Markers of Myocardial Injury

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Objectives

- CKMB is no longer the ideal cardiac marker
- Troponins I & T are the cardiac markers of the 21st Century
- Redefining Myocardial Infarction
- Multi-biomarker risk stratification
- Biomarkers in renal disease
Diagnosis of AMI

Based on 2 out of 3 of WHO criteria (Circulation, 1979)

- Prolonged chest pain
  - "Silent infarct", Painless infarct

- ECG changes
  - Lacks sensitivity

- Serum enzyme concentrations
  - CKMB lacks sensitivity in diagnosis of perioperative MI
  - Protein markers, e.g. troponins, myoglobin & others emerging in the 21st century
Limitation of CKMB

- FP incidents in perioperative patients without cardiac injury
- **False elevations in**
  - Skeletal muscle injury
  - Marathon runners
  - Chronic renal failure
  - Hypothyroidism
- MI detection not timely enough for thrombolytic intervention. MB peaking takes $>12\text{h}$
Need for New Cardiac Markers

- Timely diagnosis of MI for thrombolytic therapy
- Identify successful reperfusion after thrombolysis in MI
- Diagnosis of perioperative MI
Early Diagnosis of MI in ED

- Expedite triage of patients in ED
- Appropriate use of ICU beds
- Timely management of thrombolytic therapy
- Missed diagnosis of AMI by ED physicians
Cardiac Markers of the 21st Century

- MB isoenzyme
- CKMM isoforms
- CKMB isoforms
- Myoglobin
- Troponin I
- Troponin T
- Brain natriuretic peptide
- Ischemia modified albumin
- C-reactive protein
Ideal Marker to Detect AMI

- High concentration in myocardium
- Absence from non-myocardial tissues
- High sen & spec in circulation
- Rapid release into blood following myocardial injury
- Remains in blood several days to allow detection
- Blood levels correlate with extent of myocardial injury & prognosis
- Rapid, simple & automated commercial assays available
- Role designed for marker in dx & mgt based on clinical studies & peer reviewed literature
Troponins

- Regulatory proteins in striated muscle
- Responsible for calcium-modulated interaction
- Exist in a number of isoforms

- Cardiac specific forms immunologically separable
  - Troponin T (TpnT)
  - Troponin I (TpnI)
Pattern of release in MI is BIPHASIC.

Detectable in blood 4-12 h, similar to CKMB

Peaks 12-38 h

Remains elevated for 5-10 days
Cardiac Troponin I & T

- Cardiospecific. Immuno distinct from skeletal muscle isoform

- In cardiac muscles, Tn's tightly bound to contratile appartus. Serum level normally low

  “Cytosolic pool”
  - 6% tpn T and 3% tpn I

- Tn T assay available in Europe in early 90's. FDA approved first Tpn I assay in the USA in 1995.
ROC Curve for TpnT

- Plot of Sensitivity (TP) vs 1-specificity (FP)
- Used for establishing best discriminator for cTpnT for predicting AMI
- Best discriminator point is 0.2 μg/L at 9 h after onset of AMI
Sensitivity/Specificity of Tpn I assay
ROC Curve for Tpn I
Sensitivity & specificity are determined respectively at MB Index of values 0 - 10.
ROC Curve for CKMB

TP (Sensitivity)

FP (1-specificity)

MBI=0

MBI=3.5

MBI=10
ROC Curve Decision Threshold
Temporal pattern of CKMB vs Tnn I
CKMB & Tpn I profiles in AMI
Marker Responses to MI

A = myoglobin or CKMB isoforms
B = cardiac troponin
C = CKMB
D = cardiac troponin after unstable angina
Clinical Classification of ACS
Diagnosis of AMI in the Troponin Era

Based on ESC/ACC’s redefinition of MI *(JACC, 2000)*

- Typical rise and fall of Troponin or CKMB with one of the following:
  - Ischemic symptoms
  - Development of Q wave on ECG
  - ST-segment elevation/depression
  - Coronary artery intervention

