Point Of Care
Cardiac Marker Testing
Emergency Medicine View

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Learning Objectives

- Overview of ED cardiac marker POC testing
- Some of the key studies
- Recent ACC/AHA & ACEP guidelines
- Strategies for success
Challenges in Chest Pain Triage
Over admissions and Missed MIs

US statistics

- 8 million visits to ER for chest pain
- Suspicious 4.5 million
- Diagnostic ECG 0.5 million
- CCU
- AMI 0.5 million
- Rx/PTCA/Other

Rule-outs 3 million
- Treat or discharge
- Uneventful course 2.88 million
- Missed ACS 120,000

Other Dx \(\rightarrow\) rule-out 1.7 million
- Unstable Angina, Non-Ischemic Cardiac Disease 2.26 Million

20% of ER malpractice cost

>$6 billion in additional costs
Issues in Diagnosis of NSTEMI

1. NSTEMI is a time dependent disease
2. Troponin values are the critical diagnostic test
3. Troponin does not elevate until >6 hours post AMI onset

CRITICAL CHALLENGE:
Can earlier markers of necrosis predict subsequent elevations in troponin?
Appearance of Three Markers of Myonecrosis

Hours After Onset of MI

Multiple of Upper Reference Range

CKMB

Myoglobin

TnI
Class I Recommendation:
Institutions that cannot consistently deliver cardiac marker TAT’s of < 1 hour should implement POC testing devices.
Ninety-Minute Exclusion of Acute Myocardial Infarction By Use of Quantitative Point-of-Care Testing of Myoglobin and Troponin I

J. McCord; RM Nowak; PA McCullough; C Foreback; S Borzak; G Tokarski; MC Tomlanovich; G Jacobsen; WD Weaver
Background & Methods

- 817 consecutive chest pain patients presenting to urban ED
- Blood markers drawn in those with nondiagnostic ECG
- 65 patients (9%) were determined to have AMI
  - 27 patients (36% of AMI patients had normal TnI at presentation)

➤ Patients presenting with AMI are often missed in the critical early hours.

90 minute AMI Exclusion Study

- **Hypothesis:**
  - Multimarker strategy (MMS) can exclude MI in under 3 hours

- **Methods:**
  - 817 consecutive patients presenting to ED for evaluation of possible ACS
  - Point of care measurement of myoglobin, TnI, and CK-MB done at presentation, 90 min, 3 and 9 hours
  - Standard laboratory CK-MB done at same time
  - Triage in ED done by physicians unaware of the point of care results

Myoglobin in Early Hours of AMI (Prior to Troponin Release)

All Patients Confirmed AMI via Subsequent Troponin positivity

McCord et al: AJC, Vol. 94. pp 864-867: October, 2004: Table 2 Adapted
Value of Myoglobin with Troponin Negative at Presentation AMI vs. Non-Cardiac Origin

McCORD et al. Circulation 2001; 104:1483-1488
Henry Ford Trial: Time to Laboratory Reporting

The combination of Myo and cTnI at 0 and 90 mins had the highest early negative predictive value and sensitivity.

<table>
<thead>
<tr>
<th></th>
<th>0, 90 min</th>
<th>0, 90 min, 3 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.9%</td>
<td>96.9%</td>
</tr>
<tr>
<td>NPV</td>
<td>99.6%</td>
<td>99.5%</td>
</tr>
</tbody>
</table>

The 3 hour blood sampling did not improve early sensitivity or negative predictive value.
2006 ACEP Guidelines re: Cardiac Biomarkers
(Level B Recommendations)

- “..single negative CK-MB mass, Troponin I, or Troponin T measured 8 to 12 hours after…onset”
- “..negative myoglobin in conjunction with a negative CKMB mass, or negative Troponin when measured at baseline and 90 minutes in patients presenting less than 8 hours after symptom onset”
- “..negative 2-hour delta CK-MB mass…with a negative 2-hour delta Troponin in patients presenting less than 8 hours after symptom onset”

“No single serum marker used alone has sufficient sensitivity or specificity to reliably identify or exclude AMI within 6 hours after symptom onset.”

