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Relevant cardiac biochemical markers in acute coronary syndromes

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ABSTRACT

Acute coronary syndromes remain the leading cause of mortality and represent an enormous cost to the health care system. The evaluation of myocardial damage in relation to cardiac operation, from a clinical and a research perspective, is of great importance; particularly for the evaluation of different cardioprotective strategies. Cardiac biochemical markers play an important role in helping physicians make the diagnosis and for risk stratification of patients. Currently, amongst many cardiac markers, cardiac troponin I seems to be the most cardiac-specific for the diagnosis of acute myocardial infarction. This article is focused on the application of biochemical markers for clinical purpose and comparison of their usages in the diagnosis of acute myocardial infarction.

KEYWORDS

Biomarkers;
Troponin I;
Acute coronary symptoms.

INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of death in most of the industrialized world. Myocardial infarction (MI) as a pathologic concept was recognized in the beginning of the 20th century[1]. At autopsy vegetation, due to endocarditis on the aortic valve, was found to have blocked the orifice of the right coronary artery.[2] According to the World Health Organization (WHO), the definition of acute MI includes the presence of two of the following three criteria: 1) Characteristic chest pain, usually of more than 30 minutes; 2) diagnostic electrocardiogram (ECG) changes; and 3) a rise and subsequent fall of serial levels of cardiac markers.[3] Acute coronary syndromes remain the leading cause of mortality in India and represent an enormous cost to the health care system.[4-6] Effective intervention in acute MI is undoubtedly dependent upon early diagnosis. In cases of massive cardiac injury, the above criteria will be met easily. However, in the event of occlusion of small coronary branches or extensive collateral circulation to the ischaemic area, the typical clinical or ECG findings may not be present.[7] Thus, diagnosis based on ECG, is a continuing challenge. The concern about missing the diagnosis in patients with acute MI has led to a lower threshold for admission in order to exclude the presence of acute MI. Lee et al reported approximately 60% to 70% of patients, with chest pain, admitted to hospital were eventually diagnosed as not having an MI but rather some different diagnosis.[8] According to the criteria for acute MI laid by the WHO, 3 cardiac markers can facilitate the diagnosis of an MI. Biochemical markers have long been the cornerstone of diagnosis and continue to play an important role, especially in the group of patients with low medium risk. Use of biochemical markers, to diag-

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nose acute MI, can be dated back to 1954 when aspartate aminotransferase (AST) was first used, which subsequently stimulated a number of investigations on different compounds.[9] Creatine phosphokinase (CPK) replaced AST in late 1960's and Lactate dehydrogenase (LDH) was started to be used as a late marker in 1970's. Since the early 1980's, the more specific CK isoenzyme, CK-MB, has become the "gold standard" for the diagnosis of acute MI and additionally, in past few years, the separation of CK-MB into two isoforms by electrophoresis (EP) has played an important role in the development of the automated enzyme immunoassays, which utilize highly sensitive and specific monoclonal antibodies to detect CK-MB and cardiac troponin.[7,9] For more than 15 years cardiac form of troponin I is known as a reliable marker of cardiac tissue injury. It is considered to be more sensitive and significantly more specific in diagnosis of MI than the golden markers of last decades CK-MB, as well as myoglobin and LDH isoenzymes. Other biochemical markers such as fatty acid binding protein, glycogen phosphorylase, plasma oxidase and, C-reactive protein have not been accepted widely in the diagnosis of AMI.

Several criteria for the ideal cardiac marker are summarized such as : The ideal cardiac marker should; 1) have sufficient specificity for the diagnosis of myocardial damage, in the presence of skeletal muscle injury, 2) be highly sensitive and capable of detecting even mild myocardial damage, 3) appear in quantities that are in direct proportion to the extent of the injury, 4) be absent or present only in trace amounts, in the circulation, under physiological condition, and have the possibility to be detected as abnormal with even minimal elevation in their levels, 5) be technically easy to measure and should not be very expensive.[9,10] Currently none of the available markers meet all these criteria. Therefore continued research on better markers and approaches in the diagnosis of acute coronary syndromes is needed.

Biomarkers serve two potential roles. They provide insight into the pathophysiology of disease, and they aid clinical decision making by clarifying diagnosis, prognosis, or response to therapy. Fulfillment of one role does not ensure fulfillment of other. In primary prevention, traditional risk factors are useful first step in the determination of who would be at risk for cardiovascular event. In the era of "global risk assessment" scores such as the Framingham score, the prospective cardiovascular Munster(PROCAM) score, the European society of cardiology systematic coronary risk Evaluation(SCORE), which are derived from multivariable statistical models, should be used[1]. However, it has been noted that considerable number of at-risk patients can not be identify on the basis of traditional risk factor alone[2].This has promoted the search for novel markers of cardiovascular risk to help improve risk prediction[3]. Such markers could either represent various blood markers relevant to the pathophysiology of atherothrombosis (eg, markers of inflammatory responses, coagulation markers, markers of platelets aggregation, lipoprotein or lipid-related variables, genetic markers, or markers of subclinical disease, which may also aid in improved risk prediction. A large panel of blood markers are available for this purpose,[4,5]

The contribution of inflammation to the pathobiology of atherosclerosis of inflammation is well characterized. In the regard, elevated level of C- reactive protein (CRP), a biomarker of inflammation, have been shown to predict vascular events.

