Troponin Should Replace CK-MB as a Marker of AMI

Michael A. Pesce, Ph.D.

Professor Emeritus of Clinical Pathology
And Cell Biology
Columbia University Medical Center
Department of Pathology
Learning Objectives

• Why Troponin is the gold standard for the detection of AMI

• How Troponin is used to detect AMI

• Why CK-MB is still used in many Hospital Laboratories as a marker of AMI

• What are the advantages of eliminating CK-MB testing for AMI
Annual ED Visits in the United States

100 Million ED Visits

6 Million - Chest Pain

3 Million Discharged

Missed AMI
30,000

3 Million High Risk

1 Million Other Diagnosis

1 Million AMI

1 Million Unstable Angina
Diagnostic Challenges

AMI patients may present to the ED with non-diagnostic ECG ~ 50% of the time.

Chest pain may be a dull pain, burning sensation or a sharp stabbing pain.

~35% of patients do not have chest pain.

50% have no history of MI or angina.
Ideal Cardiac Marker for Myocardial Injury

- Found in high concentrations in myocardium
- Organ Specific – detected only in heart muscle
- Released rapidly after the onset of pain
- Concentration is proportional to the extent of damage
- Remains elevated for several days
- Easy to measure
- Rapid turnaround time
- Cost effective
Cardiac Biomarkers

- CK-MB
- Troponin I and T
- Myoglobin
- BNP
- NT ProBNP
- Ischemia Modified Albumin
CKMB Biochemistry

Role:
Creatine + ATP $\rightarrow$ ADP + Phosphocreatine + Energy
(muscular contraction)

CK: Dimer composed of 2 monomers: M (43,000 Da) and
B (44,500 Da) $\rightarrow$ CK BB or CK MB or CK MM

CK BB = CK1 Increased in neurological diseases;
prostatectomy; digestive cancers

CK MB = CK2 Increased with AMI

CK MM = CK3 Increased in myopathy, hypothyroidy, polymyositis,
rhabdomyolysis, traumatism, intensive exercise, AMI
# Tissue Distribution Of CK & CK Isoenzymes

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Range of Total CK (U/gm tissue)</th>
<th>Range of CK Isoenzymes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal Muscle</td>
<td>1080-3050</td>
<td>96-100 0-4 0</td>
</tr>
<tr>
<td>Heart Muscle</td>
<td>190-692</td>
<td>58-86 15-42 0-1</td>
</tr>
<tr>
<td>Brain</td>
<td>73-200</td>
<td>0 0 100</td>
</tr>
<tr>
<td>Bladder</td>
<td>162</td>
<td>0-2 0-6 92-100</td>
</tr>
<tr>
<td>Placenta</td>
<td>250</td>
<td>19 1 80</td>
</tr>
<tr>
<td>Colon</td>
<td>200</td>
<td>0-5 0-4 95-100</td>
</tr>
<tr>
<td>Ileum</td>
<td>175</td>
<td>0.3 0-4 93-100</td>
</tr>
<tr>
<td>Stomach</td>
<td>170</td>
<td>0-5 4 96</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>140</td>
<td>74 4 22</td>
</tr>
</tbody>
</table>
CKMB Kinetics

AFTER AMI

Increase  3-6 Hours
Peak    10-24 Hours
Return to Normal 48-72 Hours

Draw blood on admission, 4, 8, and 24 hr.
CKMB IN AMI

Advantages:

• Detects AMI 3-6 Hours After Chest Pain
• Methodology is Rapid and Automated
• Turnaround Time <60 Minutes
• CKMB was the gold standard for AMI detection in the 1980’s
Limitations of CKMB in AMI

Elevated CKMB Levels can be observed in:

- Skeletal Muscle Involvement
- Duchenne Muscular Dystrophy
- Polymyositis
- Alcohol Myopathy
- Thermal or Electrical Burn Patients
- Carcinomas
- Colon, Lung, Prostate, Endometrial
CK –MB Index

The CK-MB index was established to distinguish between cardiac and skeletal muscle damage. The CKMB index is calculated:

\[
\text{CKMB index} = \frac{\text{CKMB} \times 100}{\text{Total CK}}
\]

A positive result is > 4%.

