acute coronary syndrome (ACS). This is caused by an atherosclerotic plaque rupture or erosion, with different degrees of superimposed thrombus.[1,2] When evaluating cardiac chest pain, the initial classification is provided by the electrocardiogram (ECG). Patients are then subdivided into those with a persistent ST-segment elevation MI (STEMI) and those without persistent ST-segment elevation. The latter is referred to as non–ST-elevation ACS (NSTE-ACS). The concentration of the biomarkers of necrosis above a certain cutoff level will differentiate the NSTE-ACS patients into those with a non–ST-elevation MI (NSTEMI) and those with unstable angina. In the case of a severe coronary event, dynamic changes in numerous biomarkers are observed.[1,2]

Every step in the development of atherosclerosis and its complications has its own respective biomarker.[3] Numerous biomarkers are being linked to the development of atherosclerosis. There are low-density lipoproteins, inflammatory proteins (eg, interleukins), and several growth factors related to plaque formation.[4-6] In addition, with the progression to an ACS, several pathophysiologic sequences such as plaque destabilization, rupture, platelet activation, and amplification of a thrombus are all accompanied by the release of specific proteins.[7] The next step in the development of an ACS is coronary stenosis and occlusion. This is sometimes accompanied by a distal embolization.[8] Depending on the severity of the oxygen demand and supply imbalance, ischemia may occur. The release of the natriuretic peptides is triggered by an increase in wall tension.[9] Severe and prolonged ischemia may lead to tissue necrosis, followed by the release of proteolytic enzymes.[10,11]

This article highlights the biomarkers currently applied in clinical practice with regard to an ACS. It focuses on their differences in pathophysiology. The biomarkers of necrosis, such as cardiac troponin (cTn), are discussed, followed by the biomarkers of a mechanical strain, known as the cardiac natriuretic peptides. In addition, we discuss the biomarkers of inflammation, such as C-reactive protein (CRP). We conclude with a prospect on the multimarker approach.

Biomarkers of Necrosis

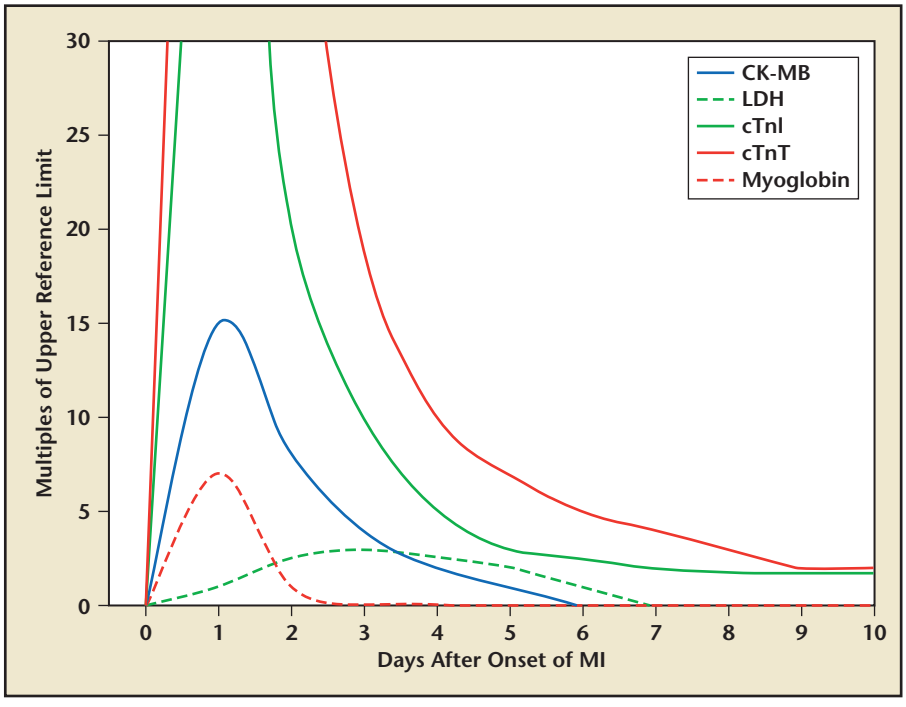
The biomarkers of myocardial necrosis play an essential role in both diagnosis and treatment strategies of patients with chest pain. The ECG and the assessment of biomarkers provide essential information in the diagnostic work-up.

Diagnostic Properties

The diagnosis of an MI depends on the presence of necrosis biomarkers in the circulation within the clinical setting of acute myocardial ischemia.[12,13] This is especially the case with an NSTEMI.

