Modern Cardiac Markers and Ischemic Heart Diseases:

A Prospective Study

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ABSTRACT

Myocardial injury can be detected by assaying blood levels of cardiac markers like Troponin I, Myoglobin, and CKMB Mass. These cardiac markers are distinct proteins released in the blood from necrotic heart muscle after Myocardial Infarction (MI) and the increased levels of these markers can indicate MI or cardiac injury in a person with chest pain or pressure. If infarction is ruled out in a person with continuing or recurring unstable angina, increased levels of these cardiac markers may indicate that the patient has heart muscle ischemia, and is at an increased risk for a future serious heart event. This study was designed to investigate the sensitivity, specificity, cost effectiveness, and the diagnostic and prognostic value of cardiac markers in patients presenting symptomatic chest pain. The perfect cardiac marker test, with a 100% early sensitivity + 100% specificity in diagnosing an MI, does not exist. Therefore, the use of multiple markers as a cardiac panel has a better chance of meeting all requirements of an ideal cardiac marker assay. A panel consisting of CK-MB and Troponin assays is recommended as a good tool for the diagnosis of patients with chest pain.

(Key Words: angina, myocardial infarction, myoglobin, CKMB mass, troponin, blood assays)

INTRODUCTION

The only tools commonly available to clinically diagnose and treat cases presenting symptoms of chest pain are ECG and cardiac enzymes. Tests like Lactate Dehydrogenase (LDH), Aspartate Transaminase (AST), and Creatine Kinase (CK), which while popular in the 1950s and 1960s, were replaced in the 1970s and early 1980s with tests measuring serum levels of the more cardiac-specific CK-MB isoenzymes. These new methods offered enhanced cardiac specificity and sensitivity, but turn-around time for test results was greatly increased. Improved turn-around time for CK-MB assays was achieved in the early 1990s with automated enzyme immunoassays, which use monoclonal antibodies to CK-MB. During that time, new immunoassays for CK-MB isoforms 2 and 1, Myoglobin, Troponin I, and Troponin T were also introduced as possible replacements for the CK-MB assay (Mercer 1997).

Current literature holds contradicting views concerning the need for the rapid availability of biochemical markers. However, Christenson et al. (2001) have shown an association with both reductions in length of hospitalization and overall laboratory costs in institutions producing shorter turn-around times on biochemical marker assays. On the other hand, the

study of National Heart, Lung, and Blood Institute noted in its National Heart Attack Alert Program literature, that billions of dollars are spent annually to hospitalize patients with non-cardiac chest pain (Cahill 1998).

Myocardial injury can be detected with greater sensitivity by assaying blood levels of cardiac markers. Cardiac markers are distinct proteins released in the blood from necrotic heart muscle after Myocardial Infarction (MI). These markers include Troponin I, Myoglobin, and CKMB Mass. Increased levels of cardiac markers indicate myocardial infarction or cardiac injury in a person with chest pain or pressure. Some myocardial infarctions are silent or manifesting few symptoms, if any. If infarction is ruled out in a person with continuing or recurring chest pain (unstable angina), an increased cardiac markers level indicates the person may have heart muscle ischemia (a decreased supply of oxygenated blood to the body), and is at an increased risk for a future serious heart event. With the development of rapid bedside assays for these proteins and turn-around times of few minutes (typically 13 minutes), their use in the evaluation of chest pain in the emergency room becomes feasible.

The clinical goal of the physician should be to initiate thrombolytic therapy within 30 minutes due to its increased effectiveness if administered within two hours of chest pain. This study was designed to investigate the sensitivity, specificity, cost effectiveness, and the diagnostic and prognostic value of cardiac markers in patients presenting symptomatic chest pain.

CARDIAC MARKERS

CK-MB Mass is the mass of isoenzymes of Creatine Kinase, now measured by immunoassay, a more rapid and more sensitive test that reduces the false positive rate to <5%. An elevated serum CK-MB is usually highly specific for Acute Myocardial Infarction (AMI), although rare false-positives exist (mainly from skeletal muscle release and renal failure). The CK-MB enzyme is cleared from the blood stream within 48 - 72 hours and the test will be normal if an AMI patient presents to the Emergency Department a few days after the AMI. The sensitivity at 4 hours is < 50%, but the sensitivity should approach 100% for AMI 10 - 12 hours after the onset of the chest pain.

