What is the Preferred Marker of Cardiac Myocyte Injury or Death in 2021?

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Today’s Presenter: Dr. William Winter, MD, FCAP

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• Cardiac Markers
• Clinical Use of Troponin in the Diagnosis of Acute Chest Pain
• Criteria for the Diagnosis of Myocardial Infarction
• Non-Myocardial Infarction Causes of Elevated Troponin
• Troponin Assays
• Q&A
Objectives

- Define and differentiate myocardial injury, acute myocardial injury, and myocardial infarction.
- List the five subtypes of myocardial infarction.
- Identify atherothrombosis as the most common cause of myocardial infarction.
- Choose the best plasma marker for the detection of cardiac myocyte injury and necrosis.
- Explain to laboratorians and clinicians the superiority of high sensitivity troponin measurements over traditional troponin measurements.
Cardiac Markers
What is a cardiac marker (a.k.a. - “cardiac biomarker”)?

Substances measured in plasma or serum . . .

... that are used in diagnosis and risk stratification of patients with chest pain and suspected acute coronary syndrome (ACS).

Suspected acute coronary syndrome:
A term applied to patients in whom there is a suspicion of acute myocardial ischemia or infarction

Which cardiac markers are currently clinically used?

**Troponin (Tn)** is the *only* cardiac marker that should be used clinically to assess possible ACS (& measure serially).

*Comment:*

**Tn** can be used to diagnose re-infarction.

<table>
<thead>
<tr>
<th>Cardiac markers no longer in use:</th>
<th>Comment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>Lacks specificity</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Improved specificity but <em>not</em> as specific (nor sensitive) as Tn</td>
</tr>
<tr>
<td>- MB isoenzyme of CK</td>
<td></td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Lacks specificity</td>
</tr>
<tr>
<td>AST</td>
<td>Both lack specificity &amp; are late markers</td>
</tr>
<tr>
<td>LD</td>
<td></td>
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</table>
What is troponin?

Part of the contractile regulatory complex

There are: 3 forms of troponin

- **TnI**: ATPase inhibitory
- **TnT**: Binds complex to tropomyosin
- **TnC**: Ca++ binding
Are skeletal muscle and myocardial troponins different?

<table>
<thead>
<tr>
<th>Troponin</th>
<th>Function</th>
<th>Specific for:</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI</td>
<td>ATPase inhibitory</td>
<td>myocardium</td>
<td>TnI</td>
</tr>
<tr>
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<td>Binds complex to tropomyosin</td>
<td>myocardium</td>
<td>TnT</td>
</tr>
</tbody>
</table>

**Abbreviations**

- **TnI** – cardiac troponin I
- **TnT** – cardiac troponin T

**Tn** is released by cardiac myocyte injury or necrosis.
Are cardiac troponins absolutely specific for cardiac muscle?

Well no… 😞

<table>
<thead>
<tr>
<th>Increased</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT (+)</td>
<td>cTnI (+)</td>
</tr>
</tbody>
</table>

Inherited & Acquired

- Myopathies
  - ~70%
  - ~4%
  - examples: Dystrophic myopathy, Myotonic dystrophy, Nondystrophic myotonia, Inflammatory myopathy, Primarily neurogenic myopathy

Source: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 14, 2018
Clinical Use of Troponin in the Diagnosis of Acute Chest Pain
How are troponin measurements predominantly used clinically?

Evaluation of suspected acute coronary syndrome (ACS)

ACS

STEMI

(Tn will be increased)

NSTEMI

EKG changes:
- transient ST segment depression
- symmetrical T wave inversion or
- tall, pointed, upright T wave

Unstable angina (UA)

NSTEMI

Evaluate acute symptoms, perform EKG & measure Tn

NI Tn

Incr. Tn

ACS ruled out

No EKG Δ's

NI Tn

Hx: Other

The most common characteristics of NSTEMI EKGs are ST depression and/or T inversion.

Normal

Evaluation of suspected acute coronary syndrome (ACS)
What term is used to describe any Tn concentration >99\textsuperscript{th} percentile?

Myocardial injury

Defined solely on the basis of Tn testing

Dx of MI has specific criteria!
Criteria for the Diagnosis of Myocardial Infarction
What is a “myocardial infarction?”

Coagulative necrosis of myocardium due to acute ischemia

Insufficient blood supply
→ causes
O\(_2\) demand > O\(_2\) supply

Inadequate delivery of oxygen → tissues

Injury
→ “X’s Line of no-return”
→ Necrosis
How can the various causes of MI be classified?

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete: STEMI</td>
</tr>
<tr>
<td>[3] Acute death prior to pathologic changes &amp; prior to increased Tn</td>
<td>Death by arrhythmia (most common)</td>
</tr>
<tr>
<td>[4] PCI, related to the PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>[5] Related to CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
</tbody>
</table>

What are the current criteria for the diagnosis of a type 1 MI according to the Fourth Universal Definition (2018)?

