Figuring Troponin into the Acute Evaluation of Chest Pain

W. Frank Peacock, M.D., FACEP
Professor, Emergency Medicine
Cleveland Clinic
2000 .... Troponin in the ED

- 257 patient ED OU study
- Low risk patients
  - Non-diagnostic ECG
  - Initial marker negative

- Troponin had poor performance for predicting acute adverse events

  Specificity 99.2%

  Sensitivity 9.5%

Peacock WF. Ann EM. 35(3); 213-20, 2000.
• **Emergency docs**
  – This **bogus assay** is useless in almost all patients
  – Only helpful if positive
    • Rarely positive, <5% of chest pain
      – The rest of chest pain requires other testing

• **Cardiologists own troponin**
  – Tactics-TIMI 18
  – IF it is detectable, it is an MI, otherwise forget it
  – If positive, **don’t even bother thinking**, just call the cath lab
Acute Cardiac Ischemia in the ED

10,869 patients

17% Total ACS

83% some other diagnosis (55% non-cardiac)

Pope JH. NEJM 2000;342:1163-70
ACEP Marker Recommendations

• **Level A recommendations**
  Don’t use markers to exclude non-AMI ACS (ie, unstable angina)

• **Level B recommendations**
  Use any of the following to exclude NSTEMI

  • **8-12 hours after symptom onset**
    – A single (-) CK-MB mass, TnI, or TnT

  • **Serial measures if < 8 hours after symptom onset**
    – Baseline and 90 mins
      » A (-) myoglobin with a (-) CKMB, or (-) Tn
    – (-) 2-hour delta
      » CK-MB and Tn
European Society of Cardiology

- A Tn @ presentation cannot R/O NSTEMI
  - Repeated Tn 6-12 hours after admission or more CP.
  - May skip 2\textsuperscript{nd} sample if no suspicious findings, and CP was > 12 hours earlier

- Tn is preferred over CKMB
- Myoglobin is not specific or sensitive enough
  - Is not recommended.
Where exactly are we going to repeat all these crazy troponins?
At What Costs?

• Some centers report 98% of all CPC test results are negative\(^1,2,3,4,5\)

• The math is obvious:
  – Emergency physicians overcome the sensitivity deficit by admitting nearly all patients with chest pain.

The other reason for CPC success
High Sensitivity Troponin

“When troponin was a lousy assay it was a great test, but now that it’s becoming a great assay, it’s getting to be a lousy test.”

Bob Jesse, UCSD Marker conference, 2008
You can’t have it both ways…
Myocardial Infarction
It’s a changing world

• An MI used to be
  – >40 and sweating with chest pain

• Now
  – It aint >40
  – It aint sweating
  – It aint even chest pain
In 2011, you will miss 423,600 Acute Myocardial Infarction’s 
1/3 have no chest pain
When your laying around the ER, everybody looks the same......

This one is having an AMI
It would be really great if they had it written on their forehead!!
Early Risk Stratification of NSTE ACS

<table>
<thead>
<tr>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td></td>
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</tbody>
</table>

- **12-lead ECG (within 10 minutes)**

- **Troponin or CK-MB assay**
  - Immediate
  - Repeated within 8-12 hrs of sx, if negative

- **Repeat ECG if negative and clinical suspicion is high for ACS**

- **TIMI or GRACE Risk Scoring**

- **BNP, CRP for risk assessment**

- **Search for non-coronary causes of symptoms**

TIMI Risk Score

- Risk factors:
  - Age $\geq$ 65 years
  - $\geq$ 3 risk factors for CAD
  - Prior coronary stenosis $\geq$ 50%
  - ST-segment deviation on ECG
  - $\geq$ 2 anginal events in last 24 hours
  - Use of ASA in last 7 days
  - Elevated serum cardiac markers CK-MB or troponin

Each risk factor is assigned 1 point, and the total represents a given patient’s TIMI Risk Score. Event rates (all-cause mortality, MI, or urgent revascularization) increase with each 1-point increase in score ($P<0.001$ by chi square test for trend)

He is a 67 year old, hypertensive, obese man. He took an aspirin this morning, he still smokes and has high cholesterol. Many of his family have CAD. He has been a diabetic for 15 years, and 4 years ago he had an MI.

Age > 65, 3 risk factors, H/O MI, took asa: TIMI Risk score = 4

19.9% chance of death, MI, or UTVR in the next 14 days

George is sitting in his bar at his restaurant across the street from the Emergency Department.
He is a 67 year old, hypertensive, obese man. He took an aspirin this morning, he still smokes and has high cholesterol. Many of his family have CAD. He has been a diabetic for 15 years, and 4 years ago he had an MI.

