Biochemical risk assessment and invasive strategies for acute coronary syndromes without ST-segment elevation
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Biochemical aspects of the non-ST-segment elevation acute coronary syndrome

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ABSTRACT

The diagnosis of an acute coronary syndrome (ACS) covers a wide range of severity. It can vary from 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 adopted in order to manage its treatment strategy. Recent interest in myocardial neurohumoral mechanisms have identified the natriuretic peptides as strong prognostic biomarkers following upon an ischemic event. During an acute event they provide information regarding the area of myocardium at risk. The biomarkers of inflammation such as the C-reactive protein (CRP) are related to both the development of atherosclerosis and the risk of an acute ischemic event. The mechanism characterising the pathophysiology of the syndrome are represented by these cardiac biomarkers. Assessing combinations of pathobiologically diverse biomarkers may provide a better risk evaluation method and further channel subsequent therapy. This is a novel concept however and needs to be validated for its incremental value by using clinical trials.
INTRODUCTION

The assessment of biomarkers is considered as increasingly important concerning all patients with chest pain. Historically, biomarkers were mainly 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 towards an earlier diagnosis of myocardial damage, assessment of risk and the treatment strategy.

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

Every step in the development of atherosclerosis and its complications has its own respective biomarker.\textsuperscript{3} Numerous biomarkers are being linked to the development of atherosclerosis. There are (low density) lipoproteins, inflammatory proteins such as interleukins as well as several growth factors related to plaque formation.\textsuperscript{4,5,6} In addition, with the progression to an ACS, several pathophysiologic sequences such as plaque destabilization, rupture, platelet activation, amplification of a thrombus are all accompanied by the release of specific proteins.\textsuperscript{7} The next step in the development of an ACS is coronary stenosis and occlusion. This is sometimes accompanied by a distal embolization.\textsuperscript{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.\textsuperscript{9} Severe and prolonged ischemia may lead to tissue necrosis, followed by the release of proteolytic enzymes.\textsuperscript{10,11}
This manuscript will highlight those biomarkers currently applied in the clinical practice with regard to an ACS. It will also focus on their differences in pathophysiology. Firstly, 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 (NP). In addition, it will provide a discussion on the biomarkers of inflammation, such as CRP. The manuscript concludes with a prospect on the multi marker approach.

BIOMARKERS OF NECROSIS

The biomarkers concerning myocardial necrosis play an essential role in both diagnostics as well as treatment strategies among patients with chest pain. The electrocardiogram (ECG) and the assessment of biomarkers provide essential information in the diagnostic build-up.

Diagnostic properties

The diagnosis of a MI depends on the presence of necrosis biomarkers in the circulation within the clinical setting of acute myocardial ischemia.\textsuperscript{12,13} This is especially the case with the non ST-elevation myocardial infarction (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.\textsuperscript{10} The relative timing and the dynamics of each protein release provides information with respect to the onset of ischemia; the presence and size of an infarction; the risk of complications and helps predict a long-term prognosis.\textsuperscript{11} (Figure 1) Remarkably, there are over 200 recognized biomarkers of myocyte injury. They correspond to myocyte structural and contractile proteins, components of the sarcolemma and cytosolic proteins.\textsuperscript{3}

During a MI the levels of sensitive and specific biomarkers such as cTn and the MB fraction of creatine kinase (CK-MB), are raised to a certain threshold.\textsuperscript{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 a MI, recent guidelines propose to divide the MI into 5 subgroups based upon diagnostic tests and pathophysiological substrates.13

**FIGURE 1**

**Dynamics in cardiac biomarkers after a myocardial infarction.**

![Graph showing dynamics in cardiac biomarkers after MI](image)

Modified from reference 11

CK-MB: creatinine kinase MB, cTn: cardiac troponin, LDH: lactate dehydrogenase, MI: myocardial infarction

**Cardiac Troponins**

The characteristic rise and fall of cTn I or T is now the preferred indicator of a MI.13-15 Troponin is a regulatory protein complex that is located on the thin filament of the contractile apparatus. It consists of 3 protein subunits: cTn T, cTn I and cTn C, which regulate the muscle contraction.15 Cardiac tissue contains relatively large amounts of cTn compared to the other proteins measured. Unlike other cardiac biomarkers used to detect cardiac damage, cardiac troponins have differing isoenzymes from those found in skeletal muscle. They are thereby entirely specific to myocardial injury.3
The diagnosis of a type 1 MI is defined as a cTn concentration exceeding 1 x the upper limit of normal (ULN) in a clinical context of an ACS. 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. However, most current cTn assays do not apply to the advised level of precision at the ULN. Contemporary diagnostic thresholds for a MI are commonly placed at the lowest concentration with an inaccuracy of 10%.