- Pathologic (morphologic) findings of AMI
Defining Increased Troponin

- Tpn T and I are not detected in healthy persons
- Significant ↑Tpn reflects myocardial necrosis
- Detectable ↑Tpn but no ↑CKMB may indicate microinfarction
- ↑Tpn identifies high-risk ACS patients for aggressive anti-thrombolytic therapy

ACC/ESC defined ↑Tpn as a measurement above 99th percentile value of reference group

To reduce false-positive outcomes, CV of ≤10% at decision limit is recommended
Clinical Issues in New Guideline (Consensus document from ESC, ACC, AHA in Circulation, 2000)

- ↑cardiac troponin reflects myocardial injury but do not indicate its mechanism
  - Not synonymous with MI or ischemic mechanism of injury. Pursue other etiologies of myocardial injury
  - Likely reflects irreversible injury
  - ↑Tpn after heart surgery; can’t differentiate injury caused by MI from procedural-induced injury
TnTs can remain elevated up to 5-10 days after AMI, usefulness in monitoring reinfarction questioned. CKMB may be more useful since elevation lasts 2-4 days.

Monitoring Myocardial Reinfarction (Clin Chem, 2005)

Conclusion from comparative biomarker profiles study: TnT alone is sufficient to rule in and rule out MI and/or reinfarction in clinical practice.

Reported incidence rate of reinfarction < 20%.

Given the limited financial resources in laboratories and healthcare, clinicians should consider monitoring just cardiac troponins for the diagnosis of MI or in-hospital infarction.
Laboratory Issues in New Guideline
(Consensus document from ESC, ACC, AHA in Circulation, 2000)

- Diversity of various tpn assays lead to confusion
  - One Tpn T assay
  - Twenty-three Tpn I assays
- Standardization will help resolving concerns
- Recommended
  - Upper RI of 99\textsuperscript{th} percentile with CV≤10%
  - Manufacturers’ responsibility to meet such imprecision
  - Diagnosis & therapeutic decisions made at low cardiac tpn cut-off points
IFCC & NACB Guidelines

- **Early marker to be performed in ED**
  - ↑ within 6 h, e.g. myoglobin. Good for r/o AMI
  - Rapid triage & thrombolytic therapy if onset is within 6-12 h

- **Definitive marker**
  - ↑ 6-12 h, sensitive & specific, e.g. TpnT, TpnI

- **Decision limits**
  - A low level suggestive of myocardial damage
  - A high level suggestive of dx of AMI

- Perform both CKMB and Tpn’s for a period of time to understand the difference in Tns vs CKMB
Tpn precision at low concentrations

- **Redefinition of MI by ESC/ACC**
  - Decision limit at > 99th percentile in reference group
  - CV at this point should be <10%

- **Study commercial Tpn assays to determine**
  - Clinically relevant imprecision profile around MI decision limit
  - Lowest concentration with 10% CV
  - Correlation of low-conc with 99th percentile ref limit

- **Conclusion** *(Clin Chem, 1/2004)*
  - Currently, no commercial assays can achieve a 10% CV at 99th percentile reference limit to accurately differentiate between “minor” myocardial injury and analytical noise
Cardiac Marker Assay Standardization

- **Need to establish**
  - Develop international reference materials to decrease between assay biases
  - Objective goals for improving/updating cutoff limits based on clinical significance

- **Existing analytical imprecision standards**
  - \( CV \leq 5.6\% \) for Myoglobin
  - \( CV \leq 9.2\% \) for CKMB
  - Not yet established for cTn’s. Arbitrarily set at CV of 10\%
Standarization Issue with Tpn I assay

- 2-20 fold conc differences among Tn I assays
  - Slopes of regression compared to Stratus assay:
    - Abbot = 3.5, Behring = 1.5, Beckman = 0.1

Assay variations

- Tpn I undergoes proteolysis
- Reagent antibodies recognizing different epitopes
- Maintain own database with one selected assay. Follow comparative trend, but not absolute values
Interference in Tnp I assay

