REX HEALTHCARE

Laboratory Bulletin...

Updates and Information from Rex Healthcare and Rex Outreach

March 2000 *Issue Number 46*

Cardiac Enzymology Update

The following article is an abridged version of a prospective single blinded study of cardiac markers at Rex Healthcare. After reviewing the results of this study with the Cardiovascular Service Line team, new assays for CK-MB, myoglobin and troponin I will be available beginning March 8, 2000 at Rex Hospital. The reference range for CK-MB will be modified as a result of the new assay. Copies of the complete study are available upon request from Dr. Benson (784-3059).

Summary

Assays for creatine kinase (CK), creatine kinase MB isoenzyme (CK-MB), troponin I and myoglobin were applied to a series of patients seen at Rex Healthcare with symptoms suggestive of cardiac disease. The purposes of the study were to validate a new CK-MB method and investigate the usefulness of troponin and myoglobin in the evaluation of cardiac disease. (An earlier study performed in July 1998 evaluated a *different* troponin method and determined that it was neither as sensitive nor specific as CK-MB. In collaboration with the Rex Cardiovascular Service Line team, it was decided that troponin would not be offered at Rex because of the cost of false positive results due to poor positive predictive value (76%) and the test added little to the CK-MB assay.) In the current study, a total of 150 specimens from 85 patients were analyzed. The medical records of all patients were reviewed to determine the presence or absence of cardiac disease, and determine whether myocardial injury occurred. The following conclusions are offered:

1. The Dade ("new") CK-MB assay is an acceptable alternative to the Beckman ("old") CK-MB assay. (Less sensitivity, but greater specificity and positive predictive value). Replacing the Beckman assay with the Dade assay will improve laboratory workflow (by consolidating CK and CK-MB on a single instrument) and should significantly reduce the turnaround time for CK-MB results.
2. The Dade ("new") troponin assay is superior to the previously studied Beckman troponin assay. (Improved sensitivity, specificity and positive predictive value).
3. Both the Dade CK-MB and Dade troponin assays are excellent markers of cardiac injury. The troponin assay is more sensitive (100% vs. 88.1%) than the CK-MB, but less specific (90.0% vs. 100%). The troponin assay has a superior negative predictive value (100% vs. 95.6%) to the CK-MB, but an inferior positive predictive value (83.9% vs. 100%). There were no patients, whose management would have been altered by knowledge of the troponin results, although 2 patients may have had marginal benefit. Some of the "false negative" CK-MB results were an artifact of sampling after the enzyme levels had already peaked. Some were due to presumed very small infarct size ("microinfarcts").
4. Troponin remains elevated longer than CK-MB (5 – 9 days vs. 1 – 2 days). This effect was documented in the study. While it would not have affected any patients in the current study, this may be of benefit in evaluating chest pain patients who delay seeking medical attention.
5. Troponin may be of benefit in identifying patients with a normal CK-MB who are at increased risk of cardiac morbidity or mortality.
6. An elevated myoglobin is not particularly helpful in the evaluation of patients with chest pain as it is nonspecific. On the other hand, the **high negative predictive value of a "normal" myoglobin (96.3%)** should be helpful in the acute management of chest pain patients in the Emergency Department (ED)
7. The combined high negative predictive values of myoglobin and troponin (96.3% and 100%) should be very helpful in discharging noncardiac chest pain patients from the ED if both are negative 8 – 12 hours after onset of chest pain. In this study population, this data **might** have been used to eliminate 3 negative cardiac catheterizations, 5 of 6 negative "stress myoscans" and 3 of 4 negative treadmill/"stress ECHOs".

8. For optimal performance, it is strongly recommended that serial testing (e.g. q 3 – 4 hours sampling) be used to evaluate the possibility of acute myocardial infarct, rather than relying on a single set of values.

