**Natriuretic Peptides & Troponin: Testing Today**

Theresa Joseph  
Medical Scientific Liaison  
Roche Diagnostics

---

**Disclosures**

- *Your Name Here* is an employee of Roche Diagnostics within the division of Medical Scientific Affairs.
- Data presented is intended for purely educational use to provide the participant with scientific, evidenced-based data in compliance with FDA guidelines.

All Trademarks, trade names, images, or logos mentioned or used herein are the property of their respective owners and are not used for purposes of promotion or as an indication of affiliation with the provider of any particular good or service.

---

**Program Description**

- This program is intended to familiarize health professionals and laboratorians with data supporting evidenced-based practice guidelines related to care of the patient with Acute Coronary Syndrome and/or Heart Failure.
- The Focus will be on diagnostic and prognostic value of troponin & natriuretic peptides.

---

**Objectives**

- Describe the biochemical and physiological effects of the cardiac natriuretic peptide and troponin system.
- Identify biological and physiological factors for consideration in the clinical application of natriuretic peptide and troponin measurements in acute and chronic disease settings.
- Analyze evidenced-based clinical outcome data related to the diagnostic and prognostic impact of natriuretic peptide and troponin use in primary and acute care settings.

---

**Biology of the NP System**

**Synthesis and Release**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>32 Amino acids (AA)</td>
<td>76 AA</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 minutes</td>
<td>60-120 minutes</td>
</tr>
<tr>
<td>Stability</td>
<td>Up to 4 hrs at room temp.</td>
<td>Up to 3 days at room temp.</td>
</tr>
<tr>
<td>Clearance</td>
<td>NP Receptor-C, Endopeptidases, kidney</td>
<td>Unclear, possibly kidney</td>
</tr>
</tbody>
</table>

Natriuretic Peptides: Influences from cardiovascular/renal dysfunction, age, BMI

Physiological Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect on B-Type NP Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>↑↑ ↑↑</td>
</tr>
<tr>
<td>Female gender</td>
<td>↑↑ ↑↑</td>
</tr>
<tr>
<td>Obesity</td>
<td>↓↓ ↓↓</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>↑↑ ↑↑</td>
</tr>
<tr>
<td>Valve disease</td>
<td>↑↑</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>↑↑</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>↑↑</td>
</tr>
<tr>
<td>Diastolic heart failure</td>
<td>↑↑</td>
</tr>
<tr>
<td>Incompletely treated heart failure</td>
<td>↑↑</td>
</tr>
</tbody>
</table>


Analytical Considerations & Age

Levels increase with age and have to be interpreted in clinical context

Analytical Considerations

Natriuretic Peptide concentrations increase progressively as GFR decreases

Influence of Natriuretic Peptide Concentrations By eGFR and Diagnosis of Decompensated Heart Failure


Influence on Natriuretic Peptide Levels

Renal Disease

Analytical Considerations

Impact of body mass index (BMI) on Natriuretic Peptides


NT-proBNP

- An aid in the diagnosis of individuals suspected of having congestive heart failure
- For risk stratification in patients with ACS and CHF
- An aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.

FDA Cleared Claims

NT-proBNP

Utility of NT-proBNP in HF

Diagnosis

- Primary care
- Acute care
- HF

Symptoms

Aid in Diagnosis of suspected HF

Prognosis

- Outcomes

Clinical Performance Represented ROC Curve

FDA cleared clinical thresholds to rule-out heart failure:
- 125 pg/ml for younger patients, 450 pg/ml for patients 75 years and older

Clinical Utility

Excluding Heart Failure

NT-proBNP assay

Patients Suspected of Having HF

- < 75 years < 125 pg/mL
- Older patient ≥ 75 years < 450 pg/mL

Heart Failure Unlikely

- Patient < 75 years > 125 pg/mL
- Older patient ≥ 75 years > 450 pg/mL

Additional CV assessment indicated

BNP assay

Patients Suspected of Having HF

- < 100 pg/mL
- > 100 pg/mL

Heart Failure unlikely

Additional CV assessment indicated


3/30/2016
Are BNP and NT-proBNP Values Interchangeable?

**Basic Differences**

- Different modes of degradation
- Different halflives
- Different cut-offs
- General recommendations apply to both BNP and NT-proBNP
- Individual values are NOT interchangeable

**Plasma Concentrations of BNP and NT-proBNP in healthy controls and patients with heart failure in stages A-D**

<table>
<thead>
<tr>
<th>Stage</th>
<th>BNP (pg/mL)</th>
<th>NT-proBNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Demographics And Clinical Characteristics**

Patients classified according to AHA/ACC heart failure classification scheme. Study included 86 healthy controls and 820 patients with HF in stages A-D. General recommendations apply to both BNP and NT-proBNP. Individual values are NOT interchangeable.
Will the Natriuretic Peptide Numbers Always Match the Clinical Picture?

