Troponin Testing: Status and Role of Cardiac Markers After The Redefinition of MI and The New Guidelines for UA/NSTEMI

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Troponin in Evolution

• **Observations:**

  – 1. World wide acceptance in literature
  – 2. Growing compliance in practice
  – 3. Continuing concern with numerous positives: Impact on Definition of MI
  – 4. Increasing pressure for early results
  – 5. Troponin standardization has not been achieved
“Missed Diagnoses of Acute Cardiac Ischemia in the Emergency Department”

- “Among the 889 patients with acute myocardial infarction, 19 (2.1 percent) were mistakenly discharged from the emergency department (95 percent confidence interval, 1.3-3.2 percent).”
- Risk of death: odds ratio 1.9 compared to admitted
- Of 10,689 presenting patients
- Criteria for MI used CKMB, not Troponin
- Sites: 10 teaching hospitals in U.S.

Chronology of Key Publications
September 2000


5. Hamm C, **Braunwald** E: (Reclassification of UA) Circulation 2000;102:118-22
Braunwald Reclassification of Unstable Angina

Formerly: UA and MI separate

Revision based on:

1. Understanding of underlying pathology
2. Recognition of risk stratification
3. Troponin separation:
   Class III, T pos or T neg

Hamm C, Braunwald E: Circulation 2000;102:118-22
Troponin Acceptance

- “Troponins have assumed a central role in risk stratification and therapeutic decision making in the ACC/AHA guidelines and in the ESC report.”
- “Cardiac troponins are regarded as preferred markers and are rapidly gaining acceptance on both continents.”

Hamm CW, Bertrand M, and Braunwald E: Lancet 2001;358:1533-38
Post Publication Comments on the UA/NSTEMI Guidelines (Braunwald, Bertrand and Hamm)

- “Coronary angiography should be done as soon as possible during hospitalization in these [high risk] patients.”

- Re: GpIIb/IIIa therapy: “The consistent benefit seen with these drugs led to recommendations of their use in addition to standard treatment—for patients with high-risk features such as increased troponin concentrations, ST segment changes, or recurrent ischemia.”

Hamm CW, Bertrand M, and Braunwald E: Lancet 2001;358:1533-38
MI Redefined: Troponin Based Key: Sensitivity and Specificity

- Sensitivity of modalities for MI:
- ECHO Wall Motion: >20% wall thickness
- Radionuclide Imaging: >10 g of tissue
- Biochemical Markers: <1 g of tissue

Note: Joint ESC/ACC Committee.
“Current technology can identify patients with small areas of myocardial necrosis weighing <1.0g. Thus, if we accept the concept that any amount of myocardial necrosis caused by ischemia should be labeled as an infarct (as proposed by this consensus conference), then an individual who was formerly diagnosed as having severe, stable or unstable angina pectoris might be diagnosed today as having had a small MI.”

“This change in the definition of MI seems reasonable because it has been definitively shown that any amount of myocardial damage, as detected by cardiac troponins, implies a worsened long-term outcome for the patient.” And “Currently available analyses demonstrate no threshold below which elevations of troponins are harmless and without negative implications for prognosis.”

Troponin Assay Sensitivity For Necrosis Assays prior to 2000 Publication

- Re: Scans and ECHO
- “Biomarkers are more sensitive, more specific, than imaging techniques for the diagnosis of myocardial necrosis. “Injury involving >20% of wall thickness –before detected by echo cardiography.” “In general, >10 g of myocardial tissue –before a radionuclide –defect can be resolved.”(p.963)

**Troponin**
- High sensitivity and specificity
- Wide time window (3-9 hours to 4-8 days)
- Reliable detection of myocardial damage of different age
Redefinition of MI

- **WHO:**
  - 1. Symptoms
  - 2. ECG changes
  - 3. Enzymes

- **Overlooked:**
  - Definite vs. Suspected

- **Joint US/European**
- **Troponin and**
  - Evidence of ischemic etiology
    - Including:
      - ECG: ST depression or elevation
      - Symptoms if ischemic
      - Angioplasty
Myocardial Infarction Redefined-A Consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction

J Am Coll Cardiol 2000;36;959-969.
“Definition of MI. *Criteria for acute, evolving or recent MI.*

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis with at least one of the following:

- Ischemic symptoms, ECG pos. or Angioplasty

Thygesen K, et al, JACC 2000;36:959-969. Note: Joint ESC/ACC Committee
How Much Necrosis is Significant?

