

Biomarkers of myocardial infarction: past, present and future

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INTRODUCTION

For the past 40 years, the use of biomarkers has been extremely valuable in the early diagnosis of acute myocardial infarctions (AMI). Sensitivity, specificity and the clinical utility have continued to increase and current research suggests that this trend will continue. This article will review the use of previous and current AMI markers and will conclude with a review of promising new markers.

AMI BIOMARKER PROTOCOL

To detect MI markers, venous blood is routinely drawn from patients with chest pain who are suspected of having symptoms of acute coronary syndrome (ACS).¹ The marker of interest is presumed to be released from the cardiac tissue which is under ischemic stress and thus may be detected in the blood sample.² A detected elevation in a particular marker may lead to early diagnosis and treatment and thus improved patient outcomes.¹

Characteristics of biomarkers centre around three main elements, namely, kinetics of release, specificity and sensitivity.³ An ideal marker of cardiac necrosis should exhibit the following characteristics: cardiac specificity, early and stable release after necrosis, predictable clearance, and be measurable quantitatively using rapid, cost effective methodologies available in the majority of clinical laboratories.⁴

PAST AND PRESENT AMI BIOMARKERS

Myoglobin

Myoglobin is a heme protein found in almost all muscle types and is especially high in cardiac and skeletal muscle.⁵ Quantitative immunoassays are currently available. This marker's strength is its high and early sensitivity post-MI. The marker's obvious weakness is the low specificity due to the presence of high levels of myoglobin in skeletal muscle.⁵ Therefore, myoglobin is suggested not to be used on its own but only in the context of other markers, EKGs and clinical evaluation.

Lactate Dehydrogenase

Lactate Dehydrogenase (LD) is an enzyme involved in anaerobic metabolism, reversibly converting pyruvate to lactate.⁶ LD is fairly ubiquitous; however, one of the five isoenzymes, LD1, is highest in cardiac tissue. LD1 is elevated post-MI and the LD1:LD2 ratio when greater than 1.0 is diagnostic of an AMI. LD1 elevation and LD1:LD2 ratio changes are detectable 8-12 hours post MI and peak at 24-72 hours.⁷

Creatine Kinase

Creatine Kinase (CK) is an enzyme found in high amounts in muscle tissue due to its role in muscle contraction.⁸ CK has two subunits, M and B, which are combined to form three isoenzymes: CK-BB (CK-1), CK-MB (CK-2) and CK-MM (CK-3).⁸ CK-MB is specific to cardiac

tissue while CK-BB is found in brain tissue and CK-MM is in skeletal and cardiac tissue.⁸ Furthermore, release of CK-MB only occurs upon death of myocardial cells and it is not released in the setting of ischemia.⁹ Therefore, CK-MB was considered to be the most useful biomarker for detecting myocardial injury. Kinetic studies have shown that CK-MB is detectable 4-8 hours after the first onset of chest pain and peaks at 18-24 hours post MI.^{8, 9} However, the CK-MB Immunoassay lacks absolute specificity, is absent in minor myocardial infarctions, and has poor prognostic value in ACS patients. Despite these weaknesses it is currently a routine part of the cardiac work-up.

In the 1970s and 1980s, CK-MB transformed the diagnosis and treatment of patients with acute cardiac events. CK-MB proved even more specific than an accurate clinical history, which is often unattainable in the critically ill or is atypical in the elderly and diabetics. CK-MB was more reliable than EKG pattern recognition which can be blind to disease depending on the location of the ischemia. CK-MB also improved specificity over myoglobin (90% vs 70% specificity, respectively) and consequently became the gold standard for identification of cardiac injury. In the absence of myocardial infarction, CK-MB may be elevated due to poor specificity in patients who present with multiple co-morbidities or conditions including renal failure, non-cardiac surgery, chest trauma, asthma, pulmonary embolism, chronic and acute muscle disease, head trauma, hyperventilation, and hypothyroidism.^{10, 11}

Troponin

While troponin proteins are present in both cardiac and skeletal muscle, the cardiac isoforms of troponin T and I are highly specific to the myocardium. Assays using specific antibodies against cardiac troponin T or I allow measurement of troponin release from the myocardium.⁴ In 2000, the European Society of Cardiology (ESC) and American College of Cardiology (ACC) task force concluded that diagnosis of AMI required biochemical evidence of necrosis and indicated the marker of choice as troponin.¹²

The increased sensitivity of cardiac troponin over CK-MB is primarily due to the fact that the percentage of troponin released into the blood after an acute cardiac event is greater for troponin than CK-MB. Troponin concentrations rise quickly after the onset of chest discomfort. Thus, in upwards of 80% of patients, a definitive diagnosis can be made within 6 hours from the onset of chest pain. Furthermore, peak concentration of CK and troponin give a reasonable estimate of infarct size. More recently, novel prototype cardiac troponin assays have been developed that are up to 10-fold more sensitive than the currently used assay and yield prognostic value on potential future MIs.^{13, 14} For comparison of troponin and other available markers please see Table 1.

