

Cardiac Biomarkers

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1. Introduction

1950's: Clinical reports that transaminases released from dying myocytes could be detected via laboratory testing, aiding in the diagnosis of myocardial infarction. The race to define clinical markers to aid in the diagnosis, prognosis, and risk stratification of patients with potential cardiovascular disease begins. Initial serum markers included AST, LDH, total CK and α -hydroxybutyrate. These enzymes are all released in varying amounts by dying myocytes. Lack of sensitivity and specificity for cardiac muscle necrosis fuels continued research.

1960's: CK known to be released during muscle necrosis (including cardiac). Quantitative assays were cumbersome and difficult to perform. Total CK designed as a fast, reproducible spectrophotometric assay in the late 1960's. CK isoenzymes are subsequently described: MM, MB and BB fractions.

In 1970's MB fraction noted to be elevated in and highly specific for acute MI.

CKMB now measured via a highly sensitive monoclonal antibody assay. It was felt for a time that quantitative CKMB determination could be used to enzymatically measure the size of an infarct. This has been complicated by release of additional enzymes during reperfusion. As CK-MB assays become more sensitive, researchers come to the paradoxical realization that it too is not totally cardiac specific. The MB fraction is determined to be expressed in skeletal muscle, particularly during the process of muscle regeneration and the search for cardiac specificity continues.

Research turns towards isolation of and development of assays for sarcomeric proteins. Myosin light chains were originally isolated and then subsequently abandoned because of specificity issues. Troponin I first described as a biomarker specific for AMI in 1987; Troponin T in 1989. Now troponins are the biochemical "gold standard" for the diagnosis of acute myocardial infarction via consensus of ESC/ACC.

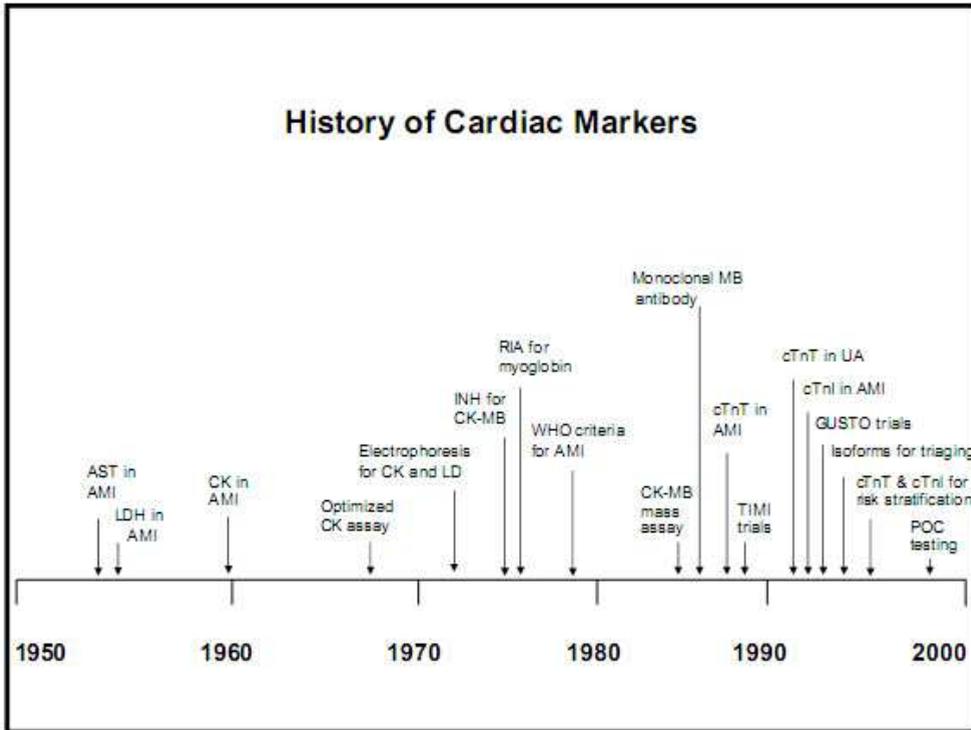


Fig. 1. Timeline showing landmark events in the development of cardiac biomarkers

1.1 Cardiac Markers: What are we looking at?

A biomarker is defined as a measurable substance or parameter that is an indicator of an underlying biological or pathological process. Therefore, depending on the underlying process that we are referring to, the cardiac markers can be classified as markers of necrosis, markers of ischemia and markers of inflammation. The features of an ideal cardiac marker would be:

- High sensitivity and specificity
- Rise and fall rapidly after ischemia
- Able to perform reliably and uniformly
- Be simple to perform
- Have turnaround time <60 min
- Not influenced by functioning of other organs, in particular, functioning of kidney.

Therefore, cardiac marker is an umbrella term which is used to define present day used necrosis markers as well as all the upstream markers of necrosis studied/under study including proinflammatory cytokines, cellular adhesion molecules, acute phase reactants, plaque destabilization biomarkers, plaque rupture biomarker and pre-necrosis ischemia biomarkers. This can be simply visualized with the help of following flow diagram:

