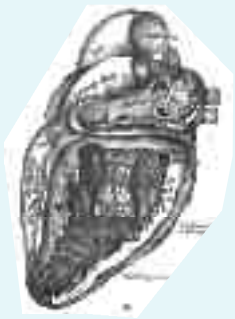
SCRIPPS NEWS

VOLUME 10 NUMBER 2 SUMMER 1996

A publication of SCRIPPS LABORATORIES, INC.



SPECIAL REVIEW:

The Best Biochemical Markers of Myocardial Infarction

Focus on
CK-MB
Myoglobin
Cardiac Troponin I
Glycogen
Phosphorylase BB
more...

Coronary atherosclerosis results in 1.5 million reported cases of acute myocardial infarction (MI) annually in the United States, accounting for approximately 500,000 deaths.[1,2] Advancements in the treatment of MI (discussed below) have increased the 30-day survival rate from approximately 75% in 1970 to 90% today.[3] Despite this, MI remains the leading cause of death in the US. Recent advancements in the biochemical detection and monitoring of MI will likely reduce the mortality rate even further.

Acute MI occurs when a lack of oxygen (ischemia) leads to the death of heart muscle (myocardial necrosis). Although there are many possible causes, the most common cause of MI is blockage of a coronary artery as a result of clot formation (thrombosis), usually at a site of advanced atherosclerosis and vessel wall injury.[4] Although the heart pumps oxygenated blood through its cavities, its hard-working tissues require supplemental oxygen from another source. The right and left coronary arteries, branching from the aorta, supply the entire heart with this additional oxygen. As such, the formation of a clot that restricts the blood flow of either coronary artery results in myocardial ischemia and shortly thereafter, myocardial necrosis. Unless medical intervention is immediate, prolonged ischemia of the myocardium results in a major cardiac arrest.

The goals of the early treatment of MI include dissolving the obstructing clot, restoring blood-flow of the occluded coronary artery, and salvaging as much myocardium as possible.[5] Treatments for MI include both pharmacologic and mechanical methods.

The primary pharmacologic methods involve the intravenous (IV) administration of various thrombolytic agents; these include streptokinase, recombinant tissue plasminogen activator (t-PA), anisoylated plasminogen-streptokinase activator complex (anistreplase), and urokinase. When administered early in the course of MI, these clot-dissolving drugs have proven effective in reducing the mortality of MI patients. In particular, IV administration of these thrombolytic agents within 1 hour of the onset of symptoms was shown to reduce mortality by 50% (from 10% mortality to approximately 5%).[6] In addition, when administered approximately 6 hours after the onset of symptoms, thrombolytic therapy resulted in a 25-30% reduction in mortality (10% to approximately 7%).[5] Furthermore, two studies noted an increased survival rate when t-PA was administered 6-12 hours post-infarct[7] and when a streptokinase-aspirin combination therapy was administered up to 24 hours post-infarct.[8] Despite the latter two reports, most studies reveal that the efficacy of thrombolytic therapy diminishes sharply over time, with the greatest benefit observed in the first 6 hours.[5,6]

Two surgical techniques, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG), have also proved very successful in treating MI patients. Using either of these techniques, successful reperfusion has been reported in as high as 92% of treated patients and in-hospital mortality has been reported as low as 6%.[9,10] Because these techniques are expensive, labor-intensive, and relatively time-consuming, they are best suited for use when thrombolytic therapy has failed to dissolve the obstructing clot, or when a patient presents to the emergency room (ER) with active bleeding or with another contraindication for thrombolytic therapy.

Early Diagnosis

With the availability of the above-mentioned treatment modalities, early and accurate diagnosis of MI is more important than ever. Early classification of patients into the categories of stable angina pectoris (the presence of lumen-restricting plaques in a coronary artery), unstable angina pectoris (characterized by plaque separation and a partially-occlusive clot), and MI (significant plaque separation and a totally-occlusive clot) is vital to determining which patients would benefit from thrombolytic therapy, which should receive surgical treatment, and which should be sent home.

Presently, only 16-40% of MI patients are administered thrombolytic drugs in the United States.[11,12] This is despite the studies discussed above and despite a 1993 European study that demonstrated a significant increase in survival when thrombolytic agents were administered by emergency personnel prior to arrival at a hospital, as compared to post-hospital drug admini-stration.[13] The limited use of thrombolytic agents is largely due to the lack of a reliable set of criteria for the early diagnosis of MI. As a result, not only is life-saving treatment delayed, but 2-5% of all MI patients are misdiagnosed and actually sent home.[14] The effects of inadequate early MI diagnosis are far reaching: Failure to diagnose MI is the largest source of malpractice expenditure resulting from the ER.[14,15,16]

ECG

To date, electrocardiography (ECG) is the most widely-used method of MI diagnosis.[17] Studies have shown that ECG can be diagnostic for MI almost immediately after MI.[18,19] Unfortunately, however, as many as 1 in 4 MI patients present to the ER with a normal or an ambiguous ECG that is not diagnostic for MI.[6,17,20,21] In addition, the interpretation of ECG changes often requires a cardiologist for a confirmed MI diagnosis.[22] As a result, ECG is inconclusive in a large percentage of cases; the reported accuracy of ECG in the diagnosis of MI ranges from 18-93%, depending on whether single or serial measurements were taken and whether "borderline" patients were included or excluded in the study.[23,24,25,26,27] ECG is a very valuable marker for MI when unequivocal pattern changes are present, but such changes are present only in a minority of patients. Therefore, despite its widespread use, ECG is not a reliable marker for MI and often requires supplemental diagnostic data.