Troponin has become the biochemical marker of choice for the detection of cardiac injury. But still lacks sensitivity within the first hour

DIAGNOSTIC REVIEW

Table 1: Summary of AMI biomarkers

Marker	Isoenzyme/Isoform	Reference range	First Detectable (post MI)	Peak of Release (post MI)	Sensitivity/ Specificity
Creatine Kinase	CK-MB	<6U/L	4-8h	18-24h	90%/80%
Lactate Dehydrogenase	LD1/LD2 ratio	<1.0	8-12h	24-72h	90%/90-99%
Myoglobin	N/A	15-120 ug/L	2-4h	10-12h	99%/70%
Troponin	cTnI, cTnT	<0.08 ug/L	2-8h	18-24h	99%/99%

of an AMI.¹⁵ Furthermore, clinical guidelines still dictate that Troponin results should be interpreted with clinical findings and EKG results and not in isolation.¹⁶

FUTURE MARKERS

While current markers have greatly improved the diagnosis and quickened the treatment of AMI patients, there is still room for improvement, especially in the area of early detection.³ The following markers are some of the potential MI markers of tomorrow that may improve sensitivity, specificity, prognostication and decrease time between (or even predict) chest pain onset and diagnosis/treatment.

Myeloperoxidase

Myeloperoxidase (MPO) is a haemoprotein produced by polymorphonuclear neutrophils (PMN) and macrophages. It converts chloride and hydrogen peroxide to hypochlorite which is released during inflammation and is involved in lipid oxidation that is contained in LDL particles. This process promotes formation of foam cell in atherosclerosis. MPO is a marker of plaque instability and therefore presents as a potential strong prognostic marker of an MI in the near future. MPO is lowest in patients with stable coronary artery disease, higher in patients with unstable angina, and highest in patients with AMI.¹⁷

Copeptin

Copeptin is the C-terminal fragment of the vasopressin precursor hormone which is released in response to low blood pressure. Also, the measurement of copeptin has been shown to have very strong negative predictive value, along with troponin, for AMI.¹⁸ Additionally, copeptin levels are elevated early after AMI and are detectable in patients who present soon after symptom onset while troponin is still negative.¹⁹

Growth differentiation factor 15

Growth differentiation factor 15 (GDF-15) is a transforming growth factor. Cardiomyocytes express and secrete GDF-15 in the setting of ischemia and reperfusion, suggesting that it might be a protective factor. As well, GDF-15 has been identified in activated macrophages, and a distinct up-regulation has been found in many tissues following injury, ischemia, and other forms of stress.²⁰

Heart-type fatty acid-binding protein (H-FABP)

H-FAB main advantage is that it is released soon after cardiac injury and thus may be a great potential improvement from myoglobin as an early biomarker. The main disadvantage is that it is not exclusive to heart (also is found in skeletal muscle – although in much smaller amounts)²¹ Additionally, it is useful in distinguishing risk even in patients without elevated BNP or Troponin.²²

B-type natriuretic peptide (BNP) and N-Terminal fragment of pro-BNP (NT-proBNP)

BNP is a neurohormone released from cardiac cells following ventricular wall stress and myocyte stretching.²² Both the active form BNP, and the inactivated N-Terminal peptide “NT-proBNP” can be mea-

sured as markers of hemodynamic stress). While investigations have shown that elevated BNP and NTproBNP levels are predictive of death and heart failure, they are not useful as indicators of new or recurrent AMI.^{23, 24} More research is being conducted to establish the use of these biomarkers for selecting treatment of acute coronary syndromes.²²

high sensitivity C-reactive protein (hsCRP)

C-reactive protein is a marker of inflammation and may be part of the mechanism of atherosclerotic plaque producing thrombus. Elevated levels are predictive of death and heart failure post MI. hsCRP is non-specific for cardiac inflammation; however, measurements of forms specific to vascular inflammation are being developed and may be more specific for AMI.²⁵

placental growth factor (PIGF)

PIGF is also a useful indicator of plaque instability – more specifically – may be a determinant/cause of plaque instability and thus is a potential drug target to prevent AMI.²⁶

WBCHO and plasma choline (PLCHO)

Whole blood choline (WBCHO) includes measurement of choline in hemolysed erythrocytes. Choline leaks from ischemic tissues into plasma. In plasma, it is eventually taken up by blood cells (hence the differentiation between these two measurements). Both whole blood choline and plasma choline levels are of use for predicting cardiac ischemia in patients with negative troponin. The use of whole blood choline may also extend to determining plaque stability. Thus, these markers might be of use for predicting myocardial infarct (detection pre-necrosis).²⁷

CONCLUSIONS

Over the past several decades, the use of cardiac biomarkers has greatly improved the diagnosis of AMIs. As more markers have emerged, sensitivity and specificity has increased and time to diagnosis and treatment has decreased. Currently, the best marker available in clinical practice is troponin; however, even troponin results should be interpreted within a clinical context and not used in isolation. Furthermore, there is still room for improvement and current research seems to suggest there are more markers still to come which will improve AMI diagnostics, prognostics and prediction.

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DIAGNOSTIC REVIEW

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