An elevated level of hs-CRP, even in the average range of 1to 3mg/L, is a strong predictor of cardiovascular death, MI, and stroke, new heart failure, and new diabetes, independent of baseline characteristics and treatments.

In stable coronary artery disease, an elevated hs-CRP level, even >1mg/L, is a significant predictor of adverse cardiovascular events independently of baseline characteristics and treatments. An elevated level hs-CRP does not appear to identify patients with stable coronary artery disease and preserved ejection fraction who derive particular benefit from angiotensin-converting enzyme inhibition.

However, there are emerging biomarkers like lipoprotein- associated phospholipase A2 (LP-PLA2) an enzyme that is produced by monocytes/macrophages, T-cells, and mast cells and has been found to generate proinflammatory and proatherogenic molecules[6]. Because LP-PLA2, in contrast to C- reactive protein(CRP), does not correlate with most other risk factors, there is an additive effect of CRP and LP-PLA2 in the risk prediction[7,8]. This may also apply to combinations of others biomarkers, though evidence so far is

limited. In the future, we might see a biomarker profile that covers various aspects of the complex pathophysiology of the atherothrombotic process, and potentially, we would be able to focus on biological patterns or systems rather than on single biomarkers.

Lipoprotein-Associated Phospholipase A_2 has predicted a 5-Year Cardiac Mortality Independently of Established Risk Factors and added Prognostic Information in Patients with Low and Medium High-Sensitivity C-Reactive Protein.

Asymmetric dimethylarginine (ADMA) is the product of endogenous L-Arginine residue methylation of proteins. Because of its similarity of structure with L-Arginine, the natural precursor for nitric oxide (NO) formation, it may act as a competitive inhibitor of endothelial NO synthase and thus reduce NO generation. It further interferes with biological effects of NO and may finally lead to uncoupling of endothelial NO synthase. The reasons for elevated ADMA concentration are not well established. ADMA concentrations are higher in patients with renal insufficiency and liver failure as a result of impaired metabolism and excretion. Therefore, it seems as if a variety of cardiovascular risk factors and disease conditions found to increase ADMA concentrations act by in increasing oxidative stress. ADMA might therefore be an indirect indicator of oxidative burden because it is more stable with a longer-half life and can be measured in peripheral blood. In, addition elevated concentrations of ADMA inhibit forearm blood flow response to acetylcholine and vascular relaxation tested by flow-mediated dilation (FMD)[9].

Interleukin (IL)-18 is a proinflammatory cytokine that has been implicated in several diseases, including atherosclerosis, and increased circulating IL-18 concentrations increase risk of future coronary heart disease (CHD). Variation within *IL18* affects IL-18 concentrations in healthy and diseased individuals and thus may influence the pathophysiology of plaques at all stages of CHD progression.

Another marker could be the quantification of triglyceride-rich lipoprotein (TRL) remnants which is useful for risk assessment of coronary artery disease and the diagnosis of type III hyperlipoproteinemia but a need for a homogeneous assay that can measure TRL remnant cholesterol in serum or plasma without pretreatment is needed. Polyoxyethylene-polyoxybutylene block copolymer (POE-POB) exhibited favorable selectivity toward VLDLR and IDL fractions. POE-POB removed apolipoprotein (apo) E and apo C-III from IDL particles in the presence of cholesterol esterase (CHER), and the particle size distribution of IDLs became smaller after the reaction. These results revealed that IDL particles are specifically modified in the presence of CHER and POE-POB, making their component cholesterol available for enzymatic assay. Addition of phospholipase D improved the reactivity toward chylomicron remnants (CMRs)

Recent studies have established oxidative modification of low density lipoprotein (LDL) as an important atherogenic factor. Examination of circulating oxidized LDL (OxLDL) levels in atherosclerotic disease by an enzyme immunoassay with use of specific antibodies against OxLDL (FOH1a/DLH3) and apolipoprotein B reveals, plasma OxLDL levels were significantly higher in patients with coronary heart disease. CAD patients had higher levels of circulating oxidized LDL .Thus, circulating oxidized LDL is a sensitive marker of CAD. Addition of oxidized LDL to the established risk factors may improve cardiovascular risk prediction[10].

Individuals with elevated blood levels of homocysteine have increased risks of cardiovascular disease[11]. Homocysteine is an important contributing factor to thrombosis, vascular injury, and vascular disease. Mechanisms for homocysteine-induced vascular disease include alterations in coagulation as well as endothelial cell and vessel wall injury. Hyperhomocysteinemia (HH[e]) can occur when homocysteine metabolism is altered by mutations in enzymes responsible for homocysteine metabolism. Characterization of these mutations identifies patient groups at risk for vascular disease[12].