Biochemical Markers of MI

To assist with MI diagnosis, ECG data is coupled with various biochemical markers of myocardial necrosis.

BIOCHEMICAL MARKERS OF MYOCARDIAL INFARCTION

Some of these markers include creatine kinase isoenzyme MB (CK-MB), cardiac troponin I and T, myoglobin, carbonic anhydrase III (CA III), and fatty acid-binding protein (FABP). Several other markers are under study or are currently in use (total CK, myosin light chain, lactate dehydrogenase isoenzymes, etc.), but the present article focuses on those markers holding the most promise for future use.

CK-MB

CK-MB is widely recognized as the leading cardiac serum marker, especially since the advent of CK-MB mass assays. The determination of CK-MB mass has proven to be more specific for myocardial necrosis than the long-standing CK-MB activity and CK-MB inhibition assays.[28,29,30,31] CK-MB is released after MI, is detectable in plasma as early as 3-4 hours after the onset of symptoms, and remains elevated for approx-imately 65 hours post infarct.[32,33] CK-MB mass levels are reportedly 50% diagnostic for MI at 3 hours and >90% diagnostic at 6 hours.[6] Such accuracy makes CK-MB mass deter-minations useful in confirming MI in patients presenting to the ER with non-diagnostic ECGs >3 hours after the onset of symptoms.[27,34]

CK-MB mass determinations, however, are not cardiac tissue specific.[6] Elevated CK-MB levels have been reported in significant percentages of patients with acute skeletal muscle trauma (59%), chronic muscle disease (78%), and chronic renal failure (3.8%).[35] Consequently, CK-MB is not useful in confirming an MI diagnosis in patients who concurrently have any of these afflictions. This notable shortcoming of CK-MB resulted in the search for other, cardiac specific serum markers of MI.

Cardiac Troponin T

A serum marker that once held promise as a cardiac specific marker for MI is the cardiac isoform of troponin T (cTnT). The past several years have seen many comparisons between CK-MB and cTnT. cTnT elevates at approximately the same time as CK-MB, with detectable levels present in the serum as early as 3-4 hours post-MI. cTnT, however, remains elevated approximately 4-5 times longer than CK-MB, with elevated levels detectable for as long as 240 hours post-MI.[36]

An area in which cTnT may provide more diagnostic data than CK-MB is the risk stratification of suspected, but unconfirmed, MI patients. Several studies have reported cTnT elevations in suspected MI patients with normal CK-MB levels.[27,37,38,39,40,41] CK-MB was elevated in all patients with confirmed MI, while cTnT was elevated in all confirmed MI patients plus several patients without confirmed MI. Further evaluation revealed that the latter group had unstable angina and, thus, were at high risk for MI. In another study, cTnT accurately predicted the outcome of patients with unstable angina: 92% sensitivity and 98% negative predictive value (the likelihood of a negative test value accurately ruling out MI).[34] The above studies suggest that CK-MB is more specific than cTnT for confirming true MI, but that cTnT is more specific for myocardial injury; as such, cTnT is deemed valuable in the risk stratification of ER patients presenting with any combination of the following symptoms: chest pain, non-diagnostic ECG, and normal CK-MB levels. cTnT would, therefore, assist the ER physician in determining which patients are at high risk for MI and should receive thrombolytic therapy, or should at least be monitored more closely.

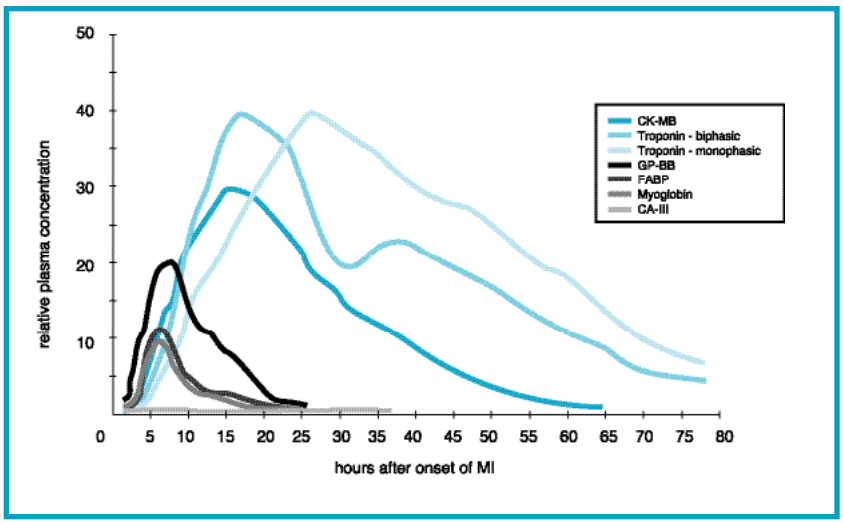
cTnT was also shown useful in monitoring a patient's response to reperfusion therapy. Currently, coronary angioplasty is the standard for monitoring recanalization, but researchers continue the search for less expensive, non-invasive techniques.[6,36] In a 1994 study, cTnT predicted reperfusion with 96% efficiency in 53 patients receiving thrombolytic agents.[42] In another study, the cTnT release kinetics were markedly different between successful and unsuccessful thrombolysis.[43] Specifically, the researchers determined the ratio of cTnT levels measured at 16 hours and at 32 hours post-infarct (16:32 hour cTnT ratio). A ratio greater than 1.0 indicated successful reperfusion with 94% efficiency. Furthermore, two additional 1994 studies reported that cTnT levels were 100% accurate in predicting successful reperfusion after coronary angioplasty and 92% accurate in patients who received thrombolytic therapy.[44,45]