Study Design

Selected blood samples sent to the Laboratory from December 20 – 28, 1999, for CK & CK-MB analysis were also analyzed by a "new" CK-MB assay, troponin I and myoglobin. The physicians caring for the patients were blinded to these study results. The CK, "new" CK-MB, troponin I and myoglobin assays were performed on the Dade RXL Dimension analyzer. The "old" (reported) CK-MB assay was performed on the Beckman Access analyzer. The CK-MB index is a mathematically derived value ([CK-MB/CK] x 100) designed to help distinguish cardiac sources of CK-MB from a skeletal muscle source. Reference ranges were as follows:

- CK (Dade) 30 – 120 IU/L
- CK-MB (Dade) ≤ 5.0 ng/mL
- CK-MB index (Dade) ≤ 3.5 (modified from manufacturer's recommendation of ≤ 4.0)
- CK-MB (Beckman) ≤ 9.5 ng/mL
- CK-MB index (Beckman) ≤ 4.0
- Troponin (Dade) ≤ 0.4 ng/mL
  (0.4 – 1.5 suggests "cardiac injury")
  (> 1.5 suggests myocardial infarct)
- Myoglobin (Dade) 16.3 – 96.5 ng/mL (Male)
  9.0 – 82.5 ng/mL (Female)

Lab results were considered "positive" if they exceeded the reference range and "negative" if they remained in the reference range. For CK-MB, greater emphasis was placed on the CK-MB index ("%CK-MB") rather than the absolute value of CK-MB. All medical records were reviewed. If it was determined that a "negative" result was due to a collection time that occurred well after the time peak for that particular enzyme in a case of acute myocardial infarct, that result was treated as a "true negative". (In most instances, this affected either myoglobin or CK-MB results on specimens collected at the end of a "CK series".) In a couple of instances, the Beckman ("old") CK-MB assay still yielded a (+) result while the Dade ("new") CK-MB had passed below the threshold for infarct. In these instances, the Beckman result was regarded as a "true positive" while the Dade result was regarded as a "false negative". This resulted in the different sensitivities of the 2 assays.

In reviewing the medical records, the presence or absence of myocardial infarct was determined by the clinical record, all available cardiac enzyme data, and EKG findings. In the overwhelming majority of cases, the data was concordant. Where the enzyme data was discordant, one author (JDB) synthesized the above data to the best of his ability to determine the presence or absence of an infarct. These cases are detailed in an appendix in the original report presented to the Cardiovascular Service Line Team.

Results (See Table on following page)

Patients: 85 (1 excluded because she left against medical advice before workup completed)
No. w/ acute myocardial infarct: 21 (25%)
No. w/ "unstable angina": 4 (4.8%)
No. w/ congestive heart failure: 5 (5.9%)
No. w/ noncardiac chest pain: 23 (27%)
Other 31 (37%)
No. of Samples: 150

Correlation with "Negative" Ancillary Studies

- 3 patients had negative cardiac catheterizations. None had elevated CK-MB, troponin or myoglobin.
- 4 patients had negative treadmill/"stress ECHO". One had "false positive" elevation of

myoglobin and troponin (with "true negative" CK-MB). 3 had no elevations in CK-MB, troponin or myoglobin.

- 6 patients had negative "stress myoscans". One had a mildly "false positive" myoglobin (86 in a woman). All other enzyme studies were negative.
- There were no "positive" treadmills, "stress ECHOs" or "stress myoscans" in the study population.

Cardiac Enzyme Comparative Statistics

Enzyme	CK	"Old" CK-MB (Beckman)	"New" CK-MB (Dade)	Troponin	Myoglobin
TN	30	102	110	81	53
TP	52	42	37	47	32
FN	2	1	5	0	2
FP	71	4	0	9	36
Sensitivity	96.2	97.6	88.1	100	94.1
Specificity	30.0	96.2	100	90.0	59.6
PPV	42.6	91.3	100	83.9	47.0
NPV	N/A	N/A	95.6	100	96.3

TN True Negative TP True Positive FN False Negative FP False Positive
PPV Positive Predictive Value NPV Negative Predictive Value N/A Not Applicable

