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THE IMPACT OF BIOMARKERS FOR THE DIAGNOSIS AND PROGNOSIS OF MYOCARDIAL INFARCTION

Physiology

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ABSTRACT

Myocardial infarction is a leading cause of death worldwide, and serum cardiac markers play an important role in diagnosing AMI (acute myocardial infarction). It is no longer recommended to use serum markers such as aspartate transaminase, lactate dehydrogenase, and lactate dehydrogenase subforms because they lack cardiac specificity and their delayed elevation prevents early diagnosis. The most sensitive and specific markers of myocardial damage appear to be cardiac troponin and creatine kinase. Recent studies have revealed several novel biomarkers and a multi biomarker approach can potentially enhance the diagnostic accuracy and provide more information for the early risk stratification of AMI. This review focuses on a variety of promising biomarkers which provide diagnostic and prognostic information.

KEYWORDS

Myocardial Infarction; Biomarkers; Diagnosis; prognosis

INTRODUCTION

Heart disease remains the most common cause of death in the developed world with 1 in 10 patients still dying of a myocardial infarction (MI) [Rogers etal, 2000]. Acute myocardial infarction (AMI) is a condition that can be due to ischemic heart disease or coronary artery disease in conjunction, and it becomes manifest when an atherosclerotic plate ruptures and a developing thrombus occludes the coronary artery totally or partially, restricting blood access to the heart (Liakos M, Parikh PB, 2018; Aydin S, Aydin S, 2016). Every year, worldwide more than 7 million people have been affected with MI. (White HD, Chew DP, 2008] However, the occurrence of myocardial damage is mainly due to hyperlipidemia, loss of plasma membrane integrity and membrane peroxidation [Krushna et al, 2009). Medications and treatments also come at a cost and therefore simple and cheap tests have become increasingly necessary to decide how to target treatment. MI is typically diagnosed by integrating the history of the presenting illness and physical examination with electrocardiogram results and cardiac biomarkers present in blood [Kavsak et al, 2010)

A good biomarker will diagnose or predict risk accurately (that is, high specificity and sensitivity), promptly provide affordable but meaningful results, and should provide this incrementally over existing markers or clinical characteristics. The term biomarker has been defined by The National Institutes of Health as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention”. Chemically cardiac markers are protein components of cells and released into circulation when myocardial injury occurs. Cardiac markers are central to the new definition of acute myocardial infarction (AMI) put forward by the American College of Cardiology and the European Society of Cardiology (Alpert et al, 2000, Document). The ideal biomarkers of AMI should be sensitive and specific in the early period after the onset of symptoms and provide prognostic information for risk assessment, which could guide clinicians to identify the best treatment options. Serum biomarkers have been used to assist in the diagnosis of acute myocardial infarction for over half a century with aspartate transaminases in the 1950s and lactate dehydrogenase in the 1970s. While sensitive for detecting cellular death, these biomarkers lacked specificity for myocardial injury. With the increasing number of available biomarkers, the practice of medicine will depend more heavily on developing appropriate testing for all patients. The aim of this paper is to review the current strategies of the detection of the biomarkers to myocardial infarction as well as to discuss some important developments in the clinical practice.

Cardiac Troponin

Troponin is a protein released from myocytes when irreversible myocardial damage occurs. 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. (Sharma et al, 2004). It is highly specific to cardiac tissue and accurately diagnoses myocardial infarction with a history of ischaemic pain or ECG changes reflecting ischaemia. Cardiac troponin (cTn), expressed as three similar isoforms (I, C, and T), is the biomarker of choice for the diagnosis of myocardial necrosis because it is the most sensitive and specific biochemical marker of myocardial ischemia/necrosis available [K. Thygesen, J. Mair, H. Katus et al, 2010]. The widely used biomarker for myocardial injury is cardiac troponin cTn. The troponin is made up of 3 subunits, which together control calcium mediated interaction of actin and myosin leading to contraction and relaxation of striated muscle. Troponin I and troponin T are expressed only in cardiac muscle; therefore these biomarkers have a high specificity for myocardial damage. CTn are detectable in peripheral circulation when damage to cardiac myocyte first leads to release of cytoplasmic cTn which accounts for 3% to 5% of (Higgins JP, Higgins JA, 2003; Katus et al, 1991) cTnI and 7% cTn T. The cTn complex is one of the components of the thin filament and it plays a significant role in the regulation of muscle contraction. This complex is composed of three isoforms, namely, cTnC, which binds Ca^{2+}, cTnI, which inhibits the ATPase activity of actomyosin, and cTnT, which interacts with actomyosin. cTn mediates the interaction between actin and myosin and thereby regulates cardiomyocyte contraction [Katrukha, 2013].