•“__any amount of myocardial damage, as detected by cardiac troponins, implies an impaired clinical outcome for the patient.”

Myocardial Infarction

- **STEMI**
  - ST elevation MI
  - Formerly:
    - Transmural
    - Q-wave infarct

- **NSTEMI**
  - Non-ST elevation MI
  - Formerly:
    - Subendocardial MI
    - Non-Q wave MI
STE MI vs. NSTEMI

• Past emphasis:
  – Open artery theory: PTCA/Thrombolysis
  – Key: ST elevation
  – “Time is muscle”

• New emphasis:
  – STEMI is important, but, fewer than NSTEMI
  – Equally or worse prognosis
  – “Time is muscle” for both
Top: Mortality Rate up to 30 days

Bottom: Mortality Rate to 6 months
Note: Crossing of the curves—NSTEMI
Greater mortality than STEMI


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MI Redefined

• Patients should be labeled – “—coronary artery disease with MI. In addition, it is essential that other descriptors of the patient’s cardiac status be included, such as: --” LV function, \textit{coronary anatomy}, and evolution (stable/unstable).

Why Are the Markers Valued? Risk Stratification!

- “Elevated levels of cTnT and cTnI convey prognostic information beyond that supplied by the clinical characteristics of the patient, the ECG at presentation, and a predischarge exercise test.”

- “—elevated (troponin) concentrations identify those at an increased risk of death.”

ACC/AHA Guideline Circulation 2000;102:1193-1209
Troponin + vs. Troponin -
Cardiac Death and Reinfarction at 30 days

Am Heart J 2000;140:917-27.

ST elevation

No-ST elevation

Low Risk

High Risk

2.86 (2.35, 3.47)

4.93 (3.77, 6.45)

3.44 (2.94, 4.03)
Risk Stratification
Survival Without Death or Nonfatal AMI
Why are there so many more positive Troponins than CKMB

- Troponin is more sensitive to smaller myocardial injuries:
  1. Longer half life
  2. No background of “normal level”
  3. Totally cardiospecific
Rupture and Embolization

Quiescent plaque

Plaque rupture

Occlusive thrombus

Platelet-thrombin micro-emboli
Microvascular Obstruction

• Embolization of microscopic, nanogram-size atherosclerotic material and/or platelet-thrombus aggregates, either spontaneously or following angioplasty/stenting

• Detected by contrast myocardial echo, perfusion scintigraphy, MRI, or dynamic ECG changes

• May be associated with increased adverse event rate and distal endothelial dysfunction
cTnI Discordance: Published Assays

- Clinician confidence in a cTnI assay must be high because:
  - 1. Clinical tools to confirm are less sensitive and less specific than cTnI
  - 2. ACS troponin positive cases are high risk
  - 3. Therapy, based on troponin data, should be administered early for maximal effectiveness
Troponin Degradation and Covalent Complexes


Asymptomatic

- **Intact cTnI**
  - Low

Reduced Flow

- **cTnI**
  - Low
- **TnC**
  - Low
- **cTnT**
  - Low

Ischemia

- **cTnI**
  - Low
- **TnC**
  - Low
- **cTnT**
  - Low

Necrosis

- **cTnI**
  - Low
- **TnC**
  - Low
- **cTnT**
  - Low

2002/06/02

Prof. Keffer
cTnI: The *Reality*

1. \([cTnI]_{s,p,wb}\) is heterogeneous
2. Reagent antibodies bind different epitopes
3. Biochemical alteration modifies antigenic conformation affecting reagent antibody binding properties to different epitopes
4. Discordant assay data are to be expected
5. Adverse clinical impact is demonstrable
“The New Definition of (MI): What does it mean clinically?”