Discussion

While CK-MB has been the "gold standard" of cardiac enzymology for over 20 years, there has been increasing interest in newer markers of cardiac injury. This interest stems from a need for more rapid diagnosis of myocardial injury and interest in using markers to stratify cardiac risk in non-infarct patients. Myoglobin is released within 1-3 hours of acute myocardial infarct and peaks in 6 – 9 hours. As it is abundant in skeletal muscle, an elevated myoglobin is not a reliable indicator of myocardial injury (59.6% specificity). However, a negative myoglobin (particularly if there is no significant change on serial measurement) is very helpful in excluding the possibility of **recent** (1 – 6 hours) acute myocardial infarct (96.3% negative predictive value). CK-MM and CK-MB **isoforms** have also attracted attention as early markers of cardiac injury. They are detectable within 2-4 hours of injury and remain elevated for 16 – 24 hours. They are more specific for cardiac injury than myoglobin. The only current method for measuring isoforms requires electrophoresis. This methodology is cumbersome and more expensive than the rapid immunoassays used for other cardiac enzyme measurements. As a result, this assay does not enjoy widespread use.

Both CK-MB and troponin I are released within 4 – 6 hours of cardiac injury and peak between 8 – 12 hours. Thus, **troponin does not offer any advantage in the speed of detecting myocardial infarct.** However, it remains elevated for 5 – 9 days, while CK-MB generally remains elevated for 1 – 2 days. Thus troponin is more useful in identifying acute myocardial infarcts in patients who present after several days of chest pain. There has been a great deal of literature touting the improved cardiac specificity troponin has over CK-MB. We have been unable to confirm this in 2 studies of chest pain patients at Rex. (The alleged superior cardiac specificity of troponin has been cited in recommending its use to monitor perioperative cardiac ischemic injury in both cardiac and noncardiac surgical patients. There were no such patients in this study.) This study did demonstrate that troponin had slightly greater sensitivity than CK-MB, in that it did provide objective evidence of ischemic heart injury in 1 patient who had normal CK-MB. This patient received invasive cardiac intervention, so it is not clear that knowledge of the troponin result would have affected management.

There has been a great deal of interest in using troponin to stratify risk in patients with noninfarct ischemic heart disease. Patients who have an elevated troponin, but a normal CK-MB, are believed to be at greater risk of short-term (1 - 3 months) morbidity and mortality. (One concept is that the troponin elevation is caused by "microinfarcts" below the threshold of detection by conventional CK-MB measurement.) It has been suggested that patients with this profile might benefit from more aggressive management. (A considerable amount of literature has been devoted to whether troponin I or troponin T is a superior marker in this regard. While each enzyme has passionate advocates, the consensus appears to be that either enzyme might be used in this manner. Currently there is only one

troponin T assay licensed for use. There are several different troponin I assays. Different performance characteristics of the assays and lack of standardization have contributed to the confusion in the literature.) The design of this study does not allow meaningful comment on the usefulness of the Dade troponin I assay for this purpose. The antibody used is identical to that used in many of the published studies which have supported the role of troponin I for cardiac risk stratification. Of the 4 patients in the study with "false (+)" troponin values, none have been readmitted to Rex. Only 1 patient had scheduled follow-up (2 were to be placed in nursing homes). The "false (+)" patient who is being actively followed has suffered no cardiac consequences to date. It is of interest, that two of these patients have chronic renal failure, even though troponin I is theoretically supposed to be free of skeletal muscle interference in renal patients.

In summary, it appears that neither myoglobin nor troponin will significantly improve the ability to diagnose acute myocardial infarct. However, both may be of value in allowing earlier discharge of noncardiac chest pain patients from the Emergency Department (and limiting the need for ancillary testing). If used in this manner, the **cost** of the assays should be more than compensated for by earlier discharge and decreased ancillary testing. Furthermore, troponin **may** be helpful in identifying patients who, while they have not suffered an acute myocardial infarct, are at increased risk for future short-term morbidity or mortality from an acute coronary syndrome. Clinical experience (or additional studies) will be needed to determine whether this is true.

Acknowledgments: ***The authors are indebted to the Core Laboratory staff for performing the analyses.***

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