Key Points to Remember

Not a stand alone test
Greatest value when complements clinical skills and other diagnostic tools
Elevations should NOT be discarded without consideration of adverse outcomes
Helpful to identify the patient's baseline NT-proBNP value and compare levels
Chronic heart failure patients tend to have chronically elevated levels of both BNP and NT-proBNP

+++ Important to look at the entire clinical picture ++++
Acute Coronary Syndromes

Elevated NT-proBNP associated with myocardial infarction during 30-day follow-up

Myocardial infarction rate

<table>
<thead>
<tr>
<th>NT-proBNP concentration</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 237 ng/L</td>
<td>2.7%</td>
</tr>
<tr>
<td>238-669 ng/L</td>
<td>5.4%</td>
</tr>
<tr>
<td>669-1669 ng/L</td>
<td>5.7%</td>
</tr>
<tr>
<td>≥ 1669 ng/L</td>
<td>7.5%</td>
</tr>
</tbody>
</table>


Acute Coronary Syndromes

Elevated NT-proBNP and 1-Year Mortality

Mortality and Subsequent Myocardial Infarction in Patients With Unstable Coronary Artery Disease

Mortality 1 year (%)

Troponin Testing

Areas of Confusion…..

Here and Now

- Changing Definition of MI
- How to interpret results
- Ever evolving Troponin Assays
  - Improved analytical precision
  - Improved ability to detect smaller concentrations of Troponin
  - Different threshold values
  - Detection of Troponin in patients not experiencing classical MI symptoms
- When to order a Troponin level
  - Good intentions may lead to unnecessary testing

Interpretation of Troponin Elevations

“Laboratorians’ Call to Action”

Reduce the Confusion

- Facilitate cTn Assay Understanding:
  - Educate Medical Staff (Clinicians, Nurses, Pharmacist, etc.)
    - Performance characteristics
    - Threshold limits
    - Interpretation of results
      - Ischemic
      - Non-ischemic
Barriers in Diagnosing ACS
Non ACS Troponin Elevation

The Usefulness of Troponin in Clinical Decision Making in Acute Coronary Syndrome

Cardiac troponin’s role in patient assessment
Clinical utility covers a wide range of clinical applications

Acute Coronary Syndrome
Guideline Directed Utilization of Cardiac Troponin

Troponin: Clinical Value
- Cardiac-specific marker
- Accurately identifies myocardial necrosis, it does not inert as to the cause(s)
- Most appropriate cardiac marker and criterion to define acute myocardial infarction, according to AHA/ACC recommendations
- Conveys prognostic information incremental to clinical characteristics
- Risk stratification in patients with coronary artery disease
- Levels correlate to infarction size
- Large diagnostic window (2 hours – 15 days)

Cardiac Muscle Contraction regulated by Troponin Complex
Troponin Structure
- Troponin complex made up of 3 protein subunits attached to tropomyosin on the actin filament
- Essential for the regulation of striated muscle contraction
- Calcium mediated
- Troponin T and I have different isoforms that are coded by separate genes in cardiac and in skeletal muscle

Defining Myocardial Infarction
Historical Perspective

2012 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 reference limit 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

WHO develops a definition of AMI to track prevalence and prognosis
- Initially only clinical symptoms and ECG changes were included with markers of myocardial necrosis as secondary criteria
- CK and CK-MB are the “gold standard” biomarkers for the definition of cardiac injury
- Troponin T Assay (Boehringer Mannheim) & Troponin I Assay (Dade Behring) approved by FDA
- Consensus committee statement of the Joint European Society of Cardiology and the American College of Cardiology (ESC/ACC) redefinition of MI: Implied that any necrosis in the setting of myocardial ischemia should be labeled as an MI. Cardiac Troponin T or I as the preferred Biomarker for diagnosis of MI.
- Global Task Force further refined the definition of MI and emphasized the different conditions which might lead to an MI
- The Third Universal Definition of MI

2012
- Troponin T – Inhibitory protein inhibiting actin and myosin interaction
- Troponin I – Calcium-binding subunit of the troponin complex
- Troponin C – Binding protein stabilizing complex to tropomyosin

3/30/2016

38
Interpretation of Troponin Elevations

Thresholds / Cutoffs

- 97th Percentile
- 99th Percentile
- 10% CV
- 10% or 20% CV

Practical Considerations – Interpretation of Troponin Elevations

Evolving Universal Definition of Myocardial Infarction: Thresholds

Adapted from Fox, Keith AA, “High Sensitivity Troponin, Strengths and Weaknesses” Presented @ ESC Congress 26-08-2012

The 99th percentile of a health reference population is...