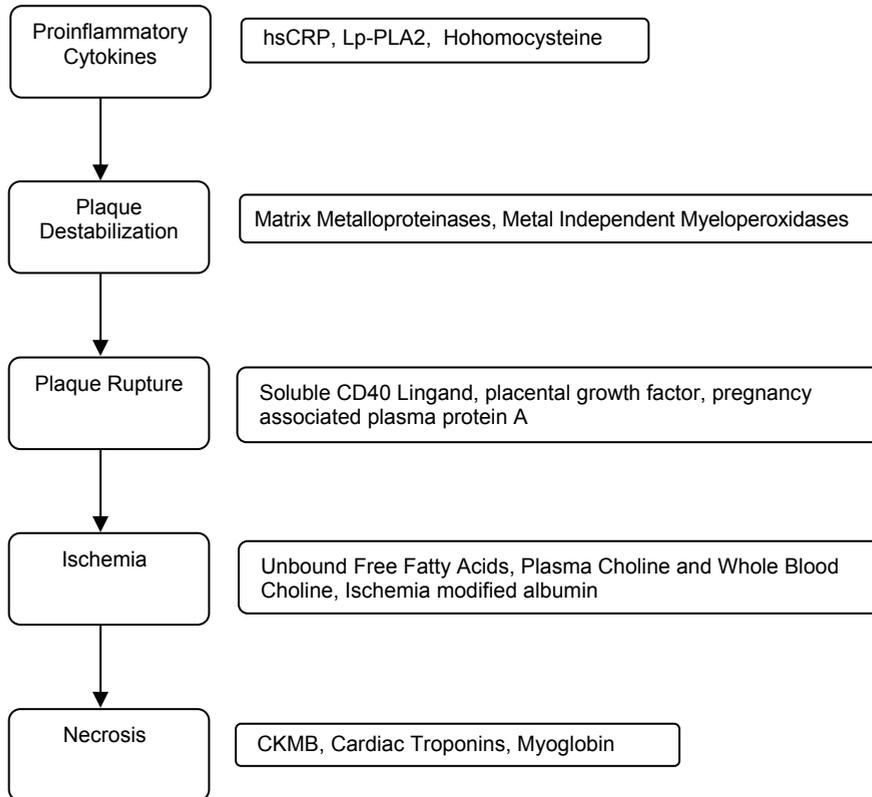


Fig. 2. Flowchart showing significance of biomarkers at various levels in the pathogenesis of acute coronary syndrome

1.2 Markers of cardiac necrosis

Cardiac markers are used in the diagnosis and risk stratification of patients with chest pain and suspected acute coronary syndrome (ACS). The cardiac troponins, in particular, have become the cardiac markers of choice for patients with ACS. Indeed, cardiac troponin is central to the definition of acute myocardial infarction (MI) in the consensus guidelines from the American College of Cardiology (ACC) and the European Society of Cardiology.

Older Definition of Myocardial Infarction- WHO 1979

1. Definite acute myocardial infarction-Definite acute myocardial infarction is diagnosed in the presence of unequivocal EKG changes and/or unequivocal enzyme changes; the history may be typical or atypical.
2. Possible acute myocardial infarction-Possible acute myocardial infarction is diagnosed when serial, equivocal ECG changes persist more than 24 hours, with or without equivocal enzyme changes; the history may be typical or atypical.
3. Old myocardial infarction-Old myocardial infarction is usually diagnosed on an unequivocal ECG in the absence of a history or enzymatic signs of acute myocardial

infarction. If there are no residual ECG changes, the diagnosis may be based on earlier, typical ECGs or on the presence of prior unequivocal serum enzyme changes.

Redefinition of Myocardial Infarction- Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Health Federation (ESC/ACCF/AHA/WHF) 2007

A typical rise and/or gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis, with at least one of the following is required:

- Ischemic symptoms
- Development of pathologic Q waves on the ECG
- ECG changes indicative of ischemia (ST segment elevation or depression)
- Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality.

In addition, pathologic findings (generally at autopsy) of an acute MI are accepted criteria.

Markers of cardiac necrosis have come a long way since 1950s. Some of the markers used in the past are no longer in use today. Current markers and those used in the past have been outlined in the table below. Those used in the past are not discussed separately further.

Current Cardiac Markers	Cardiac Markers of the Past
<ul style="list-style-type: none"> • CK-MB • Myoglobin • CKMB Isoforms • Troponin I and T 	<ul style="list-style-type: none"> • Total CK Activity • Aspartate Aminotransferase Activity • Lactate Dehydrogenase Activity • LD1/LD2 Ratio

Table 1. Various present day and past cardiac biomarkers

2. Creatine kinase

The enzyme creatinine kinase (formerly referred to as creatinine phosphokinase) exists as three isoenzyme forms: CK-MM, CK- MB, and CK-BB. These isoenzymes are found in the cytosol and facilitate the egress of high energy phosphates into and out of mitochondria.

CK: Dimer composed of 2 monomers: M (43,000 Da) and B (44,500 Da)---- > CK BB or CK MB or CK MM Role: Creatine + ATP <---> ADP + Phosphocreatine + Energy (muscular contraction) CK BB : Increased in neurological diseases ; prostatectomy; digestive cancers CK MB : Increased with AMI CK MM :Increased in myopathy, hypothyroidism, polymyositis, rhabdomyolysis, muscle trauma, intensive exercise, AMI
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Table 2. Isoenzymes of Creatinine Kinase

Distribution of CK: Creatine Kinase (CK) isoenzyme activity is distributed in a number of tissues. The percentage of CK-MB fraction found in the heart is higher than in most other tissues. However, sensitive radioimmunoassays are able to detect small amounts of B

chain protein in skeletal muscle, and some muscles have been reported to contain up to 10 percent B chain protein. Most muscles have much more CK per gram than heart tissue. As a result, despite containing only a small percent of B chain protein, skeletal muscle breakdown can lead to absolute increases in CK-MB in the plasma. Therefore, skeletal muscle damage can confound the diagnosis of an MI, as CK-MB can be released. The following are examples:

