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A review on cardiac biomarkers

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ABSTRACT

Cardiac biomarkers are of great importance in the timely, accurate diagnosis and management of acute coronary syndrome as well as the prognosis. Diagnosis in the golden period is of utmost importance to institute therapy at the earliest and possibly reverse the myocardial damage. Cardiac biomarkers are also a powerful tool for triaging. The use of a large number of cardiovascular biomarkers, meant to complement the use of the electrocardiogram, echocardiography cardiac imaging, and clinical symptom assessment, has become a routine in clinical diagnosis, di□erential diagnosis, risk stratification, and prognosis and guides the management of patients with suspected cardiovascular diseases. There is a broad consensus that cardiac Troponin and natriureticpeptides are the preferred biomarkers in clinical practice for the diagnosis of the acute coronary syndrome and heart failure, respectively, while the roles and possible clinical applications of several other potential biomarkers are still under study.

INTRODUCTION

Cardiac biomarkers are substances that are released into the blood when the heart is damaged or stressed. Measurements of these biomarkers are used to help diagnose acute coronary syndrome (ACS) and cardiac ischemia, conditions associated with insufficient blood flow to the heart.Cardiac biomarkers are central to the new definition of acute myocardial infarction (AMI) as defined by the American College of Cardiology and the European society of Cardiology[1]. A biomarker is “a characteristic that is objectively measured and quantified as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention.”

Several cardiac markers have been used in the diagnosis and management of cardiovascular (CV) disease. However, a lack of sensitivity and specificity to cardiac muscle necrosis continues to be the need to look for newer specific molecules. Cardiac biomarkers are of great importance in the timely, accurate diagnosis and management of ACS as well as the prognosis.

LABORATORY TEST

Cardiac biomarkers, proteins that are released when muscle cells are damaged, are frequently ordered to help differentiate ACS from a heart attack. These include:

Cardiac Troponins:

Troponins are the contractile proteins in muscle cells, which present very early in the bloodstream, 3 to 9 hours post infarct. Cardiac-specific isoforms have been identified, and among the three troponins in the contractile component of the myocardium, troponin-I and troponin-T are widely used[2]. Both are highly specific and sensitive for myocardial damage, though troponin-T is known to increase in unstable angina. Cardiac troponin (cTn) I, increases in 4 to 6 hours, peaks at 12 hours, and returns to basal levels in 3 to 10 days, whereas troponin-T stays elevated for 12 to 48 hours and falls to normal in 10 days[3]. MI is highly unlikely if troponins are not elevated, and a point-of-care testing device is used considerably at the bedside to exclude cardiac damage in patients with chest pain. cTn testing is an essential component of the diagnostic workup and management of ACS.

The introduction of a high-sensitivity troponin (hs-Trop)

assay has been very useful in patients with nonST-elevation myocardial infarction (NSTEMI), which allows diagnosis by a single blood test, thus permitting early treatment than otherwise might be advised. Some studies have concluded that a single hsTnT level ≤ 6 ng/L indicated a very low risk of AMI, whereas serial levels exceeding 19 ng/L identified patients with < 1% risk of adverse cardiac events[3,4]. In highly suspected cases of AMI, high sensitive troponin assay can be used effectively to "rule out" in about 60% cases when the value remains low at 0 hour with no change after 1 hour. When it is elevated at 0 hour with a large increase at 1 hour, it is a "rulein" and is diagnostic of an AMI[5].

CK-MB :

The CK-MB fraction being more specific to the myocardium quickly replaced the CK and is considered the gold standard. CK-MB forms nearly 30% of CK in the myocardium, and a rise of > 5% of the total CK activity suggests damage to the cardiac muscle. CK-MB appears in the bloodstream 4 to 6 hours after onset of chest pain and peaks between 10 and 12 hours after the myocardial infarction (MI). It was the best marker for early detection for many decades. The best time for detection is between 6 and 48 hours beyond which it is cleared; hence in cases oflate arrivals, normal CK-MB could present an incorrect picture. Also, a trend detected in serial measurements provides better information than single measurements. Therefore, MI is unlikely if CK is not increased in patients with chest pain and a failure of elevated CK levels to fall indicates that there is an extension of the infarct. It is shown that in high-risk patients, even minor elevations have important prognostic implications[6].

Myoglobin:

The small heme protein that assists in oxygen transport in all muscle tissues, is released within 1 hour and rises more rapidly than cTn or CK-MB, peaks in nearly 8 to 10 hours, and returns to normal within 24 hours. Thus, it is a sensitive early indicator of cardiac damage, and though nonspecific to the myocardium, it has found use as an excellent negative predictor of myocardial injury. If there is no rise seen in serum myoglobin levels in two samples analyzed 2 to 4 hours apart, it virtually rules out AMI[17].