Myoglobin is a protein that stores oxygen in the tissues. It is the most sensitive early marker of myocardial injury. It typically first appears in the serum within 1 - 2 hours of AMI, peaks at 4 - 6 hours; and returns to baseline in 6 - 12 hours. The test has a very low specificity (elevated levels found in many conditions e.g., exhaustive exercise, trauma, surgery, shock, renal failure) with many false positive test results. As an indicator of reperfusion, serum Myoglobin is probably at least as good as serum CK-MB and serum Troponin and it peaks earlier.

Cardiac Troponin I (CTnI) is contractile regulatory protein. Its testing may be more sensitive because it is found only in cardiac tissue and ambient serum levels are extremely low in healthy individuals. The serum Troponin levels remain elevated for 10 - 14 days and CTnI testing is useful for detecting an AMI if the patient presents to the Emergency Department many days after an episode of chest pain (wide diagnostic window). Measurement of the serum Troponin at presentation, and 4 and 8 hours after presentation is highly accurate in predicting the risk of adverse cardiac events.

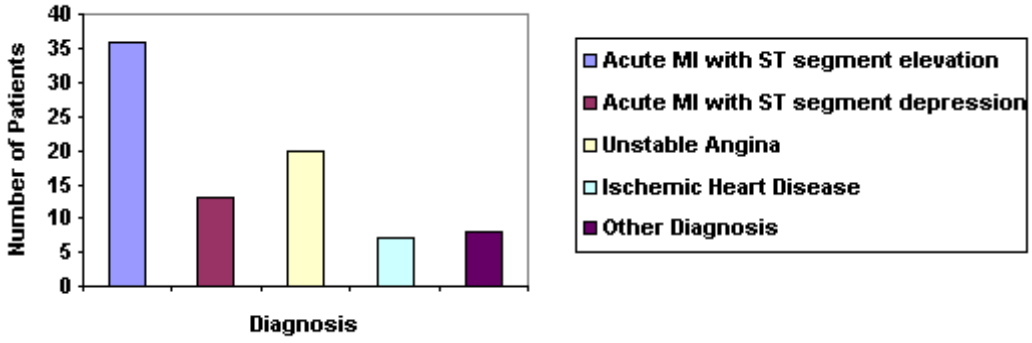
MATERIALS AND METHODS

Our study was conducted at the Emergency Room of Riyadh Medical Complex. Patients were eligible for our study population if they presented symptoms with less than 12 hours of anterior or left-sided chest pain. Data from 84 patients (81 males and three females, age ranged from 22- 88) were collected from May 2001 until August 2001. According to their diagnosis, they were classified into 5 groups. A special proforma was designed to collect the required information (Appendix). Blood was obtained for cardiac marker assays within 15 minutes of arrival to the Emergency Room and again six hours later. A rapid, quantitative bedside assay for Troponin I, Myoglobin and CKMB Mass was performed on the samples on Stratus CS, Dade Behring cardiac marker instruments. The results were immediately available to the treating physicians. Patients also had serial EKG's performed, blood drawn for CPK, and MB fractions taken. Medical histories, and physical examinations were obtained according to a hospital protocol. Myocardial infarction at the time of admission was judged by a double fold increase in CPK within 24 hours of admission with an elevated CKMB fraction or if CKMB index is > 5 [CKMB index = (CKMB × 100)÷ CK]. Patients were followed in the wards until discharge.

RESULTS

The majority of the patients (86%) were of lower socio-economic status and heavy smokers. Eighty-one males and 3 females age-ranged from 22-88 were classified into 5 groups according to the final diagnoses (Histogram 1).

Histogram 1: Distribution of Patients According to Final Diagnosis.