The reason for using this index is that patients with an AMI will release more CKMB than patients with skeletal muscle damage. For example a patient with muscle wasting with a total CK of 10,000U/l with an elevated CKMB of 100 will have a CKMB index of 1.0% which suggests no cardiac involvement.
Troponin Characteristics

- **Troponin C (18 kd)**
  - Calcium-binding subunit
- **Troponin I (26.5 kd)**
  - Actomyosin-ATP-inhibiting subunit
- **Troponin T (39 kd)**
  - Tropomyosin-binding subunit

The troponin complex consists of three different proteins (TnC, TnI, and TnT) that regulate the calcium-mediated contractile process of striated muscle.
Tissue Specificity of Troponin I and T

- Troponin C is the same in all muscle tissue
- Troponin I and Troponin T are detected in heart muscle and are cardiac specific
- Circulating concentrations of cTnI and cTnT are very low
- Early release due to cytosolic pool
- Prolonged release due to degradation of muscle fibers
- cTnI and cTnT remain elevated for several days
- The false-positive CKMB results that are due to skeletal muscle involvement should be eliminated with use of the Troponin assays.
Release of troponin after injury

- cTnT-I-C complex
- Myocyte Extracellular space
• Troponin Release From Damaged Myocytes

• irreversible membrane damage

• free
troponin (2-6%)

• bound troponin complex

• cytoplasmic origin

• structural origin

• Cytoplasm Blood

• Days After Onset of AMI
## Troponin I and T Kinetics

### Cardiac Specific Marker

<table>
<thead>
<tr>
<th>Post AMI</th>
<th>Troponin I</th>
<th>Troponin T</th>
<th>CKMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>Hrs</td>
<td>4-6</td>
<td>3-6</td>
</tr>
<tr>
<td>Peak</td>
<td>Hrs</td>
<td>14-24</td>
<td>10-24</td>
</tr>
<tr>
<td>Return to Normal</td>
<td>Days</td>
<td>5-7</td>
<td>6-10</td>
</tr>
</tbody>
</table>
Time-course of Cardiac Biomarkers

Note: The time scale above (x-axis) is not linear.
Specificity of cTnl, CK-MB Mass & Myoglobin In Noninfarct Patients with Chronic Renal Failure or Severe Polytrauma

<table>
<thead>
<tr>
<th>Pathology &amp; Markers</th>
<th>No. (%) of Positive Sera</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Polytrauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB mass</td>
<td>14 (58)</td>
<td>42</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>21 (88)</td>
<td>12</td>
</tr>
<tr>
<td>cTnl</td>
<td>0 (0)</td>
<td>100</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB mass</td>
<td>4 (8)</td>
<td>92</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>43 (88)</td>
<td>12</td>
</tr>
<tr>
<td>cTnl</td>
<td>0 (0)</td>
<td>100</td>
</tr>
<tr>
<td>Time Period</td>
<td>Sensitivity % Troponin I</td>
<td>Sensitivity % Troponin T</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Admission</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>1 hr</td>
<td>45</td>
<td>58</td>
</tr>
<tr>
<td>3 hr</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>6 hr</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>12-24 hr</td>
<td>96</td>
<td>99</td>
</tr>
</tbody>
</table>
Importance of Serial Sampling in the Detection of AMI

- Allows for differentiation of acute versus chronic troponin elevation
- No agreement on what the frequency of troponin testing should be
- AHA Guidelines 0, 6, 12 hours.
- Universal Definition of MI 0, 3, 6 hours,
- European Society of Cardiology 0, 6, 9 hours.

JACC vol 61 No.22 2013
European Heart Journal June 2010.
Third Universal Definition of Myocardial Infarction

To diagnose Type 1 or Type 2 MI, a blood sample must detect a rise or fall Troponin I or T, with at least one value above the 99th percentile with at least one of the following:

Symptoms of ischemia
New ST-segment or T-wave changes or new left bundle branch block
Development of pathologic Q waves
Imaging evidence of new loss of viable myocardium or new wall-motion abnormality
Finding of an intracoronary thrombus by angiography or autopsy.
Case Study 1

62 y.o. man presents to the Emergency Department with crushing chest pain of 2 hours duration. EKG shows S-T elevation and a new Q wave.

<table>
<thead>
<tr>
<th>Time</th>
<th>Total CK (40-250 U/L)</th>
<th>CK-MB (&lt; 3.0 ng/mL)</th>
<th>CK-MB Index (&lt; 4.0%)</th>
<th>Troponin (&lt; 0.04 ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Admission</td>
<td>120</td>
<td>2.1</td>
<td>1.8</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>6 hrs Later</td>
<td>380</td>
<td>19.6</td>
<td>5.2</td>
<td>2.0</td>
</tr>
<tr>
<td>12 hrs Later</td>
<td>550</td>
<td>42.2</td>
<td>7.7</td>
<td>10.0</td>
</tr>
<tr>
<td>24 hrs Later</td>
<td>250</td>
<td>10.5</td>
<td>4.1</td>
<td>20.0</td>
</tr>
</tbody>
</table>

**INTERPRETATION**

This man had an acute myocardial infarct.
Case Study 2

62 y.o. man presents to the Emergency Department following a car accident. The patient "blackout" while driving and now has chest pain as well as chest wall tenderness. EKG is not diagnostic. He was brought to the ED 1h after the accident.