- Myocardial injury after cardiopulmonary resuscitation
- Cardioversion
- Defibrillation
- Cardiac and non-cardiac surgical procedures
- Blunt chest trauma with possible cardiac contusion
- Cocaine abuse

Total CK, CK-MB and CK-MB to Total CK ratio: Since CK is widely distributed in tissues, elevations in total serum CK lack specificity for cardiac damage, which improves with measurement of the MB fraction. The normal range of CK also varies considerably; a twofold or greater increase in the CK concentration is required for diagnosis. This criterion can be problematic in older individuals who, because of their lower muscle mass, may have low baseline serum total CK and, during MI, may have elevated serum CK-MB with values of total CK that rise but remain within the normal range. For these reasons, total CK has not been used in the diagnosis of myocardial damage for years. CK-MB has high specificity for cardiac tissue and was the preferred marker of cardiac injury for many years. An elevated CK-MB is relatively specific for myocardial injury, particularly in patients with ischemic symptoms when skeletal muscle damage is not present. Assays for CK-MB can be performed easily and rapidly. Most assays measure CK-MB mass; such measurements are more sensitive than activity assays. The relative index calculated by the ratio of CK-MB (mass) to total CK can assist in differentiating false-positive elevations of CK-MB arising from skeletal muscle. A ratio of less than 3 is consistent with a skeletal muscle source, while ratios greater than 5 are indicative of a cardiac source. Ratios between 3 and 5 represent a gray zone. No definitive diagnosis can be established without serial determinations to detect a rise. Studies to evaluate the CK-MB relative index compared with the absolute CK-MB have revealed increase in specificity but with a loss of sensitivity. The CK-MB/CK relative index is useful if patients have only an MI or only skeletal muscle injury, but not if they have both. In the combined setting of acute MI and skeletal muscle injury (rhabdomyolysis, heavy exercise, polymyositis), the fall in sensitivity is significant. It is worth noting that the diagnosis of acute MI must not be based on an elevated relative index alone, because the relative index may be elevated in clinical settings when either the total CK or the CK-MB is within normal limits. The relative index is only clinically useful when both the total CK and the CK-MB levels are increased.

Timing of Release: Creatinine Kinase starts rising in the blood 4-6 hours after the onset of chest pain. It peaks at 10-24 hours and then returns to normal after 48-72 hours. Since CK levels return to baseline 48 to 72 hours after infarction, it can be used to detect reinfarction. New elevations that occur after normalization are indicative of recurrent injury, again with the caveats in regard to sensitivity and specificity indicated above. However, for these reasons, CK-MB cannot be used for late diagnosis.

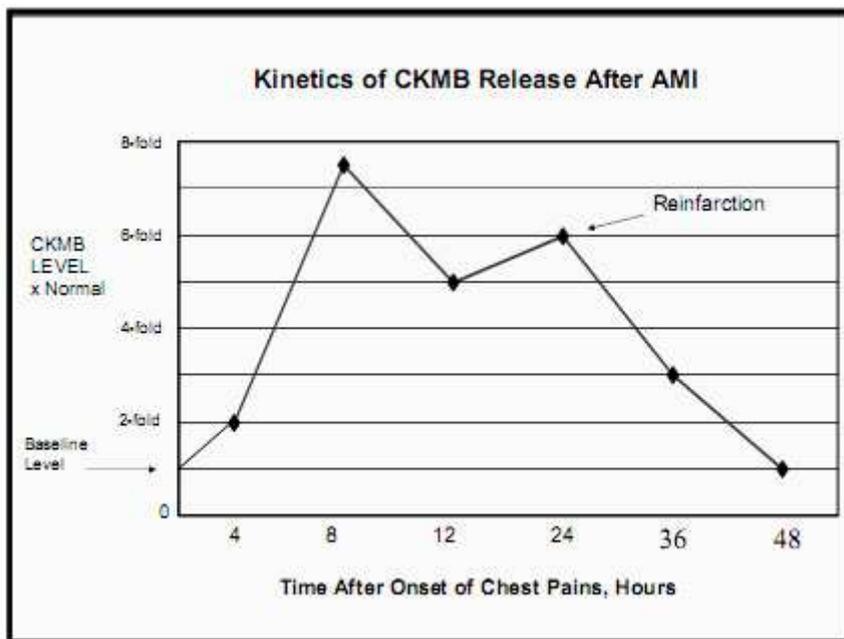


Fig. 3. Kinetics of CKMB release after AMI

Sensitivity and Specificity of CKMB: In AMI, CKMB usually is evident at 4 to 8 hours, peaks at 15 to 24 hours (mean peak=16×normal) with sensitivity and specificity >97% within the first 48 hours. By 72 hours, two thirds of patients still show some increase in CK-MB. Sampling every 6 hours is more likely to identify a peak value. False negative results may be caused by poor sample timing (e.g. only once in 24 hours or sampling <4 hours or >72 hours after AMI). Similarly, false positive may be caused by a variety of factors including but not limited to myocardial injury after cardiopulmonary resuscitation, cardioversion, defibrillation, cardiac and non-cardiac surgical procedures, blunt chest trauma with possible cardiac contusion and cocaine abuse.