- Abbot’s “Sanwich” Immunoassays for Tn:
  - Primary or “capture” antibody from mouse
  - Secondary or “label” antibody from goat
  - Complex formed is “capture” ab-Tn-”label” ab

- “Heterophilic antibodies (HAs) in human serum
  - anti-mouse antibodies & antibodies against foreign proteins
  - Prevalence of HAs in general population up to 40%
  - Act as “antigens” binding nonspecifically to reagent antibodies, resulting in false increase of Tnl
MI Redefined: Role of Tpn Testing

- Consensus documents
  - NACB/IFCC guidelines (1999)
  - ACC/ESC/AHA guidelines (2000)

- Specimen collection
  - Admission, 4h, 8h, 12h or next morning
  - ACC/ESC recommends an early marker (myo/CK-MB isoform) in addition to a definitive marker (TpnT or Tpnl)

- Cutoff concentrations for cardiac markers
  - NACB recommends 2 decision limits for Tpn
    - Low limit for myocardial injury (97.5th percentile ref gp)
    - High limit for injury qualifies as MI (WHO criteria)
  - ACC/ESC recommends 1 cut point at 99th percentile ref gp
## Tpn Precision at low Concentrations (Clin Chem 327-332, 2004)

### Criteria

- **99th percentile reference limit** at 10% CV for the evaluated troponin I assays

### SUNY Chemistry Lab

- **Lo control** at 1.16 ug/L (CV = 17.1%)
- **Hi control** at 2.89 ug/L (CV = 9.5%)

### Table 1: Cut-off values of cardiac troponin assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>LLD</th>
<th>99th percentile</th>
<th>10% CV*</th>
<th>ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCH STAT Troponin-I, Abbott Diagnostics</td>
<td>0.009</td>
<td>0.012</td>
<td>0.032</td>
<td>0.3</td>
</tr>
<tr>
<td>AxSYM Troponin-I ADV, Abbott Diagnostics</td>
<td>0.02</td>
<td>0.04</td>
<td>0.16</td>
<td>0.4</td>
</tr>
<tr>
<td>i-STAT,† Abbott Laboratories</td>
<td>0.02</td>
<td>0.08 (WB)</td>
<td>0.1</td>
<td>ND</td>
</tr>
<tr>
<td>Centaur, Bayer Diagnostics</td>
<td>0.02</td>
<td>0.1</td>
<td>0.35</td>
<td>1.0</td>
</tr>
<tr>
<td>Access AccuTnl Troponin I, Beckman Coulter</td>
<td>0.01</td>
<td>0.04</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Triage Cardiac Panel,† Biosite</td>
<td>0.19</td>
<td>&lt; 0.19</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Dimension RxL, Dade Behring</td>
<td>0.04</td>
<td>0.07</td>
<td>0.14</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Stratus CS,† Dade Behring</td>
<td>0.03</td>
<td>0.07</td>
<td>0.06</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Immulite, Diagnostic Products Corporation</td>
<td>0.1</td>
<td>0.2</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Vitros, Ortho-Clinical Diagnostics</td>
<td>0.02</td>
<td>0.08</td>
<td>0.12</td>
<td>0.4</td>
</tr>
<tr>
<td>Response,† Ortho-Clinical Diagnostics</td>
<td>0.03</td>
<td>&lt; 0.03 (WB)</td>
<td>0.21</td>
<td>ND</td>
</tr>
<tr>
<td>Elecsys, Roche Diagnostics</td>
<td>0.01</td>
<td>&lt; 0.01</td>
<td>0.03</td>
<td>0.1</td>
</tr>
<tr>
<td>Reader,† Roche Diagnostics</td>
<td>0.05</td>
<td>&lt; 0.05 (WB)</td>
<td>ND</td>
<td>0.1</td>
</tr>
<tr>
<td>Tosoh AIA, Global Medical Instrumentation Inc.</td>
<td>0.06</td>
<td>&lt; 0.06</td>
<td>0.06</td>
<td>0.31-0.64</td>
</tr>
</tbody>
</table>

Note: LLD = lower limit of detection, CV = coefficient of variation, ROC = receiver operating characteristic, ND = not determined, WB = whole blood.