Elevated levels of cardiac troponins can occur due to open-heart surgery, post percutaneous coronary intervention, acute pulmonary embolism, end-stage renal disease, pericarditis, myocarditis, Stanford A aortic dissection, acute or chronic heart failure, strenuous exercise, cardiotoxic chemotherapy, radiofrequency catheter ablation of arrhythmias, cardioversion of atrial fibrillation or atrial flutter, defibrillation for ventricular fibrillation or tachycardia, amyloidosis, cardiac contusion from blunt chest wall trauma, sepsis, and rhabdomyolysis (Korff et al, 2006). troponin elevation alone was found to identify patients likely to benefit from intensive antiplatelet therapy or an early invasive management strategy (Newby LK, Ohman EM, Christenson RH, et al, 2001, Morrow DA, Cannon CP, Rifai N, et al, 2001)

Creatine kinase

Creatine plays a key role in cellular energy metabolism. The creatine kinase enzyme reversibly phosphorylates it to phosphocreatine. Then, when phosphocreatine is reverted to creatine, its phosphate bond breaks, and such a break provides enough energy to allow phosphorylating a molecule of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Thus, phosphocreatine acts as an energy reserve to synthesize ATP rapidly, with no need for oxygen. The reaction is the following one: Creatine + ATP ---- Phosphocreatine + ADP + H^{+}. This reaction plays a crucial role in heart contraction [Ventura-Clapier, R.; Vassort, G, 1980].

CK is a dimeric molecule composed of two subunits designated M and B. Combinations of these subunits form the isoenzymes CK–MM, CK–MB, and CK–BB. A significant concentration of CK–MB isoenzyme is found almost exclusively in the myocardium, and the appearance of elevated CK–MB levels in serum is highly specific and sensitive for myocardial cell wall injury. Following onset of symptoms of myocardial infarction CK and CK–MB increase in serum within 3 to 6 hours; the peak levels occur between 16 and 30 hours. Significantly, CK–MB disappears from the serum at a more rapid rate than CK. For example, CK–MB returns to normal by 24 to 36 hours, whereas the elevated CK levels may be detected for up to 60 hours. This "window" dictates that CK and CK–MB must be determined as soon as possible after the onset of symptoms, and repeated several times in the first 48 hours. Peak CK–MB levels range from 15 to 30% of total CK post infarction.

Creatine kinase is included mainly in skeletal muscle, cardiac muscle and brain, and is involved in energy production. Serum creatine kinase (CK) levels in healthy individuals are influenced by age, sex, race, pregnancy, muscle mass and physical activity, and is well known to be elevated following any damage to or disease of the above-mentioned organs (Brancaccio et al, 2007). A very economical mechanism for energy transfer may be required for several energy consuming processes in excitable tissues, such as muscle and neural tissue (Kammermeier 1987b). Recent experiments and calculations showed that the phosphocreatine shuttle between mitochondria and cytosolic microcompartments represents an intracellular mechanism to assure a high efficiency of energy transduction via ATP. The shuttle mechanism requires the presence of creatine kinases (CK, E.C. 2.7.3.2) at the site of ATP production (" mitochondrial" CK) and at the site of consumption ("cytosolic" CK) (Bessman 1985, 1987).

Lactate dehydrogenase

LDH is a housekeeping protein expressed in all living cells, with the highest activities found in the heart, liver, muscles, kidneys, lungs, and blood cells. LDH plays an essential role in glycolysis and gluconeogenesis by catalyzing the reversible conversion of lactate to pyruvate with concomitant interconversion of NADH and NAD^+ as an oxidoreductase.

AST

The first biomarker used to aid in the diagnosis of acute MI was aspartate aminotransferase (AST). In 1954, Ladue et al. proposed that AST released from cardiomyocytes undergoing necrosis would be useful in diagnosing acute MI [Ladue etal, 1954]. In a typical patient with acute myocardial infarction, AST activity exceeds the normal range within 8 to 12 hours following the onset of chest pain, reaches a peak elevation of two- to tenfold in 18 to 36 hours, and declines to the normal range within 3 to 4 days.

Myeloperoxidase

Myeloperoxidase (MPO) is a metalloproteinase produced by the polymorphonuclear leukocytes and macrophages. It initiates the production of reactive oxygen species that are important for the development of atheroma and plaque rupture (Khan et al, 2007). MPO has been widely investigated and comprehensive reviews done [Teng et al, 2017, Dominguez-Rodriguez A, Abreu-Gonzalez, 2011]. Reviews showed that MPO levels may be independently related to early detection of otherwise sub clinical CAD, its severity, diagnosis of MI, prediction of adverse events and monitoring the response to therapy. Also, some conflicting results were reported due to different non-standardised assays used and due to MPO being nonspecific (increased levels in other inflammatory processes, although it is generally less involved in systemic inflammation than CRP). More studies are warranted to establish its role in clinical practice.