TIMI Risk score = 4

19.9% chance of death, MI, or UTVR in the next 14 days

George is laying in the ED, diaphoretic, with crushing CP, nauseated, BP = 100/70
Closing Time

- You don’t have to go home, but you can’t stay here....
  - Green Day
The challenge

Admit them all:
and let the insurance company sort them out...

Discharge them all:
and let God sort them out...
Consequences............

- What happens to an emergency doc who gets it wrong.....?
Miss it again...

- Where does a high risk ER doc go..
The Now and Then of High Sensitivity Troponins

**Last decade**
- Detectable Tn
  - 99th %ile cutpoint
- Worse specificity
- Better sensitivity
  - No real clinical disposition impact
- Serial testing of less value
  - Allow early MPI?

**Next decade**
- Good bye specificity
  - 2 cutpoints?
  - Second marker
    - copeptin, ST-2, MPO, IMA, etc
- Hello sensitivity
  - Exclude ischemia?
- Challenges
  - The role of cardiology consults
  - EDUCATION.............
Chest Pain at Presentation

Current Troponin
- 88% Negative
- 12% ACS

High Sensitivity Troponin
- 75% Negative
- 25% Gonna die of something
Tn Elevation w/o Overt Cardiac Ischemia

- Trauma
  - contusion, ablation, pacing, ICD firings, cardioversion, endomyocardial biopsy, cardiac surgery, interventional closure of ASDs
- CHF
- Aortic valve disease and HOCM with significant LVH
- HTN
- Hypotension, often with arrhythmias
- Postoperative noncardiac surgery patients who seem to do well
- Renal failure
- Critically ill patients, esp with diabetes, respiratory failure, gi bleeding, sepsis
- Drug toxicity, eg adriamycin, 5 FU, herceptin, snake venoms, carbon monoxide poisoning
- Hypothyroidism
- Abnormalities in coronary vasomotion, including coronary vasospasm
- Apical ballooning syndrome

- Inflammatory diseases
  - myocarditis, eg. Parvovirus B19, Kawasaki disease, sarcoid, smallpox vaccination, or myocardial extension of BE
- Post PCI patients who appear to be uncomplicated
- Pulmonary embolism, severe pulmonary hypertension
- Sepsis
- Burns, esp if TBSA > 30%
- Infiltrative diseases including amyloidosis, hemachromatosis, sarcoidosis and scleroderma
- Acute neurological disease
  - CVA, subarchnoid bleeds
- Rhabdomyolysis with cardiac injury
- Transplant vasculopathy
- Vital Exhaustion
Tn, it's not just for AMI anymore

**State-of-the-Art Paper**

**Exercise-Induced Cardiac Troponin Elevation**

Evidence, Mechanisms, and Implications

Rob Shave, PhD,* Aaron Baggish, MD,† Keith George, PhD,‡ Malissa Wood, MD,‡ Jurgen Scharbag, MD,§ Gregory Whyte, PhD,‡ David Gazze, PhD,‖ Paul D. Thompson, MD‖

Middlesex, Liverpool, and London, United Kingdom; Potsdam, Germany; Boston, Massachusetts; and Hartford, Connecticut

**Elevated Cardiac Troponin I in Sepsis and Septic Shock:**

No Evidence for Thrombus-Associated Myocardial Necrosis

David R. Altmann1, Wolfgang Korte2, Micha T. Maeder3, Thomas Fehr4, Philipp Haager1, Hans Rickli5, Gian-Reto Kleger6, Regulo Rodriguez7, Peter Ammann8

**European Heart Journal (2010) 31, 1836–1844**

doi:10.1093/eurheartj/ehq234

**FASTTRACK**

Thrombosis and antithrombotic therapy

Highly sensitive troponin T assay in normotensive patients with acute pulmonary embolism

Mareike Lankeit1, Dietrich Friesen1, John Aschoff1, Claudia Dellas1, Gerd Hasenuß1, Hugo Katus2, Stavros Konstantinides1, and Evangelos Giannitsis2
Cardiologists are in a tizzy
- All these “false positives”

Acute Care docs think this is great
- There is no such thing as a false positive when you’re talking about being DEAD
Which one of these people is going to die??
Low Level Troponins
One Cut-off or Two?

- Myocardial necrosis
-AMI Sp=99%
-AMI Sp=85%
-Wait and see, do more tests
How do we sort out this mess?