CK and coronary reperfusion : The time to peak CK levels and the slope of CK-MB release can be used to assess whether reperfusion has occurred after fibrinolysis and, when used in conjunction with clinical variables, can predict whether TIMI 0 or 1 and TIMI 2 or 3 grade flow is present. The 2004 task force of the ACC/AHA concluded that serial measurements of CK-MB can be useful to provide supportive noninvasive evidence of reperfusion after fibrinolysis (class IIa recommendation). However, it should be noted that CK-MB criteria cannot identify the presence of TIMI 3 flow, which is the only level of perfusion associated with improved survival after fibrinolysis. Thus, many may elect invasive evaluation despite biomarker evidence of reperfusion. The 2004 ACC/AHA task force recommended specific guidelines for the diagnosis of reinfarction after an acute ST elevation MI. Within the first 18 hours of the initial MI, a recurrent elevation in CK-MB concentration alone should not be relied upon to diagnose reinfarction, but should be accompanied by recurrent ST segment elevation on ECG and at least one other supporting criterion (such as recurrent chest pain or hemodynamic decompensation). For patients more than 18 hours from the initial MI, a

biomarker rise and at least one additional criterion is sufficient for the diagnosis. Similar criteria were established for patients presenting with possible reinfarction after percutaneous coronary intervention or coronary artery bypass grafting.

3. Cardiac Troponins

Cardiac Troponins (cTn) control the calcium-mediated interaction of actin and myosin. It exists in three isoforms: troponin C, troponin I and troponin T. Troponin C exists in all muscle tissues. cTnI is however, completely specific for the heart. cTnT released in small amounts by skeletal muscles, though clinical assays do not detect skeletal TnT. Both have cytosolic or early releasable and structural pools, with most existing in the structural pool. They are more specific compared to CKMB in detection of infarction and are the preferred biomarker for the diagnosis of acute MI (Class I recommendation from the ACC/AHA task force on diagnosis of AMI).

Characteristics	Troponin C	Troponin I	Troponin T
Weight	18 KD	26.5 KD	39 KD
Function	Calcium binding subunit	Actomyosin-ATP-inhibiting subunit	Anchors troponin complex to the tropomyosin strand
Cardiac Specificity	None	Yes	Yes

Table 3. Troponin Characteristics. KD: Kilo Dalton

3.1 Timing of release

Cardiac troponins begin rising in the blood 4-6 hours post infarction (same time as CKMB). It peaks in 12-24 hours but may take weeks to return to normal. The timing of release, peak and normal return as compared to CKMB has been presented in a graphical form below.

3.2 Sensitivity and specificity of cardiac troponins

Cardiac troponins are as sensitive as CK-MB during the first 48 hours after acute myocardial infarction. The sensitivity is 33% from 0-2 hours, 50% from 2-4 hours, 75% from 4-8 hours and approaching 100% from 8 hours after onset of chest pain. The specificity is close to 100%. Troponin elevations have been reported in a variety of clinical scenarios other than acute coronary syndromes. The following is a list of some of the causes for the elevation of troponin in the absence of a thrombotic occlusion of the coronary artery:

- Tachy- or bradyarrhythmias, or heart block
- Critically ill patients, especially with diabetes, respiratory failure or sepsis
- Hypertrophic cardiomyopathy
- Coronary vasospasm
- Acute neurological disease, including stroke or subarachnoid hemorrhage

- Cardiac contusion or other trauma including surgery, ablation, pacing, implantable cardioverter-defibrillator shocks, cardioversion, endomyocardial biopsy, cardiac surgery, following interventional closure of atrial septal defects
- Rhabdomyolysis with cardiac injury
- Congestive heart failure - acute and chronic
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Aortic dissection
- Aortic valve disease
- Apical ballooning syndrome - Takotsubo Cardiomyopathy
- Infiltrative diseases (ie, amyloidosis, hemochromatosis, sarcoidosis, and scleroderma)
- Inflammatory diseases (ie, myocarditis or myocardial extension of endo-/pericarditis, Kawasaki disease)
- Drug toxicity or toxins (ie, adriamycin, 5-fluorouracil, herceptin, snake venom)
- Burns, especially if affecting >25 percent of body surface area
- Extreme exertion
- Transplant vasculopathy

The 2007 joint ESC/ACCF/AHA/WHF task force recommends that an elevated value of cardiac troponin, in the absence of clinical evidence of ischemia, should prompt a search for other causes of myocardial necrosis as listed above.

3.3 Troponin assays

The skeletal and cardiac isoforms of troponin T and troponin I are distinct, and skeletal isoforms are not detected by the monoclonal antibody-based assays currently in use. This specificity for cardiac isoforms is the basis for the clinical utility of cTnT and cTnI assays. Contemporary troponin assays are quite sensitive and can detect very small amounts of myocardial necrosis (<1 g). Troponin C is not used clinically because both cardiac and smooth muscle share troponin C isoforms. The ESC/ACC recommended that the diagnosis of MI be based on troponin levels in excess of the 99th percentile of a reference control group. As cTnT and cTnI levels are undetectable in most normal subjects, the 99th percentile is very low (eg, 0.04 to 0.5 micrograms/L). However, most assays are imprecise at this low level, and so it has been recommended that the definition of MI be raised to that value at which a specific assay has a coefficient of variation of 10 percent or less. New guidelines embrace 99th percentile for two reasons. This level is also low (0.1 to 1.2 micrograms/L), but higher than the 99th percentile standard. Due to variations in assay precision and individual laboratory policies, the upper limit of normal varies between laboratories, but in all cases is above the 99th percentile.