Upon myocyte cell death, several cardiac proteins are released into the bloodstream: myoglobin, cTn T and I, creatine kinase (CK), and lactate dehydrogenase are the most common.[10] The relative timing and the dynamics of each protein release provides information regarding the onset of ischemia, the presence and size of an infarction, and the risk of complications, and helps predict a long-term prognosis (Figure 1).[11] Remarkably, there are

Figure 1. Dynamics in cardiac biomarkers after a MI. CK-MB, creatine kinase MB; cTnI, cardiac troponin I; cTnT, cardiac troponin T; LDH, lactate dehydrogenate; MI, myocardial infarction. Adapted with permission from Boyce N.[11]



over 200 recognized biomarkers of myocyte injury. They correspond to myocyte structural and contractile proteins, components of the sarcolemma and cytosolic proteins.[3]

During an MI, the levels of sensitive and specific biomarkers such as cTn and the MB fraction of CK are raised to a certain threshold.[1,2,12-14] However, these biomarkers reflect myocardial damage but do not relay its mechanisms. Therefore, in the case of a suspected NSTE-ACS, the enzyme rise should be related to the clinical setting of acute ischemia. In an attempt to further clarify the diagnostic challenges regarding the presence of an MI, recent guidelines propose dividing MI into five subgroups based on diagnostic tests and pathophysiologic substrates.[13]

Cardiac Troponins

The characteristic rise and fall of cTn I or T is now the preferred indicator of MI.[13-15] Troponin is a regulatory protein complex that is located on the thin filament of the contractile apparatus. It consists of three protein subunits—cTn T, cTn I, and cTn C—which regulate the muscle contraction.[15] Cardiac tissue contains relatively large amounts of cTn compared with the other proteins measured. Unlike other cardiac biomarkers used to detect cardiac damage, cardiac troponins have different isoenzymes from those found in skeletal muscle. They are thereby entirely specific to myocardial injury.[3]

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The diagnosis of a type 1 MI is defined as a cTn concentration exceeding 1 times the upper limit of normal (ULN) in the clinical context of an ACS.[13] The ULN is defined as a concentration exceeding the 99th percentile of a reference control group. An acceptable deviation measured by the coefficient of variation (CV) at the 99th percentile is currently defined as 10% or less.[14] However, most current cTn assays do not have the advised level of precision at the ULN. Contemporary diagnostic thresholds for MI are commonly placed at the lowest concentration with an inaccuracy of 10%.[14]

Recently, new high-sensitivity troponin assays have been developed. These tests can reliably detect changes in the concentration at or below the 99th percentile for a normal population.[14,16,17] Although these high-sensitivity assays achieve the commonly recommended guideline precision of < 10% CV at the lower reference limit, the current clinical experience is still limited. Recent studies seem promising, as they suggest a marked increase in sensitivity and thereby improve the clinical outcomes of patients with suspected NSTE-ACS.[16,17]

Risk Assessment and Treatment Strategies

In addition to diagnostic properties, elevation in either cTn T or cTn I has an important prognostic value.[17-19] Marginally elevated concentrations of these proteins are associated with future adverse cardiac events.[19] This implies an essential role within the risk assessment. Both Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) risk scores incorporate biomarker elevation in a prominent manner.[20,21] Therefore, cTn elevation often implies a medium to high risk on the given scoring systems. Patients with cTn elevation are thought to benefit more from both extensive pharmacologic treatment and early revascularization.[22]

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Biomarkers of Mechanical Strain

The suspicion that the heart could have an endocrinal function was raised more than 50 years ago. At the time, it had been shown that dilatation of cardiac atria produced natriuresis.[23] Two cardiac hormones have now been identified. The first is atrial natriuretic peptide (ANP), formerly called atrial natriuretic factor. The second is brain natriuretic peptide (BNP), named after its falsely presumed cerebral origin.[24] In the late 1980s, a Japanese group demonstrated an ANP-like natriuretic peptide from a porcine brain and called this peptide BNP. However, later experiments showed that BNP was produced in cardiac myocytes.[25,26]

Physiology of BNP

Cardiac myocytes produce the BNP prohormone (proBNP) in response to an increase in wall stress. This protein is then split by the enzyme furin into the hormone BNP and a splitting byproduct called N-terminal (NT)-proBNP.[27] The physiologic effects of BNP include diuresis, vasodilatation, inhibition of renin production, and cardiac myocyte growth.[27] Whether the splitting peptide NT-proBNP has biological effects on its own is currently unknown. Although renal excretion is currently regarded as the main clearance mechanism for both proteins, clearance patterns

differ. NT-proBNP has a remarkable longer half-life (120 min) than BNP (20 min).[28] This results in higher serum concentrations of NT-proBNP as compared with BNP.