Further investigation revealed that the key to cTnT's accuracy in predicting the successful recanalization of an occluded coronary artery lies in how it is released into circulation. cTnT is released in either a single, continuous peak or in a biphasic pattern with a large peak appearing at 10-18 hours post-MI and a smaller peak at 70-100 hours post-MI.[36] The release kinetics of cardiac-related proteins like cTnT depend on the intracellular compartmentalization of the protein in question and on the blood flow in the specific region of myocardial necrosis. A protein that is present in the cytoplasm of cardiac myocytes is washed out of the infarct area relative to the blood flow in that area. Variations in the blood flow at the infarct site result in corresponding variations in the release of cytosolic proteins. On the other hand, the release of structurally-bound proteins is independent of the blood flow of the infarct region and is very specifically related to tissue necrosis and subsequent tissue degradation.

cTnT is 5% cytoplasmic and 95% structurally-bound in the myocardium, while CK-MB is 100% cytoplasmic.[36] As such, the early release of cTnT (that which is released in a pattern similar to CK-MB in the first 3-4 hours post-MI) represents only the small cytoplasmic fraction, lasts approximately 30 hours, and results in the first peak observed in the cTnT release kinetics.[36] The second cTnT peak frequently observed in MI patients occurs 30 - 100 hours post-MI, after CK-MB levels have returned to normal. This peak represents the release of the structurally-bound cTnT and corresponds to the degradation of the troponin-containing myocardial contractile apparatus. These release kinetics suggest that cTnT is potentially more useful than CK-MB in estimating infarct size as the size of the second peak is directly related to the amount of myocardial tissue necrosis.

A 1995 study reported that the biphasic release of cTnT is observed only in those MI patients in which the cytoplasmic fraction of cTnT is cleared quickly into circulation as a result of successful reperfusion therapy.[36] As in the 1994 reports, a 16:32 hour cTnT ratio greater than 1.0 indicated that most of the cytoplasmic cTnT was released early, a result of restored coronary artery circulation. The authors also noted that patients with critical coronary artery occlusion displayed the other release kinetic for cTnT, a single, prolonged elevation. Presumably, severe blockage at the infarct site prevents the early release of cytoplasmic cTnT because blood flow is significantly restricted. Eventually, the structurally-bound cTnT fraction is released, resulting in the delayed, continuous elevation of serum cTnT. The authors concluded that patients displaying the single peak cTnT release kinetics have a poor prognosis, are at higher risk for acute cardiac complications, and must be monitored more closely than those patients with biphasic release.

The above studies had cTnT on the verge of widespread diagnostic use, supplying diagnostic data that is complementary to that supplied by ECG and CK-MB mass determinations. That was until non-cardiac patients were detected with elevated cTnT levels. Several recent reports indicate that cTnT is elevated in chronic renal disease, skeletal muscle disease and trauma, and is present in regenerating skeletal muscle (see Scripps News V9N3).[6,46,47,48,49,50,51] Such studies led Dr. JH Keffer[6] to conclude in the March '96 issue of the American Journal of Clinical Pathology, "Pending clarification of the issues of cardiospecificity, cross-reactivity in skeletal muscle disorders, re-expression of the cardiac isoform in skeletal muscle in adults, serum levels in myopathic states, and change in the configuration and cost of the assay, the cTnT assay cannot be recommended for widespread adoption in its current form." Likewise, a similar conclusion was reached by Dr. M Löfberg et al.[51] in the July '96 issue of Clinical Chemistry. Such conspicuous statements have rather abruptly turned the attention of MI researchers to the cardiac specific marker, cTnI.



Cardiac Troponin I

Cardiospecificity has long been the focus of the search for an efficacious biochemical marker for MI, and with the advent of sensitive immunoassays for the cardiac isoform of troponin I (cTnI), it appears that a cardiac specific serum marker has been found. As mentioned above, CK-MB and the once promising cTnT are often elevated in many non-cardiac conditions. cTnI on the other hand, is very specific for myocardial injury; unlike cTnT, it is rarely elevated in chronic renal disease, skeletal muscle disease and trauma, and it is not present in regenerating skeletal muscle.[6,46,47,48,49,50,51]

The exceptional cardiac specificity of cTnI is likely due to the differences in the amino acid sequences of the cardiac and skeletal muscle isoforms. cTnI shares only 60% homology with fast-twitch and slow-twitch skeletal TnI and contains an additional amino acid sequence at the N-terminus that is not found in either of the skeletal isoforms.[52,53,54] It is likely that this additional amino acid sequence, not found in cTnT, enhances the immunodetection of cTnI in human serum.