- Do we really gotta be doing serial troponins anymore?
- All these positive troponins that may/may not be AMI
Do we really gotta be doing serial troponin’s anymore???
How do we sort out this mess?

• All these positive troponins that may/may not be AMI

• Multimarkers
  – Delta Myoglobin, CKMB

• MPI
  – Bedside echo

• CTA
Early MPI or CTA
• **The decade of 2000-10**
  – Will be remembered as when the cardiologists owned troponin
    • Used to be an MI marker
      – Those days are gone

• **Acute Care**
  – Taking troponin back from the cardiologists!
  – IT IS NOT AN AMI MARKER ANYMORE
    • Now it’s a 14 day death marker
      – I don’t care about 30 days or 180 days from now
      – I **REALLY** don’t care about a year from now
So next time you get a detectable troponin....

- Put on your thinking cap!
- You want to send that patient home??
- How’s the next 2 weeks looking?
  - Who cares about the next yr if your dead in 2 weeks?
Increase in ED visits /year

400 beds

2011 perspectives: 60,000

56,000 in 2009-2010

46,088 in 2007

42,531 ED visits in 2006
Emergency Department Overcrowding

Spirivulis P.C. et Al. . The association between hospital overcrowding and mortality.

The Medical Journal of Australia 2006; 184; 184 ( 5 ): 208 - 212
Importance of early therapies as consequence of prompt diagnosis

- In 46,599 patients with ADHF (ADHERE)
- a delay in Treatment was associated with:
  - 250% ↑ in acute mortality;
  - 150% ↑ in Hospital length of stay

ED Overcrowding: Throughput related solutions

Twanmoh J.R. et Al. . When overcrowding paralyzes an ED. Manag Care 2006; 15 (6): 54-59

Laboratory: Fast and usefull
BIOMARKERS
Flow-chart for the diagnosis of HF in untreated patients with symptoms suggestive of HF using natriuretic peptides

Clinical examination, ECG, Chest X-ray, Echocardiography

Natriuretic peptides

- BNP < 100 pg/ml
  - NT-proBNP < 400 pg/ml
  - Chronic HF unlikely

- BNP 100-400 pg/ml
  - NT-proBNP
  - Uncertain diagnosis

- BNP > 400 pg/ml
  - NT-proBNP > 2000 pg/ml
  - Chronic HF likely

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ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure
Myocardial Function

Rehospitalizations Times

Gheorghiade M, Acute Heart Failure Syndrome (Am J Cardiol suppl. vol.96, 2005)
NT Pro BNP serial assessments

S. Di Somma et al.  AJEM (2007) 25,335-339
Figure. Percentage variation of B-type natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide and (NTproBNP) after treatment in patients with acute decompensated heart failure from admission to discharge.

In-hospital brain natriuretic peptide and N-terminal prohormone brain natriuretic peptide variations are predictors of short-term and long-term outcome in acute decompensated heart failure

Salvatore Di Somma*, Laura Magrini and Enrico Ferri

See related research by Noveanu et al., http://ccforum.com/content/15/1/R1

Abstract

Acute decompensated heart failure is one of the most important causes of hospitalisation worldwide. Natriuretic peptides have shown their usefulness in the diagnosis and management of heart failure. Their variations during hospitalisation also appear useful to predict outcomes. In particular, data from the literature demonstrate that reduction from admission to discharge of brain natriuretic peptide and N-terminal prohormone brain natriuretic peptide in these patients is a predictor of future cardiovascular events.
NPs Prognostic value: In Hospital BNP variations after treatment and Prognosis: The Italian RED study

Prabability of new cardiovascular events or rehospitalitation

S. Di Somma, A. Maisel et al. Critical Care 2010
Emergency overcrowding: an incurable disease?

Angel Estella*

See related review by Forero et al, http://ccforum.com/content/15/2/216

Figure 1. Flows of input and output in an emergency department.
BNP Levels for Patients With vs. Without Events

- Without Events
- With Events

p < 0.007

S. Di Somma et al. 2011 in preparation
Comparison between BNP fingerstick and BNP triage

The graph shows the correlation between BNP standard and BNP fingerstick measurements with a correlation coefficient $r=0.95$ and $p<0.0001$. This indicates a strong positive correlation between the two methods.
Heart Failure Home monitoring with BNP
• Atrial Fibrillation
• eGFR <60 mL/min
• Flash pulmonary edema
• Acute mitral value
• Obesity (BMI >35 Kg/m2)
• Mitral stenosis
• Constrictive pericarditis
Figure 1  Comparison of Diagnostic Biomarkers

(A) Receiver-operating characteristic curves for B-type natriuretic peptide (BNP) (green line), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (red line), and mid-regional pro-atrial natriuretic peptide (MR-proANP) (blue line) for detecting acute heart failure. (B) Spearman’s correlation between BNP and MR-proANP. AUC = area under the curve; CI = confidence interval.