1. **Acute MI with ST-segment elevation (n=36):** Thirty patients received thrombolytic therapy and (6) received therapy for angina. Out of those that received thrombolytic therapy, (16) had three elevated cardiac markers, (8) had two, (4) had only one, and (2) had normal cardiac markers. Five of the patients received therapy for unstable angina had normal cardiac markers and (1) had only one elevated cardiac marker (Myoglobin).

2. **Acute MI with ST-segment depression (n=13):** Four patients received thrombolytic therapy of which (3) had two elevated cardiac markers and the other had normal cardiac markers but elevated CKMB enzyme and CKMB index. Nine patients received therapy for

unstable angina in which (5) patients had two elevated cardiac markers, (2) had only one elevated cardiac marker and (2) had both normal cardiac markers and normal CKMB and CKMB index.

3. **Unstable angina (n=20):** Only (1) patient was given thrombolytic therapy and he had three elevated cardiac markers in addition to CKMB enzyme. Nineteen patients were given therapy for angina. Out of (19), only one had three elevated cardiac markers, (5) had two, (1) had only one elevated cardiac marker. The remaining (12) patients in this group had normal cardiac marker levels.

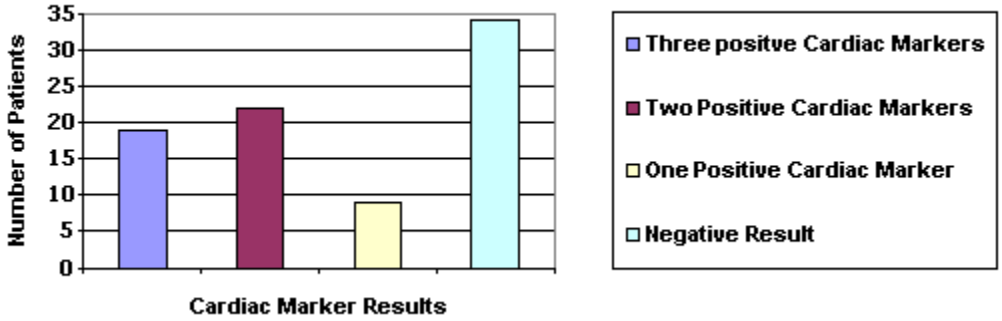
4. **Ischemic Heart Disease (n=7):** Only (1) patient with elevated levels of all three cardiac markers received thrombolytic therapy. Five patients received therapy for angina, (4) of them had normal cardiac markers and (1) had elevated levels of one cardiac marker. Only (1) patient in this population had normal levels of all three cardiac markers, but also had elevated CKMB enzyme and received neither thrombolytic therapy nor therapy for angina.

5. **Other Diagnosis (n=8):** Only (1) patient in this group had elevated levels of two cardiac markers, (3) patients had normal cardiac markers but elevated CK and CKMB and (4) had normal cardiac markers, CKMB and CKMB index. No thrombolytic therapy was given to any patient in this group. Four patients received therapy for angina and (4) received neither thrombolytic therapy nor therapy for angina.

All patients were admitted to the hospital, no case of death was registered with any patient in this study.

Cardiac Markers and Clinical Diagnoses Of the (84) patients documented in this study, (19) had positive results for elevated levels of all three cardiac markers, (22) showed positive results for two of the three cardiac markers, (9) had showed positive results for at least one of the three cardiac markers. Thirty-four patients had negative result for all three markers examined in this study (Histogram 2).

Histogram 2: Distribution of Patients According to Number of Positive & Negative Cardiac Marker Results.



CPK-MB and clinical diagnosis:

On admission, (48) patients had elevated levels of CKMB enzyme. Twenty-seven of them received thrombolytic therapy, (20) received therapy for angina, and (1) did not receive either thrombolytic or anti-anginal therapy (false positive). Troponin I was positive in (29)

patients of these patients, Myoglobin in (19), and CK Mass in (35). One cardiac marker was positive in (3) patients; two cardiac markers were positive in (15); three cardiac markers were positive in (17). Exactly (13) patients had negative cardiac markers.

False positives: There were no false positives.