Cardiac Neurohormones in Pathologic States

Over the past decade, evidence has accumulated regarding natriuretic peptide testing for the diagnosis, risk assessment, and therapeutic monitoring of patients with heart failure (HF). Recently, research has focused on these biomarkers in the setting of an ACS.

It is well known that cardiac ischemia increases wall tension and triggers gene activation, production of messenger ribonucleic acid, and assembly of the precursor to natriuretic peptides (Figure 2).[29] In patients with an ACS, BNP levels rise gradually, peaking at approximately 24 hours after the acute event.[30,31] As the left ventricle has the greatest mass of all the cardiac chambers, the dynamics of BNP and NT-proBNP largely reflect the increase in wall tension of the left ventricle.[3] This increase in wall tension depends on multiple variables such as preload, afterload, ventricular volumes, and myocardial properties. It is currently not clear which variables contribute most to the release of natriuretic peptides. Nevertheless, there appears to be a correlation between the degree of elevation of NT-proBNP serum concentration and the extent of ischemia.[32-34]

Although both BNP and NT-proBNP are released in response to cardiac ischemia, neither peptide offers sufficient sensitivity to rule out the diagnosis of an ACS.[35] It is important to add that many other pathologic conditions also cause elevations in BNP and NT-proBNP.[36] However, NT-proBNP has certain specific diagnostic properties. It was recently shown that NT-proBNP can be implemented in identifying an evolving MI in high-risk individuals.[35,37]

Risk Assessment and Treatment Strategies

There is accumulating evidence that natriuretic peptides can be used in the risk assessment of patients across the entire ACS spectrum. NT-proBNP has an additional benefit in the risk assessment of low- and high-risk NSTE-ACS and in STEMI.[35,38,39] In particular, when used in patients with a suspected NSTE-ACS and negative cTn concentrations, NT-proBNP is able to identify the population at higher risk.[35,38] Commonly used risk scores can be enhanced by incorporating the BNP or NT-proBNP values.[39,40] Although it is sometimes difficult to determine the etiology of natriuretic peptide elevation, NT-proBNP and BNP are powerful predictors of adverse outcomes.[41] It appears that they integrate multiple pathophysiologic insults into a single prognostic variable.

Several substudies regarding interventional and pharmacologic strategies have been evaluated regarding the interaction of BNP or NT-proBNP levels in patients with ACS. However, they failed to identify a clear beneficial treatment strategy for patients with BNP or NT-proBNP elevation.[41,42] For this reason, BNP or NT-proBNP risk assessment measurements have only been given a "qualified" recommendation (Class IIb, level of evidence: B) in the latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines for unstable angina/NSTEMI.[2] The focused update, released by the ACC/AHA in 2011, did not cover this subject.[43] Accordingly, additional research is needed to clarify the potential role of natriuretic peptides in the selection of patients for specific therapeutic interventions.

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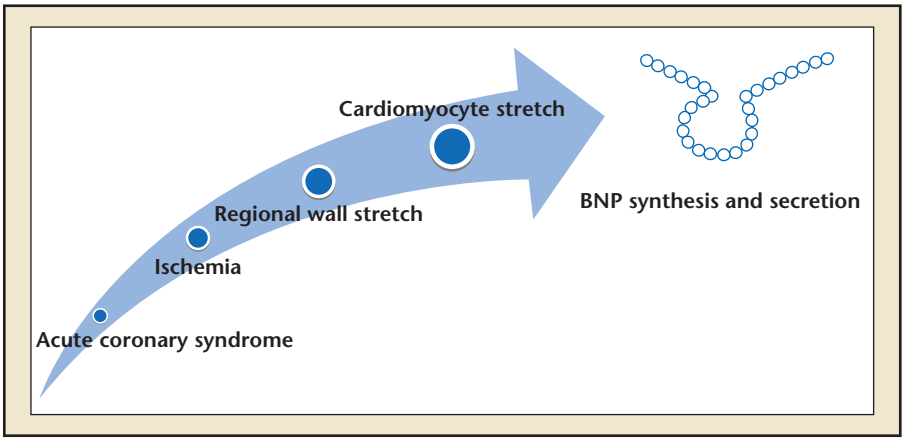
Figure 2. The mechanism of BNP production during an acute coronary syndrome. BNP, brain natriuretic peptide.



Biomarkers of Inflammation

Elevated levels of inflammatory biomarkers indicate an increased risk of coronary heart disease. Atherosclerosis, formerly considered a bland lipid storage disease, involves an ongoing inflammatory response.[44] Inflammation appears to play a fundamental role in mediating all stages of this disease from initiation through to progression and ultimately to its thrombotic complications.[45] In recent years,

many different inflammation biomarkers have been investigated. These include CRP, fibrinogen, metallic metalloproteinase-9, monocyte chemotactic protein 1, resistin, lipoprotein-associated phospholipase A2, interleukin-6, tumor necrosis factor-α, and β-fibroblast growth factor.[5,6,46,47] It is beyond the scope of this manuscript to describe all of these biomarkers.