Several studies confirm that cTnI is elevated in cardiac injury and suggest that it has equal sensitivity and greater specificity than both CK-MB and cTnT in detecting myocardial injury [this has been reviewed in two issues of Scripps News: Volume 7 Number 2 (1993) and Volume 9 Number 3 (1995)].[55,56,57] The release kinetics of cTnI are similar to those of cTnT; detectable levels are present between 4-6 hours post-MI, peak at approximately 14 hours, and remain elevated for several days.[58] It has been suggested that the sustained elevation of cTnI may eliminate the need for assays for lactate dehydrogenase isoenzymes, currently used as a biochemical marker for MI when a patient is admitted to a hospital several days after the onset of chest pain.[17,59,60] cTnI has also demonstrated biphasic release patterns similar to cTnT.[61,62] Further study will likely demonstrate that, like cTnT, the biphasic vs. monophasic release patterns of cTnI will be useful in the risk stratification of suspected MI patients.

Although fewer studies are available for cTnI than for cTnT in MI risk assessment, two 1995 studies reported that sustained cTnI elevations were prognostic of a poor outcome in MI patients.[63,64] More recently, an April '96 report indicated that cTnI was equivalent to cTnT in predicting adverse events in 74 suspected MI patients.[61] In the latter study, the threshold value of 1.6 µg/L cTnI provided the best sensitivity and specificity for predicting MI; this is somewhat lower than the cTnI kit manufacturer's cut-off of 2.5µg/L. This suggests that before cTnI can be recommended to assist in determining whether a suspected MI patient should receive thrombolytic or other therapy, further study involving larger patient populations is required to assign an accurate cTnI threshold value.

Regarding the assessment of reperfusion therapy, a 16:32 hour ratio has not been evaluated for cTnI as it has for cTnT, but preliminary indications are that cTnI is at least as useful ascTnT.[6] In a January '96 study involving 25 patients receiving t-PA within six hours of the onset of chest pain, cTnI demonstrated 82.4% sensitivity in predicting successful coronary artery reperfusion and was 100% specific for non-reperfusion.[65] The authors used the ratio of serum cardiac values at 90 minutes vs. 0 minutes after administration of t-PA to evaluate the effectiveness of cTnI, CK-MB, and myoglobin. Serum levels of each marker were significantly elevated in response to successful reperfusion. The deciding factor in determining the best marker was the cardiac specificity of cTnI. Such specificity eliminates the possibility of elevated cTnI levels due to conditions other than MI; this is not the case with CK-MB and myoglobin.

A similar study involving cTnT and CK-MB suggested that accurate assessment of reperfusion could be made with measurements at 0 and 60 minutes.[66] It is reasonable to assume that similar results would be obtained with cTnI as well, but additional study is required.

cTnI has also been shown useful in detecting the presence of MI in both cardiac and non-cardiac surgeries. Perioperative MI is the most common cause of death in non-cardiac surgery, but is difficult to diagnose with the current biochemical markers.[67] In a 1994 study, 108 patients undergoing either vascular or spinal surgery were monitored for MI by using ECG, two-dimensional echocardiography, CK-MB, total CK, and cTnI.[67] Of the 8 patients with ECG-confirmed MI, all had cTnI elevations (100% sensitivity) and 6 had CK-MB elevations (75% sensitivity). Of the 100 patients without MI, 19 had elevated CK-MB (81% specificity) and 1 had elevated cTnI (99% specificity); presumably, CK-MB elevations were due to release from non-cardiac tissues. Similarly, in a 1995 study, cTnI accurately detected the presence of three microinfarctions that went undetected by CK-MB determinations.[68] The authors concluded that cTnI is useful in monitoring cardiac specific ischemia during surgical procedures and is valuable in the evaluation of the various cardioprotective measures used in cardiac-related surgeries.

An area in which cTnI falls short is the diagnosis of MI within the first few hours after the onset of chest pain. cTnI, and similarly CK-MB and cTnT, can take up to 6 hours to elevate rendering it useless in the critical 0-6 hour window in which thrombolytic therapy is most effective. One of the more extensively studied biochemical markers for the early detection of MI is the oxygen transport protein, myoglobin.

Myoglobin

Myoglobin has long been recognized as the earliest biochemical marker for the diagnosis of MI.[69] At approximately 17,500 MW, myoglobin is small enough to pass easily into circulation upon cardiac injury; as such, elevated levels are often present within 2 hours post-MI. Serum myoglobin peaks at approximately 6-9 hours, but is cleared from circulation rapidly and returns to normal within 24-36 hours.[70]

Myoglobin is highly sensitive for myocardial injury, but because it is abundant in both cardiac and skeletal muscle, it lacks adequate specificity.[69,71,72] In an effort to increase cardiac specificity, myoglobin has been used in conjunction with carbonic anhydrase III and fatty acid-binding protein.