*Per manufacturer.
†Point-of-care assay FDA-cleared as high-sensitivity assay 2004 (CS).
Source: Apple et al.57
Precision of TpnT assay on Roche

10% CV at 0.03 μg/L (ng/mL)
CTnT in Kidney Failure


- cTnT in the serum of patients with kidney failure is predominantly the free intact form, as in patients with ACS.
- cTnT in renal failure reflects cardiac pathology.
Tpn & Detection of Reinfarction
LD1/LD2 vs Tpn I in AMI
Most Recent Review on Tpn

Troponin: the biomarker of choice for the detection of cardiac injury

Luciano Babuin and Allan S. Jaffe
CMAJ, November 8, 2005
Cardiac Markers used in Labs

Y2000
- CKMB, myoglobin & TnI or TnT: 29%
- CKMB & TnI or TnT: 62%
- Use markers alone or other combinations: 9%

Y2001
- CKMB, myoglobin & TnI or TnT: 27%
- CK-MB and Troponin T or I: 37%
- Troponin T or I only: 16%
- Other: 12%
- CK-MB only: 6%
- 2% Troponin T or I and Myoglobin

n=105
Tpn after Cardiac Surgery

![Bar graph showing mortality at 42 days vs. cardiac troponin I level. Mortality increases with higher cardiac troponin I levels.]
**Tpns without Ischemic Heart Disease**

<table>
<thead>
<tr>
<th>Conditions in which troponin levels may be elevated without overt ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trauma (e.g., contusion, ablation, pacing, ICD firings, cardioversion, endomyocardial biopsy, cardiac surgery)</td>
</tr>
<tr>
<td>• Congestive heart failure, acute and chronic</td>
</tr>
<tr>
<td>• Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Hypotension, often with arrhythmias</td>
</tr>
<tr>
<td>• Noncardiac surgery without complications</td>
</tr>
<tr>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Severe asthma</td>
</tr>
<tr>
<td>• Critical illness, especially diabetes, respiratory failure, hemolytic uremic syndrome</td>
</tr>
<tr>
<td>• Drug toxicity (e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms)</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td>• Coronary vasospasm, including apical ballooning syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions requiring further investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inflammatory disease (e.g., myocarditis, parvovirus B19 infection, Kawasaki disease, myocardial extension of bacterial endocarditis)</td>
</tr>
<tr>
<td>• Percutaneous coronary intervention without complications</td>
</tr>
<tr>
<td>• Pulmonary embolism, severe pulmonary hypertension</td>
</tr>
<tr>
<td>• Sepsis</td>
</tr>
<tr>
<td>• Burns, especially if total body surface area affected is &gt; 30%</td>
</tr>
<tr>
<td>• Infiltrative diseases, including amyloidosis, hemochromatosis, sarcoidosis and scleroderma</td>
</tr>
<tr>
<td>• Acute neurologic diseases, including cerebrovascular accident and subarachnoid bleed</td>
</tr>
<tr>
<td>• Rhabdomyolysis with cardiac injury</td>
</tr>
<tr>
<td>• Transplant-related vasculopathy</td>
</tr>
<tr>
<td>• Vital exhaustion</td>
</tr>
</tbody>
</table>

Note: ICD = implantable cardioverter defibrillator.
End of Cardiac Markers
New antithrombotic drugs: Low-molecular-weight heparin and glycoprotein IIb/IIIa receptor antagonists improve clinical outcome in troponin-positive patients with unstable angina, little or no effect in troponin-negative patients.

Antithrombolytic Therapy

Objective: To recanalize occluded arteries to reduce mortality.

Reperfusion status: "Washout" phenomenon indicates successful reperfusion. Early marker, e.g., myoglobin useful in prediction of success/failure of reperfusion.