Fibrinogen (also called factor I) is a 340 kDa glycoprotein synthesized in the liver hepatocytes and megakaryocytes, which normally has a concentration between 1.5 - 4.0 g/L (normally measured using the Clauss method) in blood plasma. Therefore the concentration in plasma is about 7 μM. In its natural form, fibrinogen is useful in forming bridges between platelets, by binding to their GpIIb/IIIa surface membrane proteins; though fibrinogen's major use is as a precursor to fibrin . Fibrinogen levels can be measured in venous blood. Normal levels are about 150-300 mg/dL. Higher levels

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are, amongst others, associated with cardiovascular disease (>460 mg/dL). It may be elevated in any form of inflammation, as it is an acute phase protein. An association between increased plasma fibrinogen and an increased risk for myocardial infarction (MI) is well established[13].

Angiotensinogen, a key protein in the renin-angiotensin system, plays an important role in cardiovascular hemostasis. Many studies have examined the association between polymorphisms in the angiotensinogen gene and risk of coronary heart disease (CHD)[14]. Several genes, including some encoding components of the renin angiotensin system, are associated with the risk of cardiovascular diseases. There have been reports linking a homozygous deletion allele of the angiotensin converting enzyme (ACE) gene (DD) with an increased risk of myocardial infarction, and some variants of the angiotensinogen gene with an increased risk of hypertension Genes encoding components of the renin-angiotensin system have been associated with elevated blood pressure (BP) and an increased risk of coronary artery disease.

Recent studies have indicated that serum bilirubin levels are inversely related to cardiovascular disease (CVD)[15]. With an expanding array of biomarkers still amongst many cardiac markers, cardiac troponin I seems to be the most cardiac-specific for the diagnosis of acute myocardial infarction.

REFERENCES

[1] D.A.Morrow, Ed.; Cardiovascular Biomarkers. Pathophysiology and Disease Management. Totowa, New Jersey: Human Press Inc. **(2006)**.

[2] De Backer G.Ambrosioni, K.Borch-Johnsen, C.Brotons, R.Cifkova, J.Dallogenville, S.Ebrahim, O.Faergeman, I.Graham, G.Manica, V.M.Cats, K.Orth-Gomer, J.Perk, K.Pyorala, J.L.Rodico, S.Sans, V.Sansoy, U.Sechtem, S.Silber, T.Thomsen, D.Wood, European Society of Cardiology, American Heart Association, American College of Cardiology; Atherosclerosis, **173**, 381-391 **(2004)**.

[3] U.N.Khot, M.B.Khot, C.T.Bajzer, S.K.Sapp, E.M.Ohaman, S.J.Brener, S.G.Ellis, A.M.Lincoff, E.J.Topol; JAMA, **290**, 898-904 **(2003)**.

[4] R.S.Vasan; Circulation, **113**, 2335-2362 **(2006)**.

[5] W.Koeing, N.Khuseyinova; Arterioscler Thromb. Vasc.Biol., **27**, 26 **(2007)**.

[6] A.Zalewski, C.Macphee; Arterioscler Thromb. Vasc.Biol., **25**, 923-931 **(2005)**.

[7] W.Koeing, N.Khuseyinova, H.Lowel, G.Trischler; Circulation, **110**, 1903-1908 **(2004)**.

[8] C.M.Ballantyne, R.C.Hoogeveen, H.Bang, J.Coresh, A.R.Folsom, L.E.Chambless, M.Myerson, K.K.Wu, A.R.Sharrett, E.Borewinkle; Arch.Intern. Med., **165**, 2479-2484 **(2005)**.

[9] R.H.Boger, S.M.Bode-Boger, A.Szuba, P.S.Tsao, J.R.Chan, O.Tangphao, T.F.Blaschke, J.P.Cooke; Circulation, **98**, 1842-1847 **(1998)**.

[10] P.Holvoet, N.S.Jenny, P.J.Schreiner, R.P.Tracy, D.R.Jacobs; Atherosclerosis, **194(1)**, 245-252 **(2007)**.

[11] William G.Christen, Umed A.Ajani, Robert J.Glynn, Charles H.Hennekens; Arch.Intern.Med., **160**, 422-434 **(2000)**.

[12] S.C.Guba, L.M.Fink, V.Fonseca; Lancet, **343(8903)**, 975-6, Apr 16 **(1994)**.

[13] Johanna G.van der Bom, Moniek P.M.de Maat, Michiel L.Bots, Frits Haverkate, et al.; Arteriosclerosis, Thrombosis, and Vascular Biology, **18**, 621-625 **(1998)**.

[14] Ming-Qing Xu, Zheng Ye, Frank B.Hu, Lin He; Circulation, **116**, 1356-1366 **(2007)**.

[15] Jing-Ping Lin, Libor Vitek, Harvey A.Schwertner; Clinical Chemistry, **56(10)**, 1535-1543 **(2010)**.