Carbonic Anhydrase III

Carbonic anhydrase III (CA-III) is a cytoplasmic enzyme present in skeletal muscle, smooth muscle, and myoepithelial cells, but not in myocardium.[70] CA-III is released into circulation upon skeletal muscle trauma and strenuous physical exercise, and is elevated in various neuromuscular diseases.[70] CA-III is not present in cardiac tissue and, therefore, is not elevated in MI. As such, CA-III determinations may be used to define myoglobin elevations as skeletal- or cardiac-related: Myoglobin elevations due to skeletal muscle trauma will have simultaneous CA-III elevations, while cardiac-specific events will not.[70]

Recently, Vuori et al.[73] evaluated myoglobin, the myoglobin/CA-III ratio (Mb/CA-III), and CK-MB for the early detection of MI. At 0-2 hours post-MI, CA-III improved the diagnostic sensitivity of myoglobin from 40% (myoglobin assays alone) to 60% (the Mb/CA-III ratio), while CK-MB was not yet elevated in any patients. At 2-6 hours, the sensitivities were 93% for myoglobin, 100% for Mb/CA-III, and 43% for CK-MB. Beyond 6 hours, the sensitivities were approximately equivalent for all markers: ~80%. Of note, at the time of admission, the sensitivities were 73% for myoglobin, 84% for Mb/CA-III, and 54% for CK-MB, while the specificities were 91%, 96%, and 97%, respectively. In an earlier study, Brogan et al.[74] reported similar results: the Mb/CA-III ratio was more sensitive than CK-MB, yet equally specific, in the diagnosis of MI within 3 hours after the onset of chest pain. These studies suggests that the measurement and calculation of the Mb/CA-III ratio is more sensitive than CK-MB determinations within the first few hours post-MI. Studies involving larger and more diverse subject populations are required, however, to determine whether the Mb/CA-III ratio will truly be useful in the early diagnosis of MI.

Fatty Acid-Binding Protein

In addition to CA-III, fatty acid-binding protein (FABP) has been shown to increase the cardiospecificity of myoglobin assays.[75,76,77,78] FABP is a small cytoplasmic protein (approximately 15,000 MW) that binds long chain fatty acids and is thought to be involved in regulating the intracellular lipid levels of cardiac myocytes.[79] Specific tissue-type isoforms exist, primarily in those tissues that rely on fatty acid oxidation as an energy source, such as heart, liver, and intestine.[79,80] Heart-type FABP is abundant in cardiac myocytes, but is also present in very small quantities in skeletal muscle and in other tissue types.[81,82,83] Immunoassays for FABP have been described.[81,84]

Upon myocardial necrosis, FABP is released into circulation and cleared in a similar pattern to myoglobin: elevations occur within 3 hours post-MI, peak at approximately 5-8 hours, and return to normal within 24-36 hours.[85] A study evaluating the tissue-specific concentrations of heart-type FABP and myoglobin determined that FABP is more abundant in myocardium than in skeletal muscle, while the opposite is true for myoglobin. As such, the ratio of myoglobin over FABP (Mb/FABP) is approximately 10-fold lower in heart tissue than in various types of skeletal muscle: ~4.5 (mg/mg) in heart tissue compared to 21-73 in various types of human skeletal muscle.[86]

The tissue-specific difference in the Mb/FABP ratio is the basis for determining the source of myoglobin elevations in patients with simultaneous MI and skeletal muscle trauma or disease. In a 1995 study involving 23 MI patients, the mean Mb/FABP ratio was 6.2, similar to that found in myocardium.[87] In a related report, all MI patients (19 of 19) had significant elevations of both myoglobin and FABP within 3 hours after the onset of chest pain.[86] Mb/FABP ratios remained constant and similar to that of heart tissue(approximately 4-7) throughout the duration of the sampling period (36 hours), suggesting that the myoglobin was released from myocardial tissue. One MI patient underwent defibrillation and the Mb/FABP ratio increased from approximately 8 to greater than 50. This implied an increase in serum myoglobin as a result of defibrillation-induced skeletal muscle damage. In a previous study, the same authors showed that serum Mb/FABP ratios

increase in response to strenuous physical exercise, due to the disproportionate release of myoglobin from skeletal muscle.[88] Although more study is required involving larger subject populations, the above studies suggest that FABP is released early in the course of MI, at approximately the same time as myoglobin, and that the determination of serum Mb/FABP ratios improve the diagnostic specificity of myoglobin assays.

Glycogen Phosphorylase BB

Glycogen phosphorylase isoenzyme BB (GP-BB) is an early marker for the detection of MI that is somewhat distinct from those described above; the diagnostic data it provides is interpreted independently of myoglobin data.

Three isoenzymes of the glycogen phosphorylase dimer are known to exist: BB in brain and heart tissue, MM in muscle tissue, and LL in the liver. Both GP-BB and GP-MM are present in heart tissue, but differing amino acid sequences make immunological distinction possible: GP-BB is 83% homologous to GP-MM (and 80% homologous to GP-LL).[89] GP-BB is 188,000 MW (two 94,000 MW subunits) and resides in the sarcoplasmic reticulum of cardiac myocytes. It is the key phosphorylase in glycogenolysis and changes from a structurally-bound to a cytoplasmic form, depending on the metabolic state of the myocardium.[90,91]