**Diagram:**
- Median cTnI conc. (μg/L) vs. Time after onset of symptoms (h)
- 50 Patients with reperfusion of AMI < 6h after onset of symptoms
- 18 Patients without reperfusion of AMI
Cardiac Troponin Release after MI
Role of Tpns in Redefinition of MI
(Consensus document from ESC, ACC, AHA in Circulation, 2000)

- ↑ cardiac troponin (I or T) values
  - Defines ischemic presentations as acute, evolving, or recent MI in acute coronary syndrome (ACS)
- Managing ACS patient with ischemic discomfort
  - ↑ Tpn = Dx of non-ST-segment elevation MI (NSTEMI)
  - Nml Tpn = Dx of unstable angina
Determine optimal MBI

![Graph showing TP (Sensitivity) vs. FP (1-specificity)]

- MBI = 0
- MBI = 3.5
- MBI = 10

TP (Sensitivity) vs. FP (1-specificity) chart
### Cardiac/Hepatic (Up to 5 latest results)

<table>
<thead>
<tr>
<th></th>
<th>2003 03 Feb 21:00</th>
<th>2003 03 Feb 13:00</th>
<th>2003 02 Feb 09:30</th>
<th>2003 02 Feb 01:20</th>
<th>2003 01 Feb 17:30</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (55-170) U/L</td>
<td>68</td>
<td>88</td>
<td>142</td>
<td>184 H</td>
<td>239 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKMB (&lt;5.0) ng/mL</td>
<td>3.47</td>
<td>4.62</td>
<td>5.90 H</td>
<td>9.00 H</td>
<td>14.06 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TROPONIN (&lt;1.5) ng/mL</td>
<td>1.26</td>
<td>3.19 H</td>
<td>1.98 H</td>
<td>4.54 H</td>
<td>4.03 H</td>
</tr>
</tbody>
</table>

- Moderate Hemolysis
Graphing occurrences from 01/04/2003 thru 02/04/2003.

- CKMB ng/mL
- TROPOIN ng/mL
<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>CKMB</th>
<th>TRO Ponin</th>
<th>CK</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Feb 2003</td>
<td>04:00</td>
<td>0.83</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>31 Jan 2003</td>
<td>21:00</td>
<td>0.83</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>31 Jan 2003</td>
<td>09:21</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Jan 2003</td>
<td>14:00</td>
<td>0.91</td>
<td>4.34</td>
<td></td>
</tr>
<tr>
<td>30 Jan 2003</td>
<td>05:30</td>
<td>1.36</td>
<td>7.02</td>
<td></td>
</tr>
<tr>
<td>29 Jan 2003</td>
<td>22:45</td>
<td>2.17</td>
<td>8.44</td>
<td></td>
</tr>
<tr>
<td>29 Jan 2003</td>
<td>14:03</td>
<td>3.64</td>
<td>11.74</td>
<td></td>
</tr>
<tr>
<td>26 Oct 2002</td>
<td>09:47</td>
<td>0.49</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>24 Oct 2002</td>
<td>01:34</td>
<td>0.87</td>
<td>&lt;0.10</td>
<td></td>
</tr>
<tr>
<td>23 Oct 2002</td>
<td>19:40</td>
<td>1.44</td>
<td>&lt;0.10</td>
<td></td>
</tr>
<tr>
<td>23 Oct 2002</td>
<td>11:57</td>
<td>1.25</td>
<td>&lt;0.10</td>
<td></td>
</tr>
</tbody>
</table>
Graphing occurrences from 01/28/2003 thru 02/04/2003.

- **CKMB ng/mL**
  - 11.74 on 01/28/2003
  - 3.47 on 02/01/2003

- **TROPONIN ng/mL**
  - 11.74 on 01/28/2003
  - 0.72 on 02/01/2003
Triaging through ED Chest Pain Center

Conventional strategy

- Chest Pain
  - ECG -
    - NO AMI: discharge (40%)
  - ECG +
    - AMI: CCU (13%)
    - non-diagnostic: admission (47%)
      - no disease (17%)
      - questionable (12%)
      - unstable angina (18%)