3.4 Point-of-care assays

The National Academy of Clinical Biochemistry (NACB) recommendations specify that cardiac markers be available on an immediate basis 24 h/d, 7 d/wk, with a turnaround time of 1 hour. Point-of-care (POC) devices that provide rapid results should be considered in hospitals whose laboratories cannot meet these guidelines. POC assays for CK-MB, myoglobin, and the cardiac troponins TnI and TnT are available. Only qualitative TnT

assays are available as POC tests, but both quantitative and qualitative POC TnI assays are currently marketed. In a multicenter trial, the time to positivity was significantly faster for the POC device than for the local laboratory (2.5 h vs 3.4 h). In another multicenter study, which evaluated the i-STAT POC TnI assay in comparison with the central laboratory in 2000 patients with suspected ACS, POC testing reduced the length of stay by approximately 25 minutes for patients who were discharged from the ED. The sensitivity of current POC assays coupled with the benefit of rapid turnaround time make the POC assays attractive clinical tools in the ED.

3.5 Prognostic value of cardiac troponins

In addition to its use in the diagnosis of MI, an elevated troponin level can identify patients at high risk for adverse cardiac events. Specifically, data from a meta-analysis indicated that an elevated troponin level in patients without ST-segment elevation is associated with a nearly 4-fold increase in the cardiac mortality rate. In patients without ST-segment elevation who were being considered for thrombolytic therapy, initial TnI levels on admission correlated with mortality at 6 weeks, but CK-MB levels were not predictive of adverse cardiac events and had no prognostic value. Other studies revealed that an elevated troponin level at baseline was an independent predictor of mortality, even in patients with chest pain and acute MI with ST-segment elevation who were eligible for reperfusion therapy. Finally, the TIMI IIIB, GUSTO IIa, GUSTO IV ACS, and FRISC trial all demonstrated a direct correlation between the level of TnI or TnT and the mortality rate and adverse cardiac event rate in ACS.

3.6 High Sensitive Troponin (hsTroponin)

High-sensitive assay is one which has a total imprecision of less than 10% at the 99th percentile and some would propose also being able to quantitate over 50% of normal values below that 99th percentile. High-sensitive cTn assays have two differentiating features from contemporary cTn assays: 1) detection of cTn in healthy persons and 2) a precise definition of what is "normal" (= the 99th percentile). Recent multicenter studies have shown that high-sensitive cTn assays improve the early diagnosis of acute myocardial infarction (AMI). To achieve the best clinical use, cTn has to be interpreted as a quantitative variable. Rising and/or falling levels differentiate acute from chronic cardiomyocyte necrosis. The term "troponin-positive" should therefore be avoided. "Detectable" levels will become the norm and have to be clearly differentiated from "elevated" levels. The differential diagnosis of a small amount of cardiomyocyte necrosis and therefore mild elevation of cTn is broad and includes acute and chronic cardiac disorders. The differential diagnosis of a large amount of cardiomyocyte necrosis and therefore substantial elevation of cTn is much smaller and largely restricted to AMI, myocarditis and Takotsubo cardiomyopathy. Two large prospective multicenter studies showed that sensitive and high-sensitive cTn assays have a higher diagnostic accuracy compared to contemporary cTn assays at presentation, in the diagnosis of AMI. Earlier "rule in" may reduce morbidity by allowing earlier revascularization, earlier transfer to the coronary care unit, and earlier initiation of evidence-based AMI treatment. Nonetheless, the improvement in sensitivity is at the expense of specificity. There is still considerable controversy in regard to how to use these assays to detect acute events such as AMI. Hence, at this time it has not been approved for clinical use and is yet in research phase.

4. Myoglobin

Myoglobin is a heme protein found in skeletal and cardiac muscle that has attracted considerable interest as an early marker of MI. Its low molecular weight accounts for its early release profile: myoglobin typically rises 2-4 hours after onset of infarction, peaks at 6-12 hours, and returns to normal within 24-36 hours. Rapid myoglobin assays are available, but overall, they have a lack of cardiac specificity. Serial sampling every 1-2 hours can increase the sensitivity and specificity; a rise of 25-40% over 1-2 hours is strongly suggestive of acute MI. However, in most studies, myoglobin only achieved 90% sensitivity for acute MI, so the negative predictive value of myoglobin is not high enough to exclude the diagnosis of acute MI. The original studies that evaluated myoglobin used the WHO definition of acute MI that was based on a CK-MB standard. With the adoption of a troponin standard for acute MI in the ACC/ESC definition, the sensitivity of myoglobin for acute MI is substantially reduced. This significantly diminishes its utility, and a number of studies have indicated that contemporary cardiac troponin assays render the use of myoglobin measurements unnecessary.

Conditions where myoglobin increases	Conditions where myoglobin does not increase
Acute myocardial infarction	Non cardiac chest pain
Vigorous exercise	Mild to moderate exercise
Open heart surgery	CHF without acute myocardial infarction
Rhabdomyolysis	Cardiac catheterization
Progressive muscular dystrophy	
Shock	
Renal Failure	

Table 4. Serum myoglobin in various clinical conditions

4.1 Timing of release, peak and return to baseline of various cardiac markers

CAD is highly prevalent in patients with CKD, making interpretation of cardiac markers important. Despite this, interpretation of elevated cardiac enzymes in patients with renal failure is often confusing at best. Elevations in serum troponin often observed in asymptomatic patients with chronic kidney disease. Even using the most conservative cutoff values, a disproportionate number of patients still have elevated troponins. The mechanism for this is unclear. In a 2002 study in *Circulation*, 733 asymptomatic patients with ESRD were evaluated. Using conservative cutoff values,

- 82% had elevated cTnT
- 6% had elevated cTnI

Of those 733 asymptomatic patients on HD, 2-year mortality rates were 52% in those with cTnI ≥ 0.1 $\mu\text{g/dL}$. These data have been corroborated in a number of smaller studies in similar populations. Serial measurements are helpful in the setting of possible ACS. cTnI appears to be much less likely to be associated with false positives in the CKD population than cTnT, making it the preferred biomarker in this setting.