Studies have shown that GP-BB is released into circulation shortly after MI.[92,93] In 1995, Rabitzsch et al.[94] evaluated 237 subjects (107 with non-traumatic chest pain, 14 with chronic stable angina pectoris, and 116 healthy volunteers) for GP-BB, CK-MB, myoglobin, and cTnT. Receiver-operating characteristic analysis indicated that GP-BB was superior to all other markers tested for the early diagnosis of MI (0-12 hours). The early release kinetics of GP-BB approximated those of myoglobin, but at 4 hours GP-BB was 70% sensitive for MI, while myoglobin was only 43% sensitive. In addition, GP-BB was the first marker to reach 100% sensitivity; this occurred at 7 hours. Myoglobin reached its peak elevation earlier than GP-BB (5 hours vs. 8 hours), but was only ~60% sensitive at that time; GP-BB, meanwhile, was >90% sensitive at 5 hours. GP-BB levels returned to normal at 20-25 hours, similar to myoglobin. These observations suggest that GP-BB may be valuable in the early, but not the late, detection of MI.

GP-BB may be sensitive enough for the risk stratification of suspected MI patients, as Rabitzsch et al.[94] reported it to be the first marker elevated in patients with unstable angina. In particular, GP-BB exhibited exceptional sensitivity in one unstable angina patient from whom serial blood samples were taken. Several distinct GP-BB peaks appeared over the course of 50 hours, corresponding to recurrent episodes of chest pain. This indicates that GP-BB is released into circulation immediately upon myocardial injury, even if only minimal necrosis exists, and is rapidly cleared from circulation. The extraordinary sensitivity of GP-BB suggests that it may be useful in identifying unstable angina patients who are at high risk for MI, although more study is required.

In addition to risk stratification, GP-BB may be useful in monitoring the course of pharmacologic or mechanical reperfusion therapies. Rabitzsch et al.[94] also demonstrated that successful reperfusion resulted in a significantly earlier release of GP-BB from the myocardium. Again, additional study is required.

Because of its large size, the appearance of GP-BB into circulation within the first few hours post-MI is enigmatic; however, it may be explained by its heightened sensitivity to myocardial oxygen deficiency. In simplified terms, myocardial ischemia significantly increases the rate of glycogenolysis in an indirect manner.[95] Subsequently, after glycogen is catabolized, GP-BB is released from the sarcoplasmic reticulum into the cytoplasm. Assisted by an ischemia-induced increase in cell membrane permeability, GP-BB passes into the extracellular matrix and, thus, into circulation.[94] As such, a 188,000 MW protein appears in circulation at approximately the same time as a protein 1/10th its size (17,500 MW myoglobin).

The above studies suggest that GP-BB may replace myoglobin in the early biochemical detection of MI. Thus far, it has shown superior sensitivity and specificity to myoglobin in the limited number of studies performed. Additional studies must involve patients with skeletal muscle trauma or disease, head trauma, renal disease, and more before GP-BB may be recommended in the detection and follow-up of MI.

In summary, it appeared that cTnT was on the brink of worldwide use before questions regarding the lack of tissue specificity were raised and confirmed. Subsequently, attention has focused on cTnI. Thus far, it appears that cTnI supplies valuable diagnostic data not provided by CK-MB. It's specificity for cadiac injury surpasses that for CK-MB and its prolonged elevation in the plasma is useful for the late diagnosis of MI. In addition, cTnI may be useful in the risk stratification of suspected MI patients and in monitoring a patient's response to reperfusion therapy. Whether or not cTnI will eventually replace CK-MB as the biochemical marker of choice depends on the outcome of future studies.

Likewise, we have reviewed an early biochemical marker of MI that shows promise in replacing an industry standard. GP-BB requires a significant amount of additional study, but its exceptional sensitivity suggest that it may one day replace serum assays for myoglobin. The specificity of GP-BB for cardiac injury remains to be adequately evaluated, and its value in risk assessment and response to therapy is unknown, but future investigation will answer these questions.

An interesting study would involve both GP-BB and cTnI and determine whether the combination could be used throughout the time course of MI. The diagnostic data supplied by GP-BB's early rise in MI may complement the data provided by cTnI's mid to late elevation. Ideally, these two markers would combine to unequivocably diagnose MI, adequately assess the risk of patients with unstable angina, and monitor a patient's response to reperfusion therapy. This, of course, remains to be proven and would require large studies involving subject populations with diverse symptoms and complications. Until then, ER physicians will continue to rely on ECG as the primary tool for MI diagnosis, CK-MB will remain the most widely used biochemical marker, and myoglobin will remain the early biochemical marker of choice.

References

1. American Heart Association. Coronary Heart Disease and Angina Pectoris. Heart and Stroke Facts: 1995 Statistical Supplement, Dallas, TX: American Heart Association, 1995.

2. Gunby P., JAMA, 327:449-450, 1993.

3. Gomez-Marin O., Folsom A.R., Kottke T.E., et al., Engl. J. Med., 316:1353-1359, 1987.

4. Dewood M.A., Spores J., Notske R., et al., N. Engl. J. Med., 303:897-902, 1980.

5. Sweeney J.P. and Schwartz G.G., Western Journal of Medicine, 164(3):238(11), 1996.

6. Keffer J.H., Am.J. Clin. Path. March: 305-320,1996.

7. "Late Assessment of Thrombolytic Efficacy (LATE) study alteplase 6-24 hours after onset of acute myocardial infarction," Lancet, 342:759-766, 1993.