<table>
<thead>
<tr>
<th>Time</th>
<th>Total CK (40-250 U/L)</th>
<th>CK-MB (&lt; 3.0 ng/mL)</th>
<th>CK-MB Index (&lt; 4.0%)</th>
<th>Troponin (&lt; 0.04ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>1,000</td>
<td>50</td>
<td>5.0</td>
<td>0.02</td>
</tr>
<tr>
<td>2 hrs</td>
<td>1,500</td>
<td>70</td>
<td>4.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

How would interpret these results?
Interpreting Troponin Results

Troponin results greater than the Upper Limit of Normal (ULN) indicates cardiac damage

• ULN is defined as the 99th percentile of a “normal” population but...

• …use the Troponin concentration where your lab’s assay can reproducibly measure levels with total imprecision of 10% CV
Increased cTnl values represent a risk, to be detected early and reliably!

- Precision profile of a cTnl assay (note: MI patients often reach value > 10 ng/ml)
- 99th percentile
- Increasing risk
- CV 10%
- Very good precision
- Not as precise - Observe the patient and retest at a later time point.
Earlier Detection of Myocardial Necrosis

- cTnI assay with better low-end imprecision
- Myocardial necrosis can be ascertained sooner in some ED patients with a high degree of precision
- 99th percentile
- Increasing risk
- CV 10%
- Very good precision

TnI (ng/ml) vs. % CV
## Troponin Methods: *Upper Limit of Normal*

<table>
<thead>
<tr>
<th>Platform</th>
<th>99th percentile</th>
<th>10% Total CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centaur</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Beckman Access 2</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>BioMerieux Vidas</td>
<td>0.10</td>
<td>0.36</td>
</tr>
<tr>
<td>DiaSorin Liaison</td>
<td>0.03</td>
<td>0.065</td>
</tr>
<tr>
<td>RxL</td>
<td>0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>Stratus CS</td>
<td>0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>IMMULITE</td>
<td>0.20</td>
<td>0.32</td>
</tr>
<tr>
<td>OCD Vitros ECi</td>
<td>0.10</td>
<td>0.44</td>
</tr>
<tr>
<td>Tosoh AIA-21</td>
<td>0.06</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Troponin T
Detection Range of Different cTn Assays

[Graph showing detection range of different cardiac troponin (cTn) assays, with normal levels, onset of myocardial infarction, ischemia or micronecrosis, and necrosis.]
• Next generation troponin assays
Comparison of Two Troponin I assays

<table>
<thead>
<tr>
<th></th>
<th>TNI Cutoff, ug/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Siemens Ultra</td>
</tr>
<tr>
<td>Baseline Sample</td>
<td>&gt;0.04</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74 (59-85)</td>
</tr>
<tr>
<td>Specificity</td>
<td>84 (79-87)</td>
</tr>
<tr>
<td>Follow up Sample</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94 (83-99)</td>
</tr>
<tr>
<td>Specificity</td>
<td>81 (77-86)</td>
</tr>
</tbody>
</table>

Tn cutoffs > 99% of reference control group and 10% CV at that level
hsTnI in ED patients with chest pain

Non-diagnostic

Ischemia?
Issues to be Decided Before Using High Sensitivity Troponin Assays

Report cutoff values for AMI using the 99 percentile, not the value at 10% CV.

May be able to diagnose AMI using a single cutoff at presentation.

Perform serial testing at presentation and at 1-3 hrs.

Use delta changes either absolute or relative to rule out or diagnose AMI.

Input by Cardiologists, Internists, ED, Pathologists and Laboratory Scientists.
## CAP Proficiency Testing for Troponin and CK-MB

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Labs</th>
<th>Number of Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Troponin</td>
<td>CK-MB</td>
</tr>
<tr>
<td>2012</td>
<td>1549</td>
<td>1376</td>
</tr>
<tr>
<td>2013</td>
<td>1451</td>
<td>1277</td>
</tr>
<tr>
<td>2014</td>
<td>1765</td>
<td>1459</td>
</tr>
</tbody>
</table>
New York State Department of Health Proficiency Testing

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Labs</th>
<th>Number of Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Troponin</td>
<td>CK-MB</td>
</tr>
<tr>
<td>2012</td>
<td>260</td>
<td>201</td>
</tr>
<tr>
<td>2013</td>
<td>259</td>
<td>203</td>
</tr>
<tr>
<td>2014</td>
<td>268</td>
<td>193</td>
</tr>
</tbody>
</table>
Why Measure CK-MB?
Disadvantages of Using Both Troponin and CK-MB

• Confusing in the interpretation of Troponin and CK-MB results (CK-MB↑Trop N, Trop↑ CK-MB N)
• Many false positive results using CK-MB
• CK-MB is not cost effective for MI detection in the ER
• Laboratory resources are needed to measure CK-MB which reduces laboratory efficiency
Summary

• Cardiac troponin is the gold standard for detecting myocardial damage in patients with suspected ACS.

• cTn is specific for myocardial injury, but not for AMI.

• CK-MB can be elevated in many non-cardiac conditions and can cause mis-diagnosis of cardiac disease.

• Troponin should replace CK-MB for the detection of AMI.