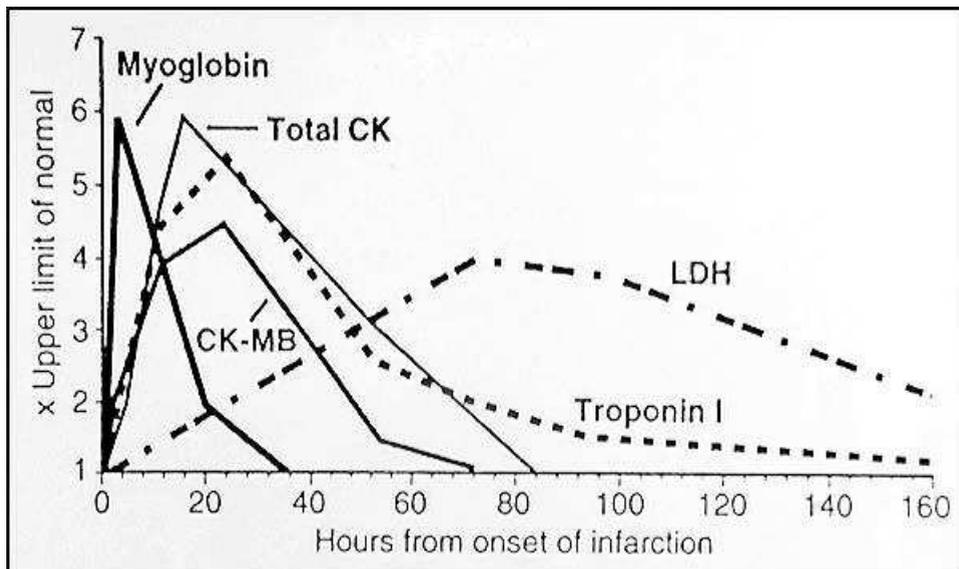


Fig. 4. A comparison of CKMB, cardiac troponins and myoglobin.

4.2 Markers of inflammation

Acute coronary syndromes are caused by vulnerable plaques. It is thought that one of the driving forces causing atheromatous plaques to rupture or erode, causing a cascade of events leading to coronary artery occlusion, is inflammation in the plaques. In this section cardiac inflammatory markers are dealt with which is at the verge of entering into clinical practice as tool for diagnosing and predicting future cardiovascular events at earlier stage and for risk stratification. Highly Sensitive Creative Protein (hsCRP), Myeloperoxidase (MPO), Matrix Metalloproteinases (MMP), Pregnancy Associated Protein A(PAPP-A), Placenta Growth Factor(PIGF) are reviewed.

4.3 C-Reactive protein (CRP)

C Reactive Protein is an acute phase reactant synthesized in liver and is elevated in inflammatory conditions. Once ligand-bound, CRP can activate the classical complement pathway, stimulate phagocytosis and bind to immunoglobulin receptors. "High-sensitivity" only means that the concentration of CRP was determined using an assay designed to measure very low levels of CRP. The American Heart Association has defined risk groups as follows: Low risk: less than 1.0 mg/L, Average risk: 1.0 to 3.0 mg/L and High risk: above 3.0 mg/L. Two assays averaged fasting or non fasting, and optimally 2 weeks apart, provide a more stable estimate of level of this marker. If a level is greater than 10 mg/L is identified, there should be a search initiated for an obvious source of infection or inflammation, which could obscure any prediction of coronary risk that might be attributed to the elevated level. The landmark study by Liuzzo et al. showed that patients presenting with unstable angina and elevated plasma concentrations of CRP had a higher rate of death, MI and need for re-vascularisation compared with patients without elevated concentrations. In more

recent trials, other investigators have confirmed the increased risk in ACS associated with higher CRP concentrations. In each of the above studies, the predictive value of CRP was independent of, and additive to, cardiac troponin. More importantly, CRP was found to have prognostic value even among patients with negative cardiac troponin and no evidence of myocyte necrosis. Methodological issues have however been highlighted and the independence between CRP and troponin release questioned. Therefore, although many studies have suggested that low-grade hsCRP elevations are independently associated with coronary risk, more complete evidence is needed to validate the use of hs-CRP as a risk assessment tool in general practice and as a target for therapy in individual patients.

4.4 Myeloperoxidase (MPO)

Myeloperoxidase (MPO) is a hemoprotein that is abundantly expressed in polymorphonuclear cells (neutrophils) and secreted during their activation. The presence of a peroxidase in the cytoplasmic granules of leukocytes was suggested at the beginning of 20th century but it was the early 1940s that it was purified for the first time. MPO plays an important role in neutrophil microbicidal action through catalyzing chloride ion oxidation to hypochlorous acid, which is a potent antimicrobial agent. On the other hand, it was demonstrated that MPO causes oxidative modification of low density lipoprotein (LDL) to a high uptake form that is considered to be a key event in the promotion of atherogenesis. Hence myeloperoxidase is believed to participate in the initiation and progression of cardiovascular diseases. MPO possesses potent proinflammatory properties and may contribute directly to tissue injury.