Prevalence and Determinants of Troponin T Elevation in the General Population


Troponin T Elevations in the General Population

cTnT was undetectable among healthy subjects in the Dallas Heart Study

Interpretation of troponin elevations

Importance of serial troponin sampling

Non ACS Troponin Elevations

Injury related to supply/demand

Of myocardial ischemia

- Heart failure
- Stress (isotrobutyl) cardiopulmonary
- Severe pulmonary embolism or pulmonary hypertension
- Sepsis and critically ill patients
- Renal failure
- Severe acute neurological disorders, for example, stroke, subarachnoid hemorrhage
- Infiltrative diseases, for example, amyloidosis, sarcoidosis
- Steroids/exercise

Injury not related to myocardial ischemia

- Cardiac contusion, surgery, ablation, pacing or defibrillator shocks
- Rhodopathy with cardiac involvement
- Myocarditis
- Cardiotoxic agents, for example, anthracyclines, trastuzumab (Herceptin)

Multifactorial or indeterminate myocardial injury

Non ACS Troponin Elevations

Adapted from Fox, Keith AA, “High Sensitivity Troponin, Strengths and Weaknesses” Presented @ ESC Congress 26-08-2012

White et al., Clinical Implications of 3rd Definition of MI. Heart 2013.


Release pattern of Troponin:
- Peak during 24 hrs
- Subsequent fall to undetectable levels
- Prolonged release lengthens diagnostic window:
  - Troponin T: 7 – 14 days
  - Troponin I: 7 – 10 days

French, J.K. and White, H.D., Heart 2004; 90:99-106
Sodi R., Advances in Clinical Chemistry 2006; 41;49-122


Interpretation of troponin elevations

- Kinetic pattern of cardiac markers: rise and fall patterns
- • Troponin levels are of value when they contribute to accurate diagnosis or inform prognosis.
  - Clinically useful Interpretation of Tn levels in:
    - Chronic Kidney Disease (CKD)
    - Heart Failure
    - Pulmonary Embolism (PE)
    - Chemotherapy-Associated Cardiac Toxicity
    - Sepsis

Nonischemic Troponin Elevations

Kidney Disease

“Cardiac Troponins and Renal Function in Nondialysis Patients with Chronic Kidney Disease”

- Aim: Assess Troponin concentrations in CKD patients not on dialysis
- Methods: N=222, follow-up 19 months, CKD Stages 3-5, Echocardiogram
- Results:
  - TnT levels above 99th Percentile in 43% of patients vs 18% with TnI
  - TnT and TnI are more commonly increased in presence of more severe CKD
  - Decreasing GFR increased odds of having detectable TnT but not TnI
  - TnT is a marker of decreased survival


Nonischemic troponin elevations

Kidney disease

TnI-Ultra did not differ significantly between CKD stages (p = 0.6)

A significant proportion of patients had TnI elevations.

“Cardiac troponin I concentration is commonly increased in nondialysis patients with CKD: Experience with a sensitive assay”

Detectable Levels of Troponin are Prognostic

Pulmonary Edema
Non-Cardiac, Critically Ill Patients
Postoperative Vascular Surgery

10th Percentile
99th Percentile

The Usefulness of Troponin in Clinical Decision Making in Acute Coronary Syndrome

FRISC II investigators: “Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomized multicenter study.”
Lancet 1999; 354: 708-718

3,048 patients


2,220 patients


7,800 patients

Commercially available cardiac troponin T test is FDA-cleared for:

Differential diagnosis of acute coronary syndrome to identify cell necrosis as seen in acute myocardial infarction
Risk stratification of patients presenting with acute coronary syndrome
Determining cardiac risk in patients with chronic renal failure
Selection of more intensive therapy and intervention in patients with elevated levels of cardiac troponin T

NEJM 2001; 344: 1879-87

Verification of FRICS II findings in GUSTO IV

Sensitivity of Troponin T for Detection of Death and MI at 30 Days in FRISC II and GUSTO IV

Risk Stratification in ACS Patients

30 Day risk of Death or MI in the GUSTO IV Trial

Extent of CAD in FRISC II

Elevated troponin levels and ECG changes reflect multi- vessel disease

TACTICS TIMI 18 and Clinical Implications

47% Reduction in Death and MI at 30 days

Points to Consider When Discussing Troponin Assays

- Both TnT and TnI are cardiac specific antigens
- Troponin assays are not the same. They should be treated as different analytes
- Clinical utilities reported in literature are not applicable to every troponin assay
- No correlation among different TnI assays can be expected unless they use the same antibody pairs
- Core lab and POCT assays should use the same antibodies to ensure agreement in results.

Natriuretic Peptide and Troponin Testing

Conclusions

- Practice Guidelines play a key role in the diagnosis and management of both Heart Failure and ACS
- Troponin and Natriuretic Peptides play a crucial role in the aid in diagnosis and prognosis of these disease processes
- Individually Troponin and Natriuretic Peptides provide diagnostic and risk stratification information for patients with Acute Coronary Syndrome and Heart Failure in both the acute and chronic setting
- Troponin and Natriuretic Peptide levels are not stand-alone tests. It is always of greatest value when they complement the clinician’s clinical skills along with other available diagnostic tools.