8. "Second International Study of Infarct Survivalm (ISIS-2) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction,"Lancet,2:349-360, 1988.

9. Ellis S.G., Silva E.R., Heyndrick G., et al., Circulation, 90:2280-2284, 1994.

10. DeWood M.A., Notske R.N., Berg R., et al., J. Am. Coll. Cardiol, 14:65-77, 1989.

11. Cragg D.R., Friedman H.Z., Bonema J.D., et al., Ann. Intern. Med., 115:173-177, 1991.

12. Pfeffer M.A., Moye L.A., Braunwald E., et al., JAMA, 266:528-530, 1991.

13. "European Myocardial Infarction Project Group: Prehospital thrombolytic therapy in patients with suspected acutemyocardial infarction," N. Engl. J. Med., 329:383-389, 1993.

14. Gibler W.B., Am. J. Emerg. Med., 12:121-122, 1994.

15. Rusnak R.A., Stair T.O., Hansen K., et al., Ann. Emerg. Med., 18:1029-1034, 1989.

16. Gibler W.B., Young G.P., Hedges J.R., et al., Ann. Emerg. Med., 21:504-512, 1992.

17. Rozenman Y. and Gotsman M., Ann. Rev. Med., 45:31-44, 1994.

18. Hauser A., Gangadharan V., Ramos R., et al., J. Am. Coll. Cardiol., 5:193-197, 1985.

19. Griffin B., Timmis A.D., Crick J.C., et al., Eur. Heart J., 8:347-353, 1987.

20. Larue C., Defacque-Lacquement H., Calzolari C., et al., Mol. Immunol., 29 (2):271-278, 1992.

21. Hamm C., Ravkilde J., Gerhardt W., et al., N. Eng. J. Med., 327 (3):146-150, 1992.

22. Jayes R.L. Larsen G.C., Beshansky J.R., et al., J. Gen. Intern. Med., 7:387-392, 1992.

23. Kannel W.B. and Abbott R.D., N. Engl. J. Med., 311:1144-1147, 1984.

24. Kannel W.B., Circulation, 75(supplII):4-5, 1987.

25. McQueen M.J., Holder D., El-Maraghi N.H., Am. Heart J., 105:258-261, 1983.

26. Rouan G.W., Lee T.H., Cook E.F., et al., Am. J. Cardiol., 64:1087-1092, 1989.

27. Mair J., Smidt J., Lechleitner P., et al., Chest, 108:1502-1509, 1995.

28. Wu A.B., Wang X.M., Gornet T.G., et al., Clin. Chem., 38:2396-2400, 1992.

29. Bhayana V., Cohoe S., Leung F.Y., et al., Clin. Chem., 39:488-495, 1993.

30. Mair J., Morandell D., Genser N., et al., Clin. Chem., 41:1266-1272, 1995.

31. Bokhari A.M., Davies J., Davies J., et al., Int. J. Cardiol., 48:249-254, 1995.

32. Mair J., Wagner I., Jakob G., et al., Clin. Chim. Acta., 231:47-60, 1994.

33. Levitt M.A., Promes S.B., Bullock S., et al., Ann. Em. Med., 27:1, 1996

34. Yang Z., Zhang W., Liu Y., Chin. Med. J. (Engl), 108 (8): 626-630, 1995.

35. Adams J.E., Bodor G.S., Davila-Roman V.G., et al., Circulation, 88(1):101-106, 1993.

36. Hongwei Y., Wenjuan Z., Hongliang F., et al., Ch. Med. J. (Engl), 108(7):501-505, 1995.

37. Hamm C.W., Ravkilde J., Gerhardt W., et al., N. Engl. J. Med., 327:146-150, 1992.

38. Bakker A.J., Koelemay M.W., Gorgels J.C., et al., Lancet, 342:1220-1222, 1993.

39. Wu A.B. and Lane P.L., Clin. Chem., 411/8(B):1228-1233, 1995.

40. Bachorik P.S., Fats of Life, 6(1):1, 1992.

41. Bachorik P.S., Fats of Life, 6(4):9-10, 1992.

42. Remppis A., Scheffold T., Karrer O., et al., Br. Heart J., 71(3):242-248, 1994.

43. Burlina A., Zaninotto M., Secchiero S., et al., Clin. Biochem., 27(2): 113-121, 1994.

44. Triggiani M., Simeone F., Gallorini C., et al., Cardiovasc. Surg., 2(4):441-445, 1994.

45. Abe S., Arima S., Yamashita T., et al., J. Am. Coll. Cardiol., 23(6):1382-1389, 1994.

46. Lofberg M., Tahtela R., Harkonen M., et al., Arch Neurol, 52(12):1210-1214, 1995.

47. Sperling M., Chen I., Flitman H., et al., Clin. Chem., 41(S6):S166, 1995.

48. Apple F., Dahlmeier B., Sharkey S., Clin. Chem., 41(S6):S167, 1995.

49. Li D., Keffer J., Corry K., et al., Clin. Chem., 41(S6):S199, 1995.

50. Bhayana V., Gougoulias T., Cohoe S., et al., Clin. Chem., 41(S6):S231-S232, 1995.

51. Bernard A., Houte G. V., Lofberg M., et al., Clin. Chem., 42:no. 7, 1996.