In a study consisted of patients diagnosed with ACS and other heart disease or unspecified chest pain, considerably higher MPO concentrations were demonstrated in the troponin-negative ACS patients on admission who became troponin-positive after 6h. This suggests that level of MPO possessed remarkably higher sensitivity than assessment of cTnI alone in all patients with ACS. MPO levels are associated with the presence of angiographically proven coronary atherosclerosis. In addition to clinical history and other tools MPO has been approved by FDA as cardiac biomarker to evaluate the patients with chest pain and at high risk for coronary artery disease.

4.5 Matrix metalloproteinases (MMP)

MMP are endogenous zinc dependent endopeptidases required for structural integrity of extracellular matrix of myocardium. TIMP (Tissue Inhibitors of Metalloproteinases) regulates MMP. MMPs may degrade myocardial ECM leading to the development of LV dilatation and heart failure and their inhibition in experimental models of AMI has been associated with reduced LV dilatation and wall stress. In a study of patients with acute myocardial infarction, TIMP-1 and MMP-9 correlated with echocardiographic parameters of LV dysfunction and remodelling after AMI and identified patients at risk of subsequent LV remodeling and associated with severe extensive CAD.

4.6 Placental Growth Factors (PGF)

Placental Growth Factor is a member of VEGF (vascular endothelial growth factor) subfamily - a key molecule in angiogenesis and vasculogenesis, in particular during the

embryogenesis. Placental growth factor expression within human atherosclerotic lesions is associated with plaque inflammation and neovascular growth. Recent studies established the role of different inflammatory markers such as hsCRP, sr amyloid A, IL-6 not only gets elevated during acute coronary syndrome (ACS) but predicts its adverse outcomes. PGF was recently shown that it is upregulated in all forms of atherosclerotic lesions. PGIF induces the following

- Vascular smooth muscle cell growth.
- Recruits macrophages into atherosclerotic lesions.
- Upregulates production of TNF alpha.
- Monocyte chemotactic protein 1 by macrophages.
- Pathological angiogenesis.

Plasma PIGF levels may be an independent inflammatory biomarker of poor outcome in patients with suspected ACS. A single initial measurement of plasma PIGF appears to extend the predictive and prognostic information gained from traditional inflammatory markers.

5. Pregnancy associated plasma protein alpha (PAPP-A)

PAPP-A was originally identified in the serum of pregnant women. PAPP-A is produced by placental tissue. Circulating PAPP-A levels increase during pregnancy and they are used in the fetal diagnosis of Down syndrome. Only recently has PAPP-A been identified in nonplacental tissues. The concentrations in the sera of nonpregnant human beings being several orders of magnitude lower than during pregnancy. The physiological role of PAPP-A is only beginning to be unraveled. PAPP-A is a high-molecular-weight, zinc-binding metalloproteinase, which acts as a specific protease of IGF binding protein-4 (IGFBP-4). There is histological evidence, using specific monoclonal antibodies, that PAPP-A is abundantly expressed in both eroded and ruptured coronary plaques, but not in stable plaques, in patients who have died suddenly of cardiac causes. Furthermore, accumulating evidence suggests that PAPP-A may play a pivotal role in the development of atherosclerosis and subsequent plaque instability in ACS patients. PAPP-A is markedly elevated in the earliest hours after the onset of symptoms in patients with STEMIs treated with heparin and primary percutaneous coronary intervention, and in animal studies, heparin administration is associated with a significant increase in PAPP-A levels, presumably because of the detachment of PAPP-A from the vessel wall. If future studies confirm that concomitant heparin administration also increases PAPP-A levels in humans, the prognostic role of PAPP-A in patients with ST elevation myocardial infarction needs to be reevaluated.

5.1 Markers of ischemia

An ideal marker is one in which there is a specific easily measurable increase that clearly aligns with a predictable outcome be it evidence of ischemia, inflammation, myocardial necrosis, plaque rupture, plaque destabilization, or heart failure. Because of the underlying shared etiologies related to the process of arteriosclerosis and the complexity of the pathological processes giving rise to adverse thrombotic outcomes, a single marker that

relates to each stage is unlikely. Rather more probable would be use of multiple markers with varying decision levels to either rule-in or rule-out a clinical decision. As the understanding of the niceties between ACS, inflammation, and coronary artery process develops, the ongoing search for better cardiac markers will continue.

5.2 Ischemia modified albumin (IMA)

The only ischemia marker that has been approved by the FDA is the modified albumin (IMA) using the albumin cobalt binding test (ACB) for assessment of myocardial ischemia. IMA occurs in 2 forms: 1.in which human serum albumin (HAS) binds mostly copper and 2.in which the damage to the N-terminus prevents metal binding. Patients without ischemia have more available metal binding sites on their HSA, than those from ischemic patients. This alteration is most likely due to damage caused by oxidative free radicals prevalent during ischemic events, and resulting in altered binding of trace metals resulting in IMA. As mentioned earlier, the FDA approved method for IMA (ACB Test by Ischemia Technologies) uses cobalt in its assay. Normal HSA will bind cobalt when it is added to a sample, leaving little residual cobalt. However, IMA cannot do the same due to its altered binding site. Patients having transient ischemic episodes without parallel myocyte death increases IMA which causes less cobalt binding and more residual unbound cobalt available. This can complex with chromogen (dithiothreitol) which can be measured photometrically. It is estimated that approximately 1% to 2% of the total albumin concentration in the normal population is IMA compared to 6% to 8% in patients experiencing ischemia. The clinical utility of IMA appears to be in its negative predictive value for ischemia and ACS, particularly when used in conjunction with other tests. While the optimum cutoff for IMA for ruling out ACS is 85kU/L, the manufacturer has suggested a higher value of 100 kU/L for risk stratification. Some of the limitations to be taken into consideration includes: a. there is an overlap between the normal population and that of individuals with cardiac ischemia; b. IMA is not specific for cardiac ischemia; c. false positive can occur in patients with cirrhosis, bacterial and viral infections, advanced cancers, stroke and end-stage renal disease and d. interpretation of IMA in certain populations, including those with peripheral vascular disease and in marathon runners is not yet clear. Hence IMA appears at this time as a potential marker in certain clinical situations but a number of possible interferences may limit its utility in patients with suspected ACS.