The diagnosis of a type 1 MI requires:

[1] Acute myocardial injury*

(+) *Rise and/or fall in Tn, $\rightarrow$1 value $>$99th percentile

[2] Other supportive findings
Symptoms c/w ischemia
New ischemic EKG $\Delta$’s and/or new Q waves
Abnormal imaging
Evidence of coronary thrombus

Non-Myocardial Infarction Causes of Elevated Troponin
What non-MI cardiac conditions can cause Tn concentrations to rise*? (1)

**Severe ischemia**

**Coronary intervention**

**Cardiac surgery (eg, CABG)**

**Other cardiac conditions**
- Heart failure
- Myocarditis
- Cardiomyopathy (any type)
- Takotsubo syndrome
- Non-revascularization cardiac surgery
  - Can include: cardiopulmonary bypass

**Comments**
- If Tn > 99	ext{percentile} + \uparrow \text{ or } \downarrow = \text{MI (types 1 or 2)}
- If \uparrow \text{Tn, etc.} = \text{MI (type 4)}
- If \uparrow \text{Tn, etc.} = \text{MI (type 5)}

* Tn can increase yet the Dx of MI may not be achieved.
What non-MI cardiac conditions can cause Tn concentrations to rise*? (2)

Other cardiac conditions (continued)

- Catheter ablation
- Defibrillator shocks
- Cardiac trauma (eg, blunt force trauma/contusion)
- Rejection of a transplanted heart
- Pericarditis

* Tn can increase yet the Dx of MI may not be achieved.
What systemic conditions can cause Tn concentrations to rise?

Systemic conditions
- Sepsis, infectious disease
- Chronic kidney disease*
- Stroke, subarachnoid haemorrhage
- Pulmonary embolism, pulmonary hypertension
- Infiltrative diseases, eg, amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critically ill patients
- Strenuous exercise

Note: Tn can be elevated in patients on renal dialysis.
- elevation is usually mild (eg, low-level).
- predicts increased risk of subsequent death
Troponin Assays
Are all Tn assays created “equally?”

No!

Types of Tn immunoassays:

Tn (“traditional”): Little changed since 1990’s

High-sensitivity Tn: Entering clinical use.

Abbreviations:

Tn
hsTn
What are the unique features of hsTn?

Improved analytical **precision** & **accuracy**
  Extremely important @ 99th percentile (CV: ≤10%)

**Reduced – lower limit of detection (LLD) (more sensitive)**
  hsTn detected in ≥50% of normal population
  ± Earlier dx of AMI; earlier r/o AMI

**Sex-specific reference intervals:**
  Upper limit of RI: Males > Females

  Example: Beckman: 20 ng/L v. 15 ng/L

Reported in **WHOLE numbers** (ng/L; SI unit)
What is a major *limitation* of the traditional Tn assays (Tn)?

“Delayed” diagnosis of AMI

- Time to detect an elevated Tn: → 3 to 6 hours
- Measurable Tn values
- Injury
- Lowest measurable [Tn] is near the 99th percentile

\[ \text{99th percentile / LLD} \]
\[ <99\% \text{ NI (not elevated; "-"}) \]

Incr. time to intervention = incr. necrosis

*We need EARLIER DIAGNOSIS!*

Graphic source: https://icon-library.com/icon/clock-icon-white-23.html
What is a major advantage of hsTn assays?

Potentially earlier diagnosis of MI

- More rapid r/o AMI: zero → 1 hour, → 2 hours, → 3 hours
- Preservation of myocardium
  - Reduced extent of necrosis

Chest pain (r/o ACS)

~≥3 hours → MI ruled in

hsTN values

99th percentile

LLD

Earlier dx of MI --> Earlier intervention
Because it can still take several hours to diagnose MI, what can be done to “speed up” the diagnostic process?

Serial EKGs are a routine part of ACS evaluation.

If a ST segment elevation occurs, STEMI is diagnosed even if the Tn has not yet turned (+). ST segment elevation in STEMI can occur very rapidly & within 1 hour.

**NOTE:** T-wave inversion and ST segment depression do not make the diagnosis of NSTEMI → need a (+) Tn.

**NOTE:** EKG changes are similar in UA & NSTEMI → require Tn testing for their differentiation.
What is a major advantage of hsTn assays?

hsTn is measurable in ≥50% of healthy individuals

hsTn lower limit of detection (LLD) is far BELOW cut-point (>99th percentile)

Assume there is chest pain w/o MI →

Proposals for r/o AMI: Abs. hs Tn: <8 ng/L
               Delta: <7 ng/L (2h)

- Pt: focus on non-MI causes of chest pain
- Improved resource utilization

Very quick rule out 😊
What are the kinetics of troponin elevation in MI?

![Graph showing the kinetics of troponin elevation in MI.](image)

- **TROPONIN-I**
  - 10-24 HRS
  - 10-14 days

- **TROPONIN-T**
  - 10-14 days
Review

Tn – ~cardiac myocyte specific

Tn – used in evaluation of suspected ACS

MI = acute coagulative necrosis of myocytes

Most common cause of MI: atherothrombosis (type 1 MI)

Dx of MI: Incr. Tn + rise/fall (+) sx, EKG Δ’s, image/fn Δ’s, evidence coronary thrombosis

Tn – ~organ specific, not specific to etiology
Myocardial injury: Tn >99th percentile

Acute myocardial injury: Tn >99th percentile with \textit{rise/fall}

Tn assays: hsTn assays are superior:
• Rule out MI in ~ 3 hours
• More rapid rule in of MI
CAP Proficiency Testing (PT) Programs

• Over 700 programs across 16 disciplines
  – Evaluate instrument and method performance
  – Indicators for laboratory quality

• Three high-sensitivity troponin programs
  – HCRT for high-sensitivity Troponin I and CK-MB (immunochemical) plus Myoglobin
  – HCRTI for high-sensitivity Troponin I and CK-MB (immunochemical), CK isoenzymes by electrophoresis, LD isoenzymes by electrophoresis, and Myoglobin
  – HTNT for high-sensitivity Troponin T assays
CAP Quality Cross Check (QCC) Programs

31 programs across six disciplines

- Monitor instrument performance
- Assess comparability across multiple instruments
- Identify potential issues before they affect patient results

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Challenges per Shipment</th>
<th>Number of Shipments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB, immunochemical</td>
<td>3</td>
<td>Two shipments per year</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Troponin I</td>
<td>3</td>
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