Table 2  Acute Heart Failure Diagnostic Performance of MR-proANP Cut at 120 pmol/l and BNP Cut at 100 pg/ml

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Accuracy (95% CI)</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP 100 pg/ml</td>
<td>95.6% (93.6–97.0)</td>
<td>61.9% (59.0–64.8)</td>
<td>73.6% (71.4–75.6)</td>
<td>96.4%</td>
<td>57.0%</td>
</tr>
<tr>
<td>MR-proANP 120 pmol/l</td>
<td>97.0% (95.2–98.2)</td>
<td>59.9% (56.4–62.8)</td>
<td>72.7% (70.5–74.8)</td>
<td>97.4%</td>
<td>56.0%</td>
</tr>
<tr>
<td>Difference</td>
<td>−1.4%</td>
<td>2.1%</td>
<td>0.9%</td>
<td>−1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Noninferiority p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; CI = confidence interval; MR-proANP = mid-regional pro-atrial natriuretic peptide; NPV = negative predictive value; PPV = positive predictive value.
Procalcitonin (PCT) algorithm for respiratory tract infections

<table>
<thead>
<tr>
<th>PCT (µg/l)</th>
<th>Bacterial infection?</th>
<th>Recommendation antibiotics</th>
<th>Important considerations and overruling criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Very likely</td>
<td>AB YES!</td>
<td>- Consider the course of PCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- If antibiotics are initiated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Repeat PCT on days 3, 5 and 7; stop antibiotics using the same cut offs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- If peak PCT are very high then stop when 80–90% decrease of peak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- If PCT remains high, consider treatment failure</td>
</tr>
<tr>
<td>0.5</td>
<td>Likely</td>
<td>AB Yes</td>
<td>- If antibiotics are withheld, control PCT after 6–24 h</td>
</tr>
<tr>
<td>0.25</td>
<td>Unlikely</td>
<td>AB No</td>
<td>- Initial antibiotics can be considered in case of</td>
</tr>
<tr>
<td>0.1</td>
<td>Very unlikely</td>
<td>AB NO!</td>
<td>- Respiratory or hemodynamic instability, severest comorbidities, ICU admission</td>
</tr>
<tr>
<td>0.01</td>
<td></td>
<td></td>
<td>- PCT &lt;0.1 µg/l: CAP with PSI V or CURB &gt;3, COPD with GOLD IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- PCT 0.1–0.25 µg/l: CAP with PSI IV &amp; V or CURB &gt;2, COPD with GOLD III &amp; IV</td>
</tr>
</tbody>
</table>

*Expert Rev. Anti Infect. Ther. 8(5), (2010)*
MR-proANP and PCT can be used to diagnose patients with AHF and/or Pneumonia:

A. Maisel, Di Somma et al in preparation
Kaplan-Meier survival curves by quartiles of MR-proADM for 568 patients with acute heart failure

Cumulative survival %

Maisel A, Di Somma S: et al. JACC 2011
Acute Cardio-Renal Syndrome

Ronco C. et al. JACC 2008,52
Heart failure: the cytokines hypothesis

**Figure 1. The Cytokine Hypothesis of Heart Failure.**

- Sympathetic nervous system
- Stimulation
- Natriuretic peptides
- Cytokines
- Cytokines impairing myocardial function
- Activated monocyte
- Proinflammatory cytokines
- Damaged myocardium
- Hypoperfused skeletal muscle
- Release into bloodstream

**Graph:**
- IL18 pg/ml vs. BNP pg/ml
- Correlation coefficient: $r=0.476$, $p=0.0076$

*S Di Somma et al. 2011*
IL-18 induced ProBNP expression in human cardiomiocyte culture