• Question: The addition of troponin
• Review U. of Mich. Data 5/99-1/00 ACS
• Conclusion: “The decision to include troponin –will result in a 16% increase in the annual number of (MI’s)– and may select a clinically less complicated patient population.”

• Meier MA, et al: Abst. 1018, ACC, 3/18/01
“What is an MI? Prospective Analysis of the Diagnostic and Prognostic Impact of Adding Troponins to the Definition of (MI).”

- GRACE Registry: subset of 3,420 patient of the total 8,213 having both peak standard CK, CKMB and troponin markers.
- Multinational, prospective observational study: 94 centers, 15 countries
- Conclusions:
  - 1. Adding Tn leads to as many as 1 to 4 additional MI’s
  - 2. “This group of patients experiences a three fold increase in short term mortality compared to normal enzyme levels and a 1.5 fold increase compared to the traditional cardiac enzyme definition.”

“Evolution of the Diagnosis of Acute Myocardial Infarction”

- Question: Impact of troponin on diagnosis and prognosis?
- Data: HCFA database, national sample of 1998-99 AMI hospitalizations: N=35713
- Tn: Principal basis of Dx in 7.1%
- Both Tn and CKMB were available in 15,921 cases

Foody JM, et al: Abst. 803, ACC, 3/19/01
“Evolution of the Diagnosis of Acute Myocardial Infarction”

• Results:
1. ‘-patients with a elevated Tn levels were consistently at higher risk for in-hospital mortality irrespective of CKMB fraction.-”
2. “Cases with an elevated Tn but a negative CKMB had the highest in-hospital mortality (13.2%).
3. “- cases with a negative Tn even in the face of a positive CKMB were at lowest risk.”

Foody JM, et al: Abst. 803, ACC, 3/19/01
What are the implications of a positive troponin for Rx?
Early Treatment Increasing

• “The advent of “point of care” measurements of troponin levels in the emergency department, together with routine electrocardiography, has made the goal of rapid identification of high-risk patients most likely to benefit from an early invasive approach readily attainable.”

Troponin in TACTICS

- Study shows: strong advantage to “early invasive” approach over conservative medical management
- Troponin pos patients showed the benefit
- Troponin neg patients: no advantage of early invasive therapy

Troponin: Key to Therapeutic Intervention

- Low Molecular Weight Heparin FRISC Studies
- GpIIb/IIa patients
  Boersma meta-analysis
- Early Invasive therapy
  TACTICS Study
- All of the above: Troponin Positive Selects those who benefit from therapy
Post GUSTO-IV assessment of the role of GpIIb/IIIa drugs

- Meta-analysis of all major trials by Boersma et al:
  - “(GPIIb/IIIa) inhibitors reduce the occurrence of death or myocardial infarction in patients with acute coronary syndromes not routinely scheduled for early revascularization.”
  - “the absolute treatment benefit was largest in high-risk patients.”
  - “No benefit was apparent in patients with a negative troponin value.”

TACTICS Troponin Experience

• “Patients with cTnI levels (undetectable) had no detectable benefit from early invasive management ---. The benefit of invasive vs conservative management through 30 days was evident even among patients with low-level -- cTnI elevation-- .”

Role of Exercise Treadmill Testing in Chest Pain Triage

Table 3: Indications and Contraindications for Exercise ECG Testing in the ED Setting

- “Requirements before exercise testing that should be considered in the emergency department setting:
  - 1. “2 sets of cardiac enzymes at 4-h intervals should be normal”

Role of Exercise Treadmill Testing in Chest Pain Triage

Editorial Lancet:

“Most importantly, patients selected for exercise testing should, on assessment for clinical risk of (ACS), be judged to have a low risk (less than 7% likelihood). Such patients will have--- normal concentrations of serum cardiac markers on two occasions, no recurrence of chest pain during a 6-9 hour observation period—” etc.

“Exercise testing in rapid-access clinics for assessment of chest Pain.” Reeder GS; Lancet 2000;356:2116-
Summary and Conclusions
Troponin and the ACS

- Troponin defines the pathophysiology of infarction, and,
- Contributes to the:
  - Diagnostic classification
  - Prognostic Identification
  - Selection for Therapeutic Intervention