Recently, new high sensitivity Troponin (hsTn) assays have been developed. These tests can reliably detect changes in the concentration at or below the 99th percentile for a normal population. 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.

**Risk assessment and treatment strategies**

In addition to their diagnostic properties, elevation in either cTn T or cTn I will have an important prognostic value. Marginally elevated concentrations of these proteins are associated with future adverse cardiac events. This implies an essential role within the risk assessment. Both TIMI and GRACE risk scores incorporate biomarker elevation in a prominent manner. Therefore, cTn elevation often implies an medium to a high risk on the given scoring systems. These patients are thought to have more benefit from both extensive pharmacological treatment and early revascularisation.

**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. Nowadays, two cardiac hormones have been identified. The first is Atrial
Natriuretic Peptide (ANP), formerly named Atrial Natriuretic Factor. The second is Brain Natriuretic Peptide (BNP), named after its falsely presumed cerebral origin. In the late 1980’s, a Japanese group demonstrated an ANP-like natriuretic peptide from a porcine brain and named this peptide BNP. However later experiments showed that BNP was produced in cardiac myocytes.

Physiology of BNP
Cardiac myocytes produce 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 by-product called NT-proBNP. The physiological effects of BNP include: diuresis; vasodilatation; inhibition of renin production and cardiac myocyte growth. 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 of 120 minutes than BNP with 20 minutes. This results in higher serum concentrations of NT-proBNP as compared to BNP.

Cardiac neurohormones in pathological states
Over the past decade, evidence has accumulated regarding NP testing for the diagnosis, risk assessment and therapeutic monitoring of patients with heart failure. 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) In patients with an ACS, BNP levels rise gradually, peaking at around 24 hours after the acute event. 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 experienced by the left ventricle. 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 NPs. Nevertheless, there appears to be a correlation between the degree of elevation of NT-proBNP serum concentration and the extent of ischemia.
FIGURE 2
The mechanism of BNP production during an acute coronary syndrome.

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 cause elevations in BNP and NT-proBNP as well.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 a 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 aetiology 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 sub-studies regarding interventional and pharmacological 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.\cite{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 ACC/AHA guidelines for unstable angina/NSTEMI.\cite{2} The focused update, released by the ACC/AHA in 2011, did not cover this subject.\cite{43} Accordingly, additional research is needed to clarify the potential role of NPs in the selection of patients for specific therapeutic interventions.

**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 on-going inflammatory response.\cite{44} Inflammation appears to form a fundamental role in mediating all stages of this disease from initiation through to progression and ultimately to its thrombotic complications.\cite{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; IL-6; tumor necrosis factor alpha and beta-fibroblast growth factor.\cite{5,6,46,47} It is beyond the scope of this manuscript to describe all these biomarkers. This clinical review will focus on CRP as this is the most commonly used inflammatory biomarker.

**CRP and hsCRP**

CRP is an acute-phase protein synthesized in the liver. Its physiological role is to bond to phosphocholine which is expressed on the surface of dead or dying cells in order to activate the complement system.\cite{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.\cite{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 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 an ACS lack both specificity and sensitivity. Therefore, the diagnostic value of hsCRP in patients with a suspected ACS seems to be 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. 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 a metabolic syndrome. In addition, CRP elevation occurs secondary to myocardial damage. This is believed to be caused by an inflammatory reaction initiated by myocardial necrosis.

**Risk assessment and treatment strategies**

The level of elevation in inflammation biomarkers predicts the outcome in patients with ACS, irrespective of the amount of myocardial damage. Across the entire spectrum of ACS, high circulating CRP levels and leucocyte counts are independently associated with cardiovascular mortality. It is therefore not surprising that certain treatments which limit inflammation also reduce coronary risk. In a recent study, statin treatment reduced the incidence of major cardiovascular events in seemingly healthy persons without hyperlipidaemia but with an elevated hsCRP. 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. 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 LDL cholesterol.

In conclusion, inflammation biomarkers are related to the development of atherosclerosis and play an important role in the progression towards 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, the basic evidence on the mechanisms supporting the role of the hepatic inflammatory proteins in atherosclerosis need to be further evaluated.

**THE MULTI-MARKER APPROACH**

Nowadays, several pathophysiologically diverse cardiac biomarkers have emerged as strong predictors of risk among patients with an ACS. Elevated levels of cTn, (NTpro)-BNP and hsCRP 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 confirms cTn to be the most useful biomarker in identifying those patients at a high risk for recurrent MI and confirms natriuretic peptides to be the most useful for identifying those at risk for heart failure and death.\(^{58,59}\) Combining the results of diverse biomarkers may provide a more powerful prognostic prediction than a single biomarker approach. However, current guidelines do not as yet 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 an 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 its most profoundly affected mechanisms.
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