S Di Somma et al. 2011
## AKI Differential Diagnosis

<table>
<thead>
<tr>
<th>Decreased (Glomerular) Function</th>
<th>Damage (Tubular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Severe Hypovolemia</td>
<td>Ischemia/Reperfusion</td>
</tr>
<tr>
<td>Early Hepatorenal Nephrotic Syndrome</td>
<td>Late Hepatorenal</td>
</tr>
<tr>
<td>Early Cardiorenal</td>
<td>Late Cardiorenal</td>
</tr>
<tr>
<td>Early Sepsis</td>
<td>Late Sepsis</td>
</tr>
<tr>
<td></td>
<td>CI-AKI</td>
</tr>
<tr>
<td></td>
<td>Acute Vasculitides</td>
</tr>
<tr>
<td></td>
<td>Acute Glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>Interstitial Nephritis</td>
</tr>
<tr>
<td>Late Nephrotoxicity</td>
<td>Early Nephrotoxicity</td>
</tr>
</tbody>
</table>
AKI Differential Diagnosis

**Decreased Function**
- Hypo-volemia (bleed)
- Early CardioRenal
- Early HRS
- Isolated Nephrotic
- Early Sepsis

**Ischemia/Reperfusion**
- Late Cardio Renal
- Late HRS
- Late Nephrotoxicity
- Late Sepsis

**Tubular Damage**
- Acute Vasculitis
- Acute GN
- AIN
- Early Nephrotoxin
- CI-AKI

**Renal Reserve**

**Biomarker Findings**
- BM-/Cr+
- BM+/Cr+
- BM+/Cr-

**Functional**
- FENa (<1%)
- FEUrea (<35%)
- ↑ RTE/MBCs
- ↑ U Osm (<500)

**Structural**
- NGAL (mid range)
- IL-18 (mid range)
- NGAL (>2000)
A single measurement of urinary NGAL distinguished AKI from other forms of kidney dysfunction in ED.

ROC curves for AKI

- prob AKI=10%
  - sens=0.854
  - spec=0.838

- prob AKI=15%
  - sens=0.688
  - spec=0.907

AUC +/- 95% CI
- 0.837 +/-0.063 Clinical judgment
- 0.799 +/-0.071 NGL at 0H
- 0.887 +/-0.055 Clinical judgment & NGL at 0H

Admission (0H) NGAL versus final disposition

Sample sizes

Unknown: 9
Discharged: 169
Expired: 24
Hospital: 52
Left against medical advice: 3
Other: 2
ICU: 11
Monitored bed: 102
Unmonitored bed: 294
AHF: Biomarkers in Acute Medicine for Fun and Outcomes

- NPs (BNP, NTproBNP, MRproANP);
- PTC;
- MRproADM;
- NGAL....
HF Risk Stratification: Who really cares?

W. Frank Peacock IV, MD
Vice Chief, Emergency Medicine
Department of Emergency Medicine
The Cleveland Clinic
Cleveland, Ohio
Risk Stratification

1) What is the probability the patient has Heart Failure?

2) If the patient has Heart Failure, what is probability that they will have a bad outcome?
Bob Dole Has ED!
Heart Failure Hospitalizations

Number Increasing in Both Men and Women

CDC/NCHS: hospital discharges include patients both living and dead.
AHA. Heart Disease and Stroke Statistics—2005 Update.
HF Admissions

ADHERE: n=150,745

ED 78%

Inpatient Unit 20%

Inpatient Unit on Observation 1%

ADHERE Registry Data.
Hospital Visits for Heart Failure

ED Presentations

Initial episode 21%

Repeat visit 79%

Rates of Hospital Readmission

- 2% within 2 days
- 20% within 1 month
- 50% within 6 months

~80% of ED visits for HF result in hospitalizations

*Requires full evaluation for reversible causes of HF

# Economic Impact of a Missed HF Diagnosis at Admission

<table>
<thead>
<tr>
<th>Length of Stay</th>
<th>Lost Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Missed Dx patients had 0.9 longer LOS</td>
<td>• 20% coded DRG 088</td>
</tr>
<tr>
<td>• $900 to 1200 higher cost/patient</td>
<td>- COPD</td>
</tr>
<tr>
<td></td>
<td>• 18% coded DRG 099</td>
</tr>
<tr>
<td></td>
<td>- Respiratory Signs &amp; Symp</td>
</tr>
<tr>
<td></td>
<td>• ~ $1200 loss per patient</td>
</tr>
<tr>
<td></td>
<td>• ~ $2100 less per patient</td>
</tr>
</tbody>
</table>

Based on study at UCMC, Christ Hospital, Jewish Hospital, Cleveland Clinic. Generalized to HF population of 1,000.
# How good is the H&P?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of HF</td>
<td>62</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>56</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>47</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>Rales</td>
<td>56</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>S3 (auscultation)</td>
<td>20</td>
<td>99</td>
<td>66</td>
</tr>
<tr>
<td>JVD</td>
<td>39</td>
<td>94</td>
<td>72</td>
</tr>
<tr>
<td>Edema</td>
<td>67</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

• Excessive rapid filling of a stiff ventricle is suddenly halted, causing vibrations that are audible as the S3.
  – Joshi, 1999

• CHF patients w/ an S3 (597/2479) at greater risk for:
  – HF hospitalization
  – death from pump failure
  – composite of death or hospitalization.