CRP and High-Sensitivity CRP

CRP is an acute-phase protein synthesized in the liver. Its physiologic role is to bond to phosphocholine, which is expressed on the surface of dead or dying cells in order to activate the complement system.[48] CRP was identified in 1930 as a substance in the serum of patients with an acute inflammation that reacted with the C polysaccharide of pneumococcus.[49] Initially, CRP was thought to be a pathogenic secretion. However, the detection of its hepatic synthesis demonstrated its origin. To detect the relatively low levels that are associated with a cardiovascular (CV) event, high-sensitivity assays have been developed.

Diagnostic Properties of CRP

Because of their nature as acute-phase proteins, the diagnostic properties of inflammation biomarkers for ACS lack both specificity and sensitivity. Therefore, the diagnostic value of high-sensitivity CRP (hs-CRP) in patients with a suspected ACS seems limited. A recent retrospective evaluation in patients presented to the emergency department with a suspected ACS showed that hs-CRP did not enhance the diagnostic accuracy for an ACS.[50] The presence of an increase in hs-CRP levels observed during an ACS may partly result from a heightened baseline inflammatory status that may be caused by the metabolic syndrome.[51] In addition, CRP elevation occurs secondary to myocardial damage. This is believed to be caused by an inflammatory reaction initiated by myocardial necrosis.[52,53]

Risk Assessment and Treatment Strategies

The level of elevation in inflammatory biomarkers predicts outcomes in patients with ACS, irrespective of the amount of myocardial damage.[46] Across the entire spectrum of ACS, high circulating CRP levels and leukocyte counts are independently associated with CV mortality.[46] It is, therefore, not surprising that certain treatments that limit inflammation also reduce coronary risk. In a recent study, statin treatment reduced the incidence of major CV events in seemingly healthy persons without hyperlipidemia but with an elevated hs-CRP.[54] The beneficial anti-inflammatory effects of statin therapy for ACS patients are well documented. The intensity of statin therapy correlates with the reduction in CRP and the risk of recurrent events.[55] Patients with low CRP levels after initiation of statin therapy showed better clinical outcomes than those with higher CRP levels, regardless of their level of low-density lipoprotein cholesterol.[56]

In conclusion, inflammation biomarkers are related to the development of atherosclerosis and play an important role in the progression toward an acute coronary event. However, their diagnostic value seems limited. During and after a coronary event, the degree of inflammation is correlated to the risk of recurrent events. Although much progress has already been made, further evaluation of the basic evidence on the mechanisms supporting the role of the hepatic inflammatory proteins in atherosclerosis is needed.

The Multimarker Approach

Currently, several pathophysiologically diverse cardiac biomarkers have emerged as strong predictors of risk among patients with an ACS. Elevated levels of cTn, (NTpro)-BNP, and hs-CRP are each associated with higher rates of death and recurrent ischemic events. Not surprisingly, the simultaneous assessment of the biomarkers of necrosis, inflammation, and mechanical strain provide complementary information.[57] Recent data confirm that cTn is the most useful biomarker in identifying those patients at a high risk for recurrent MI and that natriuretic peptides are the most useful for identifying those at risk for HF and death.[58,59]

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Combining the results of diverse biomarkers may provide a more powerful prognostic prediction than a single biomarker approach. However, current guidelines do not, support the routine use of such a strategy due to a lack of validation within large studies.[1,2,8] Nonetheless, the specific ratio of biomarker elevations could provide a unique opportunity to understand the mechanisms at work in a particular case of ACS. This understanding may enable clinicians to combat risk more

effectively and provide a more tailored therapy for an individual with ACS by depending on the most profoundly affected mechanisms.

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MAIN POINTS

- The assessment of biomarkers is considered as increasingly important with regard to outcomes and management strategies of patients with an acute coronary syndrome (ACS).
- The characteristic rise and fall of cardiac troponin (cTn) I or T is now the preferred indicator of myocardial infarction (MI). Unlike other cardiac biomarkers used to detect cardiac damage, cardiac troponins are entirely specific to myocardial injury.
- The level of elevation in inflammatory biomarkers predicts outcomes in patients with ACS, irrespective of the amount of myocardial damage.
- Recent data confirm that cTn is the most useful biomarker in identifying those patients at a high risk for recurrent MI and that natriuretic peptides are the most useful for identifying those at risk for heart failure and death.
- Combining the results of diverse biomarkers may provide a more powerful prognostic prediction than a single biomarker approach.