False negatives: Twenty-nine patients had normal Cardiac Marker; these were considered to be false negatives. Ten of them were diagnosed as Myocardial Infarctions, (12) as unstable angina, (4) as Ischemic Heart Diseases, and (3) were given other diagnosis.

EKG and Cardiac Markers

Normal EKGs were present in (9) patients. At least one positive cardiac marker test was present in (4) patients and negative in (5) patients. One myocardial infarction was included in this group.

Non-diagnostic EKGs (paced or bundle branch block) were present in (6) patients. Two of these patients had positive cardiac marker tests. No myocardial infarctions were in this group.

Cardiac Markers and events during follow-up

There were no deaths from cardiac causes during the follow-up period. Myocardial infarction after admission did not occur in any of the patients. Cardiac markers provided additional prognostic information, after EKG status and CPK-MB were taken into account.

DISCUSSION

The majority of the cases examined in this study were young Asian and middle age males (22-45 years) with a history of hypertension and heavy smoking. Further, the patients were found to be suffering from tension, long working hours (12 hours), and low salary. These factors could be major contributory factors to an acute ischemic stroke.

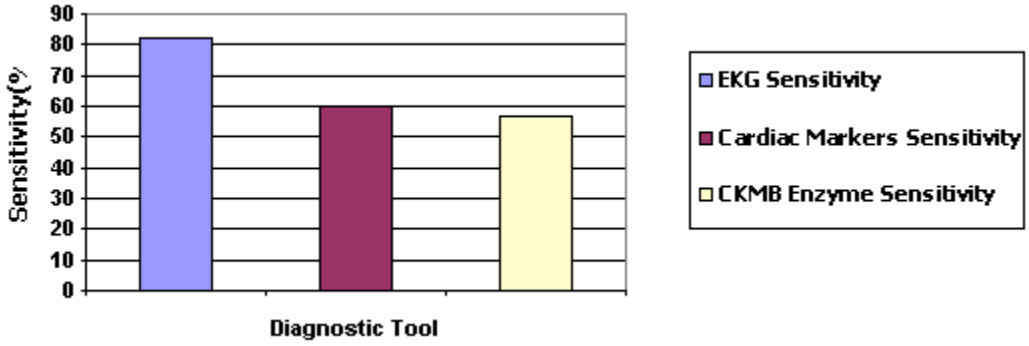
Cardiac marker panels confirm the diagnosis in 60% of the cases (50 patients with highly positive results), excluded it in 6% (5 patients with negative results), and failed either to confirm or to exclude it in 34% (29 patients with negative results). Out of the 29 patients with negative results, three patients received thrombolytic therapy and 26 received therapies for angina. The cumulative diagnostic value of cardiac markers was found to be about 65%. This ratio could be increased if more than one cardiac marker was requested and properly selected according to reliable chest pain onset. It was noted that patients with at least one positive result were admitted and evaluated further, and that a single test on admission is not sufficient. At least two cardiac markers should be selected and requested.

A negative Troponin I assay does not exclude the diagnosis of unstable angina and does not exclude myocardial infarction of less than 7 hours duration. As with CK-MB, this assay should not be used to determine whether or not to admit or discharge a patient presenting to the emergency department with chest pain. Myoglobin, the oxygen-binding protein found in both cardiac and skeletal muscles, is released from cardiac muscle soon after an infarction, and the level rises and falls within 6 hours. Although Myoglobin would appear to be ideal for

early detection and treatment of myocardial infarction, its performance is not consistent. Troponin levels greater than 2.0 ng/mL indicate a person has had a significant myocardial injury, such as an infarction, and is at an increased risk for future serious heart events. Levels between 0.5 & 2.0 ng/mL indicate a diagnosis of unstable angina, other cardiac disorders, or chronic kidney failure (Nordenson 2001).

Diagnosis, risk assessment, and the decision as to whether inpatient or outpatient management is indicated, should be based on the history, physician examination, and EKG. Two negative test results on admission and again at four hours later (or at least six hours from the onset of chest pain) allow safe and early discharge. However, the diagnostic sensitivity of EKG in chest pain is 61% (Jones 2000), but in our study it was found to be 82% (Histogram 3), and this high ratio could be contributed to the consistent and experienced staff interpretation of EKG.