2006 ACEP Guidelines
Conclusions

- Within the first 8 hours of symptoms: Multi-marker
- After 8 hours: Single CK-MB or Troponin

Class I - Cardiac biomarkers all patients

Troponin is preferred marker

“..exact timing of serum marker measurement should take into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized as well as the release kinetics of the marker being measured.”

Class IIb "within 6 hours of onset..."

- an earlier marker (e.g., myoglobin) in conjunction with a late marker (e.g., troponin).

- 2-h delta CK-MB mass in conjunction with 2-h delta troponin.

- myoglobin in conjunction with CK-MB mass or troponin when measured at baseline and 90 min"

Class IIb - “Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS”

An isolated, early elevation [of myoglobin] in patients with non-dx ECG should not be relied on to make the diagnosis of MI
A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department.

Data from three HCA hospitals collected February 9 through May 31, 2004

1, 2, and 3 hour marker intervals

If any of the three criteria below were met, the patient was considered positive for an MI:

- A TnI ≥ 0.4 ng/mL on any draw
- A Δ myoglobin of ≥ 50% between sequential draws with any detectable TnI by the last draw
- A Δ myoglobin of ≥ 50% between sequential draws with a concomitant increase in CK-MB without detectable TnI on any of the draws

### Serial draw multi-marker algorithm

- **99.9%** negative predictive value
- **99.7%** accuracy

**Diagram: Diagnosis Algorithm Results**

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>145</td>
<td>12</td>
<td>157</td>
</tr>
<tr>
<td>-</td>
<td>3</td>
<td>5041</td>
<td>5044</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>148</td>
<td>5053</td>
<td>5201</td>
</tr>
</tbody>
</table>

**95% CI**

- **Sensitivity**: 98.0% - 100.2%
- **Specificity**: 99.8% - 99.9%
- **Accuracy**: 99.7% - 99.9%
- **PPV**: 92.4% - 96.5%
- **NPV**: 99.9% - 100.0%
## Straface, et al. – Results

- **Serial draw Troponin only algorithm**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>101</td>
<td>12</td>
<td>113</td>
</tr>
<tr>
<td>-</td>
<td>47</td>
<td>5041</td>
<td>5088</td>
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  **95% CI**
  - Sensitivity: 68.2% (60.7% - 75.7%)
  - Specificity: 99.8% (99.6% - 99.9%)
  - Accuracy: 98.9% (98.6% - 99.2%)
  - PPV: 89.4% (83.7% - 95.1%)
  - NPV: 99.1% (98.8% - 99.3%)

  **0.40 ng/mL (WHO ROC)**

  **Diagnosis**
  - + 144
  - - 252
  - Total 396

  **95% CI**
  - Sensitivity: 97.3% (94.7% - 99.9%)
  - Specificity: 95.0% (94.4% - 95.6%)
  - Accuracy: 95.1% (94.5% - 95.7%)
  - PPV: 36.4% (31.6% - 41.1%)
  - NPV: 99.9% (99.8% - 100.0%)

- **0.05 ng/mL (~99th %tile)**

  **Diagnosis**
  - + 144
  - - 252
  - Total 396

  **95% CI**
  - Sensitivity: 68.2% (60.7% - 75.7%)
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  **Serial draw Troponin only algorithm**

  **Poor Sensitivity**
  - Too Many False Negatives

  **0.40 ng/mL (WHO ROC)**

  **Diagnosis**
  - + 144
  - - 252
  - Total 396

  **95% CI**
  - Sensitivity: 97.3% (94.7% - 99.9%)
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  - Accuracy: 95.1% (94.5% - 95.7%)
  - PPV: 36.4% (31.6% - 41.1%)
  - NPV: 99.9% (99.8% - 100.0%)

  **Poor Specificity**
  - Too Many False Positives
Another Study with Similar Results

<table>
<thead>
<tr>
<th></th>
<th>Hours Post Admission</th>
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<tbody>
<tr>
<td></td>
<td>0-6</td>
</tr>
<tr>
<td><strong>% Sensitivity</strong></td>
<td></td>
</tr>
<tr>
<td>AMI cutoff: 0.30 ng/mL</td>
<td>60.0</td>
</tr>
<tr>
<td>99&lt;sup&gt;th&lt;/sup&gt; Percentile: 0.012 ng/mL</td>
<td>97.1</td>
</tr>
<tr>
<td><strong>% Specificity</strong></td>
<td></td>
</tr>
<tr>
<td>AMI cutoff: 0.30 ng/mL</td>
<td>95.4</td>
</tr>
<tr>
<td>99&lt;sup&gt;th&lt;/sup&gt; Percentile: 0.012 ng/mL</td>
<td>59.2</td>
</tr>
</tbody>
</table>