Brain natriuretic peptide (BNP)

Natriuretic hormones are a family of related peptides with similar peptide chains as well as degradation pathways. Cardiac natriuretic peptides include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), while other natriuretic peptides, such as C-type natriuretic peptide and urodilatin, are not produced and secreted by cardiac tissue but by other tissues (Cowie and Mendez, 2002). B-type natriuretic peptide (BNP) and its prohormone, N-terminal pro-BNP (NT-proBNP), are neurohormones secreted from cardiac ventricles in response to ventricular wall stress (de Lemos et al, 2003) BNP, an established biomarker for patients with heart failure, and NT-proBNP are elevated in patients with ACS and can identify ACS patients who are at higher risk for adverse cardiovascular events, including heart failure and death (de Lemos et al, 2001; Morita et al, 1993; Jernberg et al, 2002).

D dimer

D-dimers can be regarded as a global marker of the turnover of cross-linked fibrin and of activation of the hemostatic system. D-dimer levels seem to be essentially independent of other cardiovascular risk factors, which suggests that they might add relevant information in addition to lipid variables and other classic risk factors. In contrast to several other markers of hemostasis, D-dimer assays are more stable and more practical to measure and therefore, may be more suitable from a technical point of view for epidemiological purposes (Lowe GDO 1999). Elevated D-dimer levels have been found to predict the risk of future coronary events independently of conventional risk factors in initially healthy, middle-aged male and female subjects, (Lowe GDO 1998 and Folsom 2001) in elderly men and women, (Cushman M 1999) as well as in patients with known peripheral arterial occlusive disease, (Fowkes 1993) and after myocardial infarction. (Moss 1999)

CRP and interleukins (IL-6 and IL-18)

The possibility that CRP might have proatherogenic actions was first suggested in 1982 by the discovery of its specific binding to LDL and VLDL [de Beer etal, 1982; Pepys et al, 1985] and was supported by its detection in atherosclerotic plaque [Zhang etal, 2005] Modestly elevated baseline concentrations of C-reactive protein (CRP), the classical acute phase protein, are associated with the long-term risk of coronary heart disease in general populations, whilst the major acute phase response of CRP following myocardial infarction is associated with death and cardiac complications (Casas et al 2008) Several population-based prospective studies of CHD (defined in this paper as non fatal MI or coronary death) have reported on associations of subtle, prolonged increases in baseline CRP levels with CHD risk [Danesh et al, 2007]. Interleukins (Interleukin 6 Inhibition and Coronary Artery Disease in a High-Risk Population: A Prospective Community-Based Clinical Study Bruno Cesar 2017)

Homocysteine

Homocysteine has been recognized as early in 1990s as a risk factor for the presence of atherosclerotic vascular disease and hyper coagulability states [Mallinow1990, Abraham R 2006]. Homocysteine has emerged as a significant marker of vascular disease, especially in patients of Asian origin. There is a strong correlation between severity of CAD and serum homocysteine levels. Homocysteine can mediate the formation of cardiovascular disease by several different mechanisms such as its adverse effects on vascular endothelium and smooth muscle cells with resultant alterations in subclinical arterial structure and function [Zhang S 2014].

Myoglobin

Myoglobin is a heam protein, located in the cytoplasm of both cardiac and skeletal muscle cells, constituting about 2% of the total muscle protein. Its relatively low molecular weight (17 kDa) and cytoplasmic location ensure its rapid release into the circulation; the plasma concentration is elevated 2±3 h after myocardial injury. The relationship between myoglobinaemia and MI was first reported in 1975 (Kagen et al, 1975). Myoglobin is a heme protein found in cytoplasm of all muscles cells. The level increases within 1 to 3 hrs after myocardial infarction reach peak elevation within 6 to 9 h, and may become normal in, 24 hrs [Mair et al, 1992].

CONCLUSION

Analysis of cardiac biomarkers has become a frontline diagnostic tool for AMI, allowing clinicians to make rapid diagnoses and plan early treatment, and thereby reducing mortality rates to a great extent. In modern medicine, troponins are widely recognized and important cardiac enzymes used to diagnose acute myocardial ischemia. Additionally, patients with elevated troponins seem to benefit from aggressive treatment strategies. Therefore, the deployment of new strategies to meet diagnostic, prognostic, and therapeutic needs is essential. By using newly emerging technologies, individually and in combination, novel biomarkers or novel biomarker protein signatures can be discovered. While there is evidence that combining biomarkers may improve the accuracy of tests, it is still necessary to define the best combinations for diagnosis or prognosis. Micro RNA research is a rapidly growing area of biomedical and translational research.

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