52. Wilkinson J. and Grand R., Nature, 271:31-35, 1978.

53. Hartner K. and Pette D., Eur. J. Biochem., 188:261-267, 1990.

54. Vallins W., Brand N., Dabhade N., et al., FEBS, 270:57-61, 1990.

55. Larue C., Calzolari C., Bertinchant J., et al., Clin. Chem., 39:972-979, 1993.

56. Mair J., Wagner I., Puschendorf B., et al., Lancet, 341:838-839, 1993.

57. Adams J., Bodor G., Davila V., et al., Circulation 88:101-106, 1993.

58. Bodor G., Porter S., Landt Y., et al., Clin Chem., 38(11):2203-2214, 1992.

59. Landt Y., Ladenson J., Porter S., et al., Clin. Chem., 41(S6):S149, 1995.

60. Murthy Van Karmen A., Clin. Chem., 41(S6):S59, 1995.

61. McNamara J.R., Schaefer E.J., Wu A.H., et al., Clin. Chem., 42, 4:650-653, 1996.

62. Jaffe A.S., ACC. Cur. J. Rev., 5:29-33, 1995.

63. Hamlyn J.M. and Manunta P., J. Hypertens, 10:S99-111, 1992.

64. Doris P.A., Jenkins L.A., Stocco D.M., Hypertension, 23:632-638, 1994.

65. Apple F.S., Henry T.D., Berger C.R., et al., Clin. Chem., 105:6-10, 1996.

66. Abe S., Arima S., Yamashita T., et al., J. Am. Coll. Cardiol., 23:1382-1389, 1994.

67. Adams J.E., Sicard G.A., Allen B.T., et al., N. Engl. J. Med., 330(10):670-674, 1994.

68. Etievent J. P., Chocron S., Toubin G., et al., Ann. Thorac. Surg., 59:1192-1194, 1995.

69. Roxin L., Cullhed I., Groth T., et al., Acta. Med. Scand., 215:417-425, 1984.

70. Vaananen H.K., Syrjala H., Rahkila P., et al., Clin. Chem., 36(4):635-638, 1990.

71. Kagen L.J. and Christian C.L., Am. J. Physiol., 211:656-660, 1966.

72. Isakov A., Shapira I., Burke M., et al., Arch. Intern. Med., 148:1762-1765, 1988.

73. Vuori J., Syrjala H., Vaananen H.K., Clin. Chem., 42(1):106-109, 1996.

74. Brogan G.X., Vuori J., Friedman S., et al., Ann. Emerg., Med., 27(1):22-28, 1996.

75. Knowlton A.A., Burrier R.E., Brecher P., Circ. Res. 65:981-988, 1989.

76. Tanaka T., Hirota Y., Sohmiya K., et al., Clin. Biochem., 24:195-201.

77. Kleine A.H., Glatz J.F., Van Nieuwenhoven F.A., et al., Mol. Cell Biochem., 116:155-162, 1992.

78. Tsuji R., Tanaka T., Sohmiya K., et al., Int. J. Cardiol, 41:209-217, 1993.

79. Glatz J.F. and Van der Vusse G.J., Mol. Cell. Biochem., 98:237-251, 1990.

80. Veerkamp J.H. and Maatman R.G., Prog. Lipid. Res., 34:17-52, 1995.

81. Roos W., Eymann E., Symannek M., et al., J. Immunol. Methods., 183:149-153, 1995.

82. Watanabe K., Wakabayashi H., Veerkamp J.H., et al., J. Pathol., 170:59-65, 1993.

83. Zschiesche W., Kleine A.H., Spitzer E., et al., Histochemistry., 103:147-156, 1995.

84. Siegmann-Thoss C., Renneberg R., Glatz J.F., et al., Sensors. Actuators., In Press.

85. Glatz J.F., Kleine A.H., Van Nieuwenhoven F.A., et al., Br. Heart., 71:135-140, 1994.

86. Van Nieuwenhoven F.A., Kleine A.H., Wodzig W.H., et al., Circulation, 92(10):2848-2854.

87. Wodzig K.W., Pelsers M.M., Kragten J.A., et al., Ned. Tijdschr. Klin. Chem., 20:119-120, 1995.

88. Van Nieuwenhoven F.A., Kleine A.H., Keizer H.A., et al., Eur. J. Physiol., 421:R40, 1992.

89. Newgard C.B., Littmann D.R., Genderen C., et al., J. Biol. Chem., 263:3850-3857, 1988.

90. Meyer F., Heilmeyer L.M., Haschke R.H., et al., J. Biol. Chem., 245:6642-6648, 1970.

91. Entman M.L., Kanjike K., Goldstein M.A., et al., J. Biol. Chem., 251:3140-3146, 1976.

92. Rabitzsch G., Schulz H., Onnen K., et al., Biomed. Biochem. Acta., 46:S584-588, 1987.

93. Rabitzsch G., Mair J., Lechleitner P., et al., Lancet., 341:1032-1033, 1993.

94. Rabitzsch G., Mair J., Lechleitner P., et al., Clin. Chem., 41(7):966-978, 1995.

95. Kalil-Filho R., Gersdtenblith G., Hansford R.G., et al., J. Mol. Cell. Cardiol., 23:1467-1479, 1991.