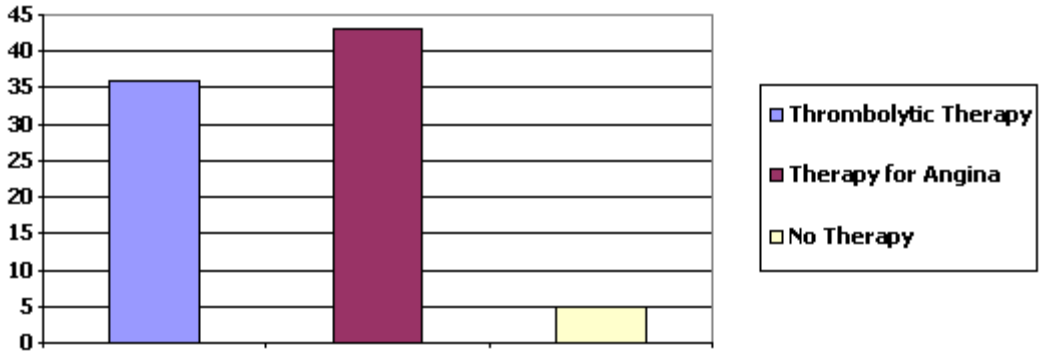
Histogram 3: Relative Sensitivity of EKG, Cardiac Markers, and CKMB Enzyme.



However, out of the 18% of the patients who were not diagnosed by EKG, cardiac markers successfully diagnosed an additional 7%. If this percentage is added to the sensitivity of EKG in our study, it presents a 89% diagnosis rate. It is highly recommended that cardiac markers be analyzed along with EKG to assist in the confirmation of a cardiac event and to increase the sensitivity in diagnosing cardiac events.

Out of the 84 patients involved in the study, 36 patients received immediate thrombolytic therapy, 43 patients received therapy for angina, and 5 patients did not receive either thrombolytic therapy or therapy for angina (Histogram 4). Those who didn't receive therapy had normal cardiac markers and EKGs and they were safely discharged. In the patients who received thrombolytic therapy, cardiac markers were highly elevated in 33 of them, while in the remaining three patients, cardiac markers were normal (false negatives). Patients with a positive Troponin I evaluation were sent directly to the cardiac catheterization laboratory for primary reperfusion therapy, unless contraindicated, and patients with a negative assay results were treated with medical therapy for unstable angina. A negative Troponin I assay obtained on arrival to the Emergency Department does not exclude the diagnosis of unstable angina or imply that the patient is at low risk (Fonarow 1996).

Histogram 4: Distribution of Patients According to Therapy.



Out of the 43 patients who received therapy for angina, elevated concentrations of cardiac markers were noticed in only 17 of them. False negative results could result from the improper selection of cardiac markers, unreliable history, non-diagnostic EKG, or the necrosis could be non-significant yet give rise to the requested cardiac marker (negative CKMB-mass and/or Myoglobin) levels, or there could be no necrosis at all (negative Troponin I).

Not all of the patients diagnosed as MI with ST segment elevation (n=36) or with ST segment depression (n=13) received thrombolytic therapy. Six of the former and 9 of the later received therapy for angina. Similarly, not all of the patients diagnosed as an unstable angina (n=20) received therapy for angina (one received thrombolytic therapy). This is because of the specific criteria needed to initiate thrombolytic therapy (e.g., a typical chest pain over 15 minutes and less than six hours not responsive to nitroglycerin, typical EKG changes with ST segment elevation in two or more contiguous leads of over 1mm in limb leads or 2mm in chest leads, absence of major contraindications, and expected benefit greater than risk if relative contraindication are present) (Argyle 1996).