Non-ACS/HF TnI Elevations
Acute Disease

- **Cardiac and Vascular**
  - Acute aortic dissection
  - Cerebrovascular accident
    - Ischemic stroke
    - Intracerebral hemorrhage
    - Subarachnoid hemorrhage

- **Respiratory**
  - Acute PE
  - ARDS

- **Muscular Damage**

- **Cardiac Inflammation**
  - Endocarditis
  - Myocarditis
  - Pericarditis

- **Infectious**
  - Sepsis
  - Viral illness

Non-ACS/HF TnI Elevations
Other Acute Disease

- Kawasaki disease
- Apical ballooning syndrome
- Thrombotic thrombocytopenic purpura
- Rhabdomyolysis
- Birth complications in infants (low birth weight, preterm)

- Acute complications of inherited disorders (neurofibromatosis, Duchenne muscular dystrophy, Klippel-Feil syndrome)

- Environmental Exposure
  - Carbon monoxide
  - Hydrogen sulfide
  - Colchicine

Non-ACS/HF TnI Elevations

Chronic disease
- ESRD
- Cardiac infiltrative disorders
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
  - Scleroderma
- Hypertension
- Diabetes
- Hyperthyroidism

Iatrogenic disease
- Invasive procedures
  - Heart transplant
  - Congenital defect repair
  - Lung resection
  - ERCP
  - RFCA
- Noninvasive procedures
  - Cardioversion
  - Lithotripsy
- Pharmacological sources
  - Chemotherapy
  - Other medications

Myocardial Injury
- Blunt chest injury
- Endurance athletes
- Envenomation
  - Snake
  - Jellyfish
  - Spider
  - Centipede
  - Scorpion

So How Do I Best Use Troponin-I Results?

- **99th Percentile Value** - Apparently healthy population, results are typically close to zero
- **AMI Cutoff** - Value that determines if a patient is having an AMI based on WHO criteria

Serial draws are recommended to detect temporal rise and fall of troponin-I levels characteristic of MI, and should be used in conjunction with other information such as other cardiac markers, ECG, clinical symptoms, etc.
Universal Definition of MI  
(Joint ESC/ACCF/AHA/WHF Task Force)

MI is: Myocardial necrosis in a clinical setting consistent with myocardial ischemia

- Rise and/or fall of cardiac biomarkers (preferably troponin) above the 99th percentile with evidence of ischemia
  - Symptoms of ischemia
  - ECG changes: ST-T, new LBBB or pathological Q waves
  - Imaging evidence: loss of myocardium or wall motion abnormality
- Sudden unexpected cardiac death involving cardiac arrest
- PCI patients: Cardiac marker elevations of 3 x 99th percentile
- CABG patients: Cardiac marker elevations of 5 x 99th percentile

Clinical Application of Sensitive Troponin Assays
Morrow, NEJM 2009

- Accuracy for AMI improved
- Increased sensitivity
- Reduced specificity and PPV
- Muscle injury versus ischemia (MI)
- Prognostic implications of low-level increases
- Additional studies looking at changes in troponin vs. short and long-term outcome
Recent Patient
EKG #1 at 3:31pm
First Markers

Time: arrival

CKMB < 1.0
Myo  47.2
Trop <  0.05
BNP <  5
EKG #3
3:54pm
### Second Markers

**Time:** 90 minutes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBMB 1.6</td>
<td></td>
</tr>
<tr>
<td>Myo 200</td>
<td></td>
</tr>
<tr>
<td>Trop &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>BNP &lt; 5</td>
<td></td>
</tr>
</tbody>
</table>
EKG #4
5:24pm
EKG #5
6:10pm

For Medical Education Use Only
Third Markers
Time: 240 minutes

CKMB 8.1
Myo 222
Trop 0.40
BNP < 5