High-Sensitivity Cardiac Troponin

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Challenges in Cardiovascular Medicine

- **Acute Coronary Syndrome (ACS)**
  - Non-ST-elevation myocardial infarction (NSTEMI)
  - ST-elevation myocardial infarction (STEMI)
  - Unstable angina (UA)
Challenges in Cardiovascular Medicine

• Annually: 605,000 new and 200,000 recurrent acute myocardial infarctions (AMI)
  • Only ~18% have longstanding angina

• 2% to 5% myocardial infarctions are missed in the Emergency Department

• Only 46% of patients arrive at the hospital within 2 hours of symptom onset
Challenges in Cardiovascular Medicine

- AMI mortality rates (patients ≥45 years):
  - Within 1 year: 18% males, 23% females
  - Within 5 years: 36% males, 47% females
- Appropriate triage and accurate diagnoses/treatment impact mortality downstream
Cardiac Troponin Complex Consists of Three Regulatory Proteins
Troponin Elevations are Greater and Persist Over Longer Time Periods

*TnT elevations persist longer than TnI due to increased mass
Fourth Universal Definition of Myocardial Infarction

- Detection of a **rise and/or fall of cardiac biomarkers (preferably troponin)** with **at least 1 value above the 99th percentile upper reference limit (URL)** together with evidence of myocardial ischemia and at least 1 of the following:
  - Ischemic symptoms
  - ECG changes indicative of new ischemia
  - Pathological Q waves
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - IC thrombus identified by angiography or autopsy
- Timing is essential, **serial testing recommended**
Myocardial Injury Differs From Acute Myocardial Infarction

Criteria for Myocardial Injury

- The term **myocardial injury** should be used when there is evidence of elevated cTn values with at least one value > 99th percentile (sex-specific) URL (new)

Criteria for Acute MI

- The term **acute MI** should be used when there is acute myocardial injury with clinical evidence (symptoms, ECG, imaging) of acute myocardial ischemia with detection of a rise and/or fall of cTn with at least one value > 99th sex-specific percentile used as the URL
Myocardial Injury vs. Acute Myocardial Infarction

- Elevated Cardiac Troponin Value(s) > 99th percentile URL
- Myocardial Injury (necrosis)
  - Ischemia
    - Acute cTn rise/fall
    - Myocardial Infarction
      - Thrombosis
      - Oxygen (Supply/Demand) Imbalance

Type 1 MI examples:
- Atherosclerotic plaque rupture, fissuring, erosion, or dissection with resulting thrombus

Type 2 MI examples:
- Severe anemia
- Severe respiratory failure
- Tachyarrhythmia
- Cardiogenic or hypovolemic shock
- Severe hypertension
Myocardial Injury vs. Acute Myocardial Infarction

Elevated Cardiac Troponin Value(s) > 99th percentile URL

Myocardial Injury (necrosis)

Ischemia

Acute cTn rise/fall

Myocardial Infarction

Thrombosis

Oxygen (Supply/Demand) Imbalance

Without ischemia

cTn rise/fall or chronic increase

Myocardial Injury

Cardiac

Examples:
- Heart failure
- Cardiomyopathy
- Myocarditis
- Cardiac contusion
- Cardiac surgery
- Defibrillator shocks

Systemic

Examples:
- Sepsis / Infection
- Critically ill patients
- Renal failure
- Stroke
- Pulmonary embolism
- Toxic agents

Type 1 MI examples:
- Atherosclerotic plaque rupture, fissuring, erosion, or dissection with resulting thrombus

Type 2 MI examples:
- Severe anemia
- Severe respiratory failure
- Tachyarrhythmia
- Cardiogenic or hypovolemic shock
- Severe hypertension
“High-Sensitivity” terminology reflects the analytical characteristics of the assay and NOT a difference in the cardiac troponin measured.