The diagnostic sensitivity of CKMB enzyme was evaluated at 57%, which is approximately equal to the sensitivity of cardiac markers (60%). According to this finding, we support the suggestion that cardiac Troponin I should replace CKMB for the diagnosis of acute myocardial infarction (Bhagat et al, 1997) as correct, however, Troponin assay appears to be a more sensitive indicator of myocardial cell injury than CK-MB (Fonarow 1996). In spite of the fact that there was no false positive results, about 34% of the patients had false negative results. These misleading results were considered to be very high and could significantly increase the risk of morbidity and mortality. In our study no deaths from cardiac causes were recorded during the follow-up period.

Rapid and accurate diagnosis is key to cost avoidance, because so many of the patients admitted to critical care units (CCUs) are later determined to be experiencing nothing more serious than heartburn or a non-cardiac event (Freiherr, 1998). Money and resources are saved by avoiding unnecessary hospital admissions. According to Dr. Maisel, "Use of the algorithm with the Triage Cardiac System resulted in a 40% decrease in Cardiac Care Unit bed utilization compared to baseline. Of patients with normal EKG's and negative markers at 90 minutes, 90% were discharged, with no adverse clinical outcomes." Studies show as many as 10% of chest pain patients are sent home misdiagnosed. Rapid diagnosis reduces cost associated with unnecessary hospital admissions including the $6 billion the American College of Cardiology estimates is spent annually ruling out heart attack occurrences in the

U.S. alone. In addition to the human cost, these undiagnosed heart attacks account for approximately 20% of U.S. medical malpractice awards.

In our study we reduced the unnecessary bed occupancy and the cost of medical care by 6% of the patients who were safely discharged after negative cardiac markers and EKG results. Further, the length of stay for hospitalized patients was reduced by approximately 1/3, and this consequently will save a corresponding percentage of the total medical cost for those patients.

CONCLUSION AND RECOMMENDATIONS

This study has shown that a raised serum concentration of cardiac markers is a major predictor of prognosis after an acute ischemic stroke. The availability of rapid measurements of serum cardiac markers that rise into the abnormal range in less than 6 hours (e.g., Myoglobin, CK-MB Mass, cardiac specific Troponin T and I) now enable clinicians to diagnose or exclude MI in uncertain cases within 8 to 12 hours from onset of chest discomfort. CK-MB is an effective marker for re-infarction, because it returns to normal levels within 48 hours after the initial episode. Myoglobin is less specific and sensitive, and its pattern of response to infarction is widely variable. Because Troponin levels remain elevated long after onset of chest pain, they are good markers for late-stage infarction but they still fail in one important aspect: the ability to detect re-infarction. Therefore, use of at least two markers has a better chance of meeting all requirements of an ideal cardiac marker assay. An EKG still remains the most specific diagnostic tool in evaluating the Emergency Department patient with chest pain, however, the initial EKG may be negative/non-diagnostic in > 40% of AMI cases (in our study it was reduced to 18%). The perfect cardiac marker test, with a 100% early sensitivity + 100% specificity in diagnosing an AMI, does not exist. Therefore, use of multiple markers as a cardiac panel has a better chance of meeting all requirements of an ideal cardiac marker assay. A panel consisting of CK-MB and Troponin assays is recommended. Implementation of cardiac markers in any hospital setup as a good diagnostic tool for the diagnosis of patients with chest pain will save the expenses of unnecessary admission and discharge (hospitalization), length of hospital stay, and the intensity of clinical care provided.

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APPENDIX

Proposed Cardiac Markers Data Sheet

Name of the patient _____ Age_____ Sex _____ Nationality_____

ER Number_____ Diagnosis_____ Reporting Time to ER_____

Time of Onset of Pain_____ Time of Sample Collection_____

Test Results Available Tests Required

CK_____, CKMB_____ __- Myoglobin

LDH_____, Urea_____ __- CKMB Mass

CHOL_____, TRIG_____ __- Troponin I

EKG Findings:

_____

Date and Time of Admission:

_____

Treatment Given: (From the Fist Day Until Discharge)

_____

_____

_____

_____

_____

_____

_____

_____

Any change in treatment protocol:

_____

Any re-infarction, if/when happened:

_____

Levels of improvement:

_____

Final outcome:

_____

Cause of Death if any:

_____

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