BNP:

BNP is synthesized and released by cardiac ventricular cells in response to volume or pressure overload[7]. Both active BNP and inactive NT-pro BNP are generated from the cleavage of pro BNP and therefore they are secreted into the bloodstream in equal concentrations[8]. While ANP is stored as the perform in the intracellular granules, BNP is predominantly synthesized when triggered by extracellular stimuli. After secretion into the bloodstream, the BNP will then bind to NP receptors (NPRs) and subsequently activate the intracellular cGMP signaling cascades to reduce the volume or pressure overload. BNP is primarily cleared through the degradation by neutral endopeptidases and partially through the uptake by NPR and renal excretion[9]. BNP and NT-proBNP, the two most commonly used natriuretic peptides, play a diagnostic role in the assessment of heart failure[10]. Theymaybeincreased due to systolic and/or diastolic dysfunction, left ventricular hypertrophy, valvular heart disease, ischemia, or a combination of these factors [11].

The increased blood flow into the ventricles/pressure creates a stretch in the ventricular wall, which is an inducer of transcription for NP. Furthermore, it modulates diuresis, natriuresis, vasodilation, inhibition of renin and aldosterone, and helps reduce the blood pressure. The prohormone (proBNP) is cleaved to BNP and NT-proBNP, where NT-proBNP is the inert inactive molecule, both of which can be assayed. The half-life of BNP is significantly shorter (≤ 20 minutes) than NT-proBNP (60120 minutes) and is removed from circulation by a receptor-mediated mechanism and degradation by neutral endopeptidases. The NTproBNP assays detect NT-proBNP and proBNP.

INFLAMMATORY AND PROGNOSTIC MARKERS

C-Reactive Protein (CRP):

CRP is a useful prognostic indicator in patients with ACS, as elevated CRP levels are independent predictors of cardiac death, AMI, and congestive heart failure [12].

Copeptin:

This is a marker in sepsis, which has been tried as an early biomarker for AMI with cardiac troponin, but much validation needs to be done. Copeptin is a stable C-terminal pro-peptide fragment of arginine vasopressin (AVP) and regulates the free water clearance and plasma osmolality by regulating absorption of water from the kidneys. Again among the biomarkers in the BACH (Biomarkers in Acute Heart Failure) trial, elevated copeptin level strongly predicted mortality even after adjusting for NT-proBNPand other traditional variables[13].

Homocysteine:

An intermediary amino acid, homocysteine is an independent risk factor for the development of atherosclerosis. About 5 to 7% of the general population has moderate hyperhomocysteinemia, which may be a result of vitamin deficiencies that can be successfully treated or genetic disorders. Hyperhomocysteinemia causes intimal thickening, disruption of the elastic lamina, smooth muscle hypertrophy, and platelet aggregation, and hence is directly implicated in vascular injury. It is therefore useful marker for risk assessment, and regular assays are available for the same[14].

Soluble CD40 ligand (sCD40L):

It is another inflammatory marker, a signaling protein that reflects both inflammation and platelet interaction with the plaque and is found increased in ACS[15]. However, often it has been of use in prognostication rather than diagnosis.

Myeloperoxidase:

It is a degranulation product of the white blood cells (WBCs) and is elevated in the blood vessels where a plaque is present and found to be increased in coronary artery disease and ACS[16].

Pregnancy-Associated Plasma Protein A (PAPP-A):

This protein is a metalloproteinase and a member of the insulin-like growth factor family of proteins. Elevated levels are indicative of an ongoing neovascularization process in the coronary arteries and an incipient plaque rupture. However, there is no established correlation with available markers; rather, it is an indicator of adverse CV events and not used routinely [17].

Choline:

It is released from phospholipids on cleavage and is suggested to indicate necrosis and ischemia. Again, it has been considered to be of value in prognostication[18].

Galectin 3:

This is a member of the protein lectin family that has a specific

binding site for β-galactosides, which is a carbohydrate recognition-binding domain. For over a decade, galectin 3 has been implicated in fibrogenesis, myofibroblast proliferation, ventricular remodeling, and inflammation. Though it is elevated in acute or chronic HF, when adjusted for renal function or other markers, it loses its prognostic meaning[19].

Midregional Proadrenomedullin (MR-proADM):

In response to the cardiac dysfunction, which is a precursor of adrenomedullin, a vasodilator, synthesized from the adrenal medulla, is released. It is elevated in HF both acute and chronic and is useful in prediction of hospitalization and mortality[20].

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2):

Also called platelet-activating factor, is synthesized by lymphocytes and monocytes and produces highly atherogenic lipid fragments that cause endothelial adhesion. It is mostly used as a research tool and in risk stratification[21].

Soluble Suppression of Tumorigenicity 2 (sST2):

It is member of IL-1 family and is believed to play a role in the cardiac remodeling and signal inflammation by its interaction with IL-33. The gene is induced strongly by the stretch of a cardiomyocyte or cardiac fibroblast [22].

CONCLUSION

Measurement of hs-CRP, NT-proBNP in addition to cTns, may be useful in risk assessment in patients with clinical symptoms of ACS. A multimarker approach, consisting of two or more pathologically diverse markers, which necessarily includes cardiac troponins, enhances risk stratification in patients of ACS.

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