<table>
<thead>
<tr>
<th>Acceptance Designation</th>
<th>Total Precision at 99&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline Acceptable</td>
<td>10%</td>
</tr>
<tr>
<td>Clinically Usable</td>
<td>&gt;10 to ≤ 20%</td>
</tr>
<tr>
<td>Not Acceptable</td>
<td>&gt; 20%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Assay Designation</th>
<th>Measurable Normal Values of Males and Females Below the 99&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 - 3rd gen hs</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>Level 3 - 2nd gen hs</td>
<td>75 to &lt; 95%</td>
</tr>
<tr>
<td>Level 2 - 1st gen hs</td>
<td>50 to &lt; 75%</td>
</tr>
<tr>
<td>Level 1 - Contemporary</td>
<td>&lt; 50%</td>
</tr>
</tbody>
</table>
Rapid Rule-Out and Rule-In of Acute Myocardial Infarction is a Key Benefit of hs-cTn Assays

Rule-Out Strategies

Contemporary cTn Assays
- Prolonged serial sampling
  - 0, 3, 6, and 9-hour measurements
- Use of undetectable hs-cTn values

hs-cTn Assays
- Accelerated serial sampling
  - (0h and 1-3h measurements)
- hs-cTn in combination with a risk score (Accelerated Diagnostic Protocols, ADPs)
- Use of a single hs-cTn measurement with a concentration tailored to meet a clinical need
Report High-Sensitivity Troponin Results Using Whole Numbers (ng/L)

• A contemporary cTn assay result of 0.014 μg/L will be 14 ng/L for an hs-cTn assay

• This designation, as an expert opinion, has been supported by many Journals and is globally recognized as a way to distinguish hs-cTn assays from contemporary cTn assays
Use a Defined Reference Population to Establish 99th Percentile Concentrations with Sex-Specific Cutoffs

- Fourth Universal Definition of MI endorses sex-specific 99th percentiles, recognizing upper reference limits (URLs) are lower in women than men
- Minimum 300 males and 300 females required to define URL
- Minimum 20 males and 20 females required to verify URL
  - Use individuals representative of your geographic area
  - Ages distributed over 20y and greater
  - Ethnic and racial mix with population
- More rigorous criteria for defining/excluding normal subjects lowers the 99th percentile: a) comorbidities, b) medication use, c) surrogate biomarkers (eGFR, HbA1C, NT-proBNP/BNP)
- Statistical approach can influence 99th percentile (non-parametric, Harrel-Davis, robust)
High-Sensitivity Troponin Assays: Serial Sampling

- Serial monitoring aids in distinguishing myocardial infarction from myocardial injury
- Serial testing may provide a better means for diagnosis than use of a population-based 99th percentile
  - Fourth Universal Definition of MI supports serial 0 and 1/2/3h
    - Later times will not miss potential very early presenters
- Absolute changes, rather than relative (percent) changes, appear preferable for hs-cTn assays at low concentrations
- ADPs and rapid rule-out strategies relevant to implementation discussions
- Biological variation may influence interpretation of serial hs-cTn concentrations.
- Definition of a significant change ("delta") is unclear and assay dependent
Report Results in ≤ 60 Minutes to Accelerate Clinical Diagnostic Decisions and Treatment Protocols

• Turnaround time ≤ 60 minutes from time specimen is received in the laboratory to reporting results in the electronic medical record

• Previous NACB (AACC Academy) recommendations: <60 min from time of blood collection to reporting results

• There should be interdisciplinary efforts to continuously strive to improve hs-cTn turnaround times
Recommendations for Point-of-Care (POC) Cardiac Marker Testing

• Limited number of hs-cTn POC assays available
• If turnaround time goals cannot be met in the central lab, POC is only justified in the ED
  • Educate providers that current POC assays are substantially less analytically sensitive
  • POC and central lab cTn results are not interchangeable
  • Understand how hemolysis could affect cTn results
• Quantitative results should be reported
• POC testing may also be necessary in rural/small hospital settings to be able to provide 24 / 7 service
Proper interpretation of hs-cTn results requires an understanding of the assay used at your institution

- Distinguishing acute from chronic injury is one of the major challenges of using hs-cTn assays
  - Analytics become very important to interpret serial changes
    - Analytical characteristics (high-sensitivity, contemporary, POC)
    - Analytical interferences (hemolysis, biotin)

Points to Remember

• High-sensitivity troponin assays are defined by the analytical characteristics
• A single troponin result does not equal a diagnosis
  • Acute MI can be safely ruled-out within 3 hours
    (hs-cTn plus risk score/diagnostic pathways/ECG findings)
• Acute changes in troponin are essential for interpretation; serial changes are assay dependent
• Majority of cTn POC assays are not high-sensitivity
  • Less precise and less sensitive; results are not interchangeable with central lab cTn assays
• Education and multi-disciplinary collaboration are essential to define institutional testing practices/protocols with hs-cTn
References


Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- Employment or Leadership: No disclosures
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