5.3 Unbound free fatty acids

Fatty acids are essential building blocks for many lipid molecules and are energy stores that can be utilized during times of fasting or increased metabolic demand. Fatty acids exist in body as esterified form (bound to glycerol or other alcohol), non-esterified form bound to albumin, and to a much smaller extent, as an unbound soluble form. Evidence exists that unbound free fatty acids increase significantly in ischemic-related events. It is not certain as of today what role the unbound free fatty acid plays in cardiac disease. It possibly partakes in the developing necrotic process and is released as a result of cell rupture or other precipitating conditions. Currently, a fluorescent probe assay is available but its clinical utility at this time is not established.

5.4 Fatty acid binding proteins (FABPs)

Fatty acid binding proteins (FABPs) are transport proteins that carry fatty acids and other lipophilic molecules like eicosanoids and retinoids across the membranes. They occur in nine different isoforms in a predictable tissue distribution and fairly long half-life of several days. The heart-type FABP (H-FABP) is released following myocardial death within 6 hours and is not specific to the heart, similar to myoglobin. It is released to a smaller extent in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary glands, and the placenta. It has been found that H-FABP may perform better and reach its upper reference limit sooner than either myoglobin or troponin. A number of enzyme immunoassays are available for H-FABP testing. Its relation to ischemia and prognosis for adverse events is likely to expound in near future.

5.5 Phospholipase

Phospholipase are the enzymes that release fatty acids from the second carbon group of glycerol. They are grouped into 4 major categories: A to D. Phospholipase A2 and D have drawn much attention in their role in assessing ischemia associated coronary artery disease. Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) also known as platelet-activating factor acetylhydrolase (PAF-AH) is a phospholipase A2 enzyme that in humans is encoded by the *PLA2G7* gene. In human atherosclerotic lesions, 2 main sources of Lp-PLA₂ can be identified, including that which is brought into the intima bound to LDL (from the circulation), and that which is synthesized de novo by plaque inflammatory cells (macrophages, T cells, mast cells). A meta-analysis involving a total of 79,036 participants in 32 prospective studies found that Lp-PLA₂ levels are positively correlated with increased risk of developing coronary heart disease and stroke. Recently, there has been a renewed interest in this molecule, not for use in cardiac assessment as it was originally approved by the FDA, but rather in stroke prediction after it was found that elevated levels of Lp-PLA₂ were associated with an almost 2-fold increase in stroke in the selected population coupled with a 6-fold increase in hypertensive individuals.

Phospholipase D (PLD) is an enzyme that catalyzes the hydrolysis of membrane bound phospholipids into phosphatidic acid and choline. In addition, it is also involved in endorsement of fibrinogen binding to platelets. Increased levels of plasma PLCHO and whole blood choline (WBCHO) levels have been seen in tissue ischemia in patients with negative troponin values. Choline is not a marker for myocardial necrosis but indicated high-risk unstable angina in patients without acute myocardial infarction (sensitivity 86.4%, specificity 86.2%). Therefore obtaining levels of both plasma PLCHO and WBCHO may prove to be a useful aid in patients suspected of ACS.

6. Conclusion

Cardiac markers have been implicated in the diagnosis and risk stratification of patients with chest pain and suspected acute coronary syndrome (ACS). Among the markers of cardiac necrosis, troponins have become the cardiac markers of choice for patients with ACS. In fact, cardiac troponin has become central to the definition of acute myocardial infarction (MI) in the consensus guidelines from the American College of Cardiology (ACC)

and the European Society of Cardiology (ESC). Current focus is on finding appropriate upstream markers which may aid in detection of myocardial ischemia and a variety of events involved in the process of pathophysiology of acute coronary syndrome especially in relation to plaque destabilization and rupture. The ideal biomarkers that offer early detection, risk stratification, selection of therapy, monitoring disease progression, and treatment efficacy remain to be elucidated.

7. References

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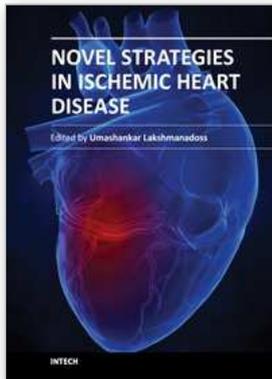
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Novel Strategies in Ischemic Heart Disease

Edited by Dr. Umashankar Lakshmanadoss

ISBN 978-953-51-0184-0

Hard cover, 450 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sadip Pant, Abhishek Deshmukh, Pritam Neupane, M.P. Kavin Kumar and C.S. Vijayashankar (2012). Cardiac Biomarkers, Novel Strategies in Ischemic Heart Disease, Dr. Umashankar Lakshmanadoss (Ed.), ISBN: 978-953-51-0184-0, InTech, Available from: <http://www.intechopen.com/books/novel-strategies-in-ischemic-heart-disease/biomarkers-in-ischemic-heart-disease>

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