ED chest pain center

- Chest Pain
  - ECG -
    - NO AMI: discharge (57%)
  - ECG +
    - AMI: CCU (13%)
    - Chest pain ER
      - stress test
        - pos: admission (30%)
        - neg: discharge (44%)

Outcome assessment:
- Improves diagnostic accuracy
- Reduces hospital costs (length of stay)
- Reduces inappropriate discharge
Determine Cut-off for MB Index

Sensitivity

Specificity

3.5
Prognostic values of TnT & TnI

- 770 pts with ischemic symptoms for predicting outcome of 30-day mortality.
- Blood drawn within 3.5h of presentation
- Concordant results = 90.4%
- Association with 30-day mortality
  - $X^2$: TnT > TnI
  - ROC curve: TnT > TnI

No recommendation from IFCC and NACB on cardiac markers for perioperative MI

In chronic hemodialysis, cTnT increase in patients without evidence of cardiac injury
Prognostic values of TpnT & TpnI

- **Study shows**
  - A +ve TpnT result at presentation more prognostic info than CKMB or EGK.
  - +ve TpnI correlates with risk.
  - TpnT > TpnI providing prognostic info on 30-day mortality

- **Conc in cytosolic pool**
  - TpnT (7-8%) > TpnI (2.5%)
  - Earlier release of TnT upon myocardial necrosis may explain higher TnT +ve pts
  - TnI not as sensitive to early minor necrosis due to smaller cytosolic compartment
CKMB Testing Frequency vs Length of Hospital Stay (LOS)

- **Study**

- **DRGs used in study**
  - 121: circulatory disorders (CD) with AMI with complications
  - 122: CD with AMI without complications
  - 123: CD with AMI and death
  - 140: angina pectoris
  - 143: chest pain

(Wu et al, Clin Chem 43, 326-32, 1997)
Box 1: Critical values to know about troponin assays

- **Lower limit of detection**: The lowest level detectable that differs from zero. Assays with a lower limit of detection are more sensitive.

- **Upper limit of normal**: Usually defined as the 95th percentile (mean ± 2 standard deviations) in a presumably normal “reference” population. For troponin, the European Society of Cardiology / American College of Cardiology task force recommended that the 99th percentile (mean ± approximately 3 standard deviations) be used as the cut-off point, above which any value should be considered abnormal.

- **Coefficient of variation (CV)**: A measure of how consistently an assay is able to produce the same result on the same sample. A CV of 10% is the level of precision suggested for troponin assays.

- **Receiver operating characteristic (ROC) curve**: The value at which the sensitivity of the troponin level is equivalent to that of the CK-MB level.

Note: CK-MB = creatine kinase MB isoenzyme.
CKMB Testing vs LOS

<table>
<thead>
<tr>
<th>DRG 121 (patient no)</th>
<th>TAT for CKMB</th>
<th>LOS</th>
<th>Range</th>
<th>Lab charge (per patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1513 4471</td>
<td>1-2/day</td>
<td>8.4</td>
<td>8.2-8.7</td>
<td>$1,759</td>
</tr>
<tr>
<td></td>
<td>3+ day or stat</td>
<td>7.7</td>
<td>7.4-8.0</td>
<td>$1,578</td>
</tr>
</tbody>
</table>

- No significant difference observed in DRGs 122, 123, 140, and 143

Authors’ conclusions:
- Infrequent CKMB testing policy associated with a longer LOS and higher lab cost.
Clinical Role of Myo in ED

- Two Myo, instead of single Myo, is much more specific for detecting AMI in the first 2 h of ED admission.
- Renal failure is much less problematic when 20 ng/mL/h is used as cut-off.
- Because of rapid rise and rapid clearance, VERY EARLY and VERY LATE MI presenters will be missed.
Clinical Usefulness of TnI & TnT

- Risk stratification in patients with acute myocardial ischemia
- To enable aggressive intervention with angioplasty or thrombolytic therapy
- To allow triage of patients suspected of MI but without definitive clinical findings
- To allow patients with low risk for MI to be sent home
Myoglobin as Cardiac Marker

- Collect at least 2 samples within 2h for myoglobin determination
- Calculate slope of myoglobin release
- Use 20 ng/mL/h as cut-off point
Cardiac Marker Assays at SUNY UMU

- CK/10
- Troponin
- CKMB
- CKMB Index

INFER AMI NEC-INIT EPISD
Acute MI

SUNY UMU
### Other Causes of Elevated CKMB

<table>
<thead>
<tr>
<th>MB Index</th>
<th>MI</th>
<th>Muscular</th>
<th>Non-MI cardiac</th>
<th>Pulmonary</th>
<th>GI</th>
<th>CNS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1-1.0</td>
<td>-</td>
<td>26</td>
<td>4</td>
<td>4</td>
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<td>7.1-8.0</td>
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<td>9.1-10</td>
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<td>&gt; 10</td>
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<td>-</td>
<td>9</td>
<td>1</td>
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</tbody>
</table>

| Total    | 34  | 57      | 79             | 12        | 3   | 9   | 11     |
Typical MI

3 samples drawn within 2 h

\[ \Delta \text{Myo} = 45 \text{ at 1h} \]
\[ = 87 \text{ at 2 h} \]
MI Concomitant with Renal Failure

3 samples drawn within 2h
CK Isoenzymes

**Isoenzymes**
- CK-3 (CK-MM) in Skeletal muscle
- CK-2 (CK-MB)
  - 10-20% in myocardium
  - <2% in skeletal muscle
- CK-1 (CK-BB)

**Macro CKs**
- Type 1
  - Complex formed between CK-BB and immunoglobulin
- Type 2
  - Mitochondria CK
MB Index

- **MB Index** = CKMB x100/CK

Rationale for using MB Index

- Using CKMB alone (RI < 5.0 ng/mL) often yields FP results

- Combined use with MB Index helps to rule-out patients with skeletal muscle injury

What cut-off value for MB Index to use?
CKMM Isoforms

- Tissue isoform (MM3) ↑ with onset of MI.
- Carboxy peptidase N converts: MM3 to MM2 to MM1
- Abnormal MM3/MM1 ratio is early indicator of MI
CKMM Isoform (cont’d)

- Use MM3/MM1 and MB together
- Look for either
  - MM3/MM1 > 0.5
  - ↑ %MB
- Specificity 77%
CKMB & Myoglobin in a Typical MI
**CKMB Isoforms**

![Image of CKMB Isoforms](image)

**Look for MB2/MB1 Upward**

<table>
<thead>
<tr>
<th>Time</th>
<th>MB1</th>
<th>MB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4 h</td>
<td>3.5</td>
<td>3.2</td>
</tr>
<tr>
<td>12 h</td>
<td>3.2</td>
<td>-</td>
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</tbody>
</table>

- MB1: MB = 2 U/L
- MB2: MB = 5 U/L
- MB = 18 U/L

**RI**

- MB2/MB1 ratio at 4 h: 3.5
- MB2/MB1 ratio at 12 h: 3.2
Myoglobin

- Oxygen binding protein of cardiac and skeletal muscle (MW=17,800 Da)
- Rapid release from infarcted area over some limited time, rapid transport to serum
- May rise significantly within 1-2 h of muscle cell damage and after onset of AMI
- Rapid renal clearance, return to normal level within 24 h
Acute Coronary Syndrome (ACS) in the Troponin era

- **ST-elevation:** AMI
- **Non-ST elevation**
  - Tpn elevation: Non-ST segment depression AMI
  - No Tpn elevation: Unstable angina
Conditions for ↑Myoglobin

- Acute myocardial infarction
- Open heart surgery
- Skeletal muscle damage, muscular dystrophy, inflammatory myopathies
- Renal failure, severe uremia
- Shock and trauma
Clinical Usefulness of Myoglobin

- Slow technology (RIA) in the past had limited extensive clinical use as a cardiac marker.
- Rapid monitor of success of thrombolytic therapy.
- Negative predictor of MI.
- Due to poor specificity, ↑myoglobin levels do not always predict myocardial injury.