• S3
  – 99% specificity for the diagnosis of CHF.
$S_3/S_4$ vs Decade of Life
Digital HS Analysis

Collins S, et al, HFSA
Pharmacologic Actions of Endogenous hBNP

Hemodynamic (Balanced vasodilation)
- Veins\(^1\)
- Arteries\(^1\)
- Coronary arteries\(^2\)

Neurohumoral
- Aldosterone\(^3\)
- Endothelin\(^2\)
- Norepinephrine\(^3\)

Renal\(^1\)
- Diuresis
- Natriuresis

Cardiac
- Lusitropic\(^4\)
- Antifibrotic\(^5\)
- Antiremodeling\(^5\)

Natriuretic Peptide Teleology

Fish ANP
~ 800 pg/mL

Human BNP
< 100 pg/mL
BNP in Dyspnea
Secondary to CHF or COPD

Figure 3. Relationship between B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP and New York Heart Association (NYHA) functional classification. Data from Roche Diagnostics and Biosite Inc.
• BNP & CrCL w/ & w/o HF

• Excluded CrCl<15 & dialysis patients

BMI and BNP

- 634 w/ HF

![Graph showing BMI and BNP relationship]

JACC 2003:138A
BNP Levels in Clinical Use

- **Low BNP** (< 50-100 pg/mL)
  - The symptoms are NOT due to HF
  - Think of a different dx (COPD, etc)

- **Medium BNP** (100 to 500 pg/mL)
  - Consider the differential (PE, PPH, etc)
  - Compare prior BNP levels

- **High BNP** (>500 pg/mL)
  - HF likely, but you’d better think about it
Impact of BNP Assay on Accuracy

ADHERE: Initial BNP vs. Acute Mortality

<table>
<thead>
<tr>
<th>BNP Quartiles</th>
<th>In Hospital Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 &lt;430</td>
<td>1.9 (n=12,161)</td>
</tr>
<tr>
<td>Q2 430-839</td>
<td>2.8 (n=12,146)</td>
</tr>
<tr>
<td>Q3 840-1729</td>
<td>3.8 (n=12,156)</td>
</tr>
<tr>
<td>Q4 &lt;1730</td>
<td>6.0 (n=12,161)</td>
</tr>
</tbody>
</table>

P<0.0001

Likelihood Ratios for Primary ADHF

<table>
<thead>
<tr>
<th>Condition</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP &lt; 100</td>
<td>0.11</td>
</tr>
<tr>
<td>S3 alone</td>
<td>2.9</td>
</tr>
<tr>
<td>BNP 100-500</td>
<td>5.4</td>
</tr>
<tr>
<td>S3 and BNP 100-500</td>
<td>7.2</td>
</tr>
<tr>
<td>S3 and BNP &gt; 500</td>
<td>9.4</td>
</tr>
</tbody>
</table>

N = 343

Positive Likelihood = Rule In Power
Negative Likelihood = Rule Out Power

ADHF Unlikely

ADHF Likely

Collins et al.
Time Dependency: It’s Not a Hard Concept

Treat Early or Die

HYPOGLYCEMIA
HYPOXIA
VENTRICULAR TACHYCARDIA
MYOCARDIAL INfarCTION
CEREBRAL INfarCTION
PNEUMONIA

Where is Heart Failure?
Prehospital Effects

- 8,315 EMS runs
  - 499 HF
  - Overall Mortality = 10.9%

- Excluded BP < 100
- Tx = ntg, ms, lasix
- Linear rln btwn high BP & Tx

- Treated n=241
- Untx’d n=252

- If EMS Tx: 36 min sooner
- Scene time: 1.9 mins longer

If treated, OR of survival 2.51 (1.37-4.55) p<0.01

Early treatment works

106 non-HF final dx.....BUT tx’d for HF by EMS

- Asthma, COPD, pneumonia, bronchitis
- Represented 15% of dyspneic patients

Mortality (p<0.05)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HF treated for HF</td>
<td>13.6%</td>
</tr>
<tr>
<td>No treatment</td>
<td>8.2%</td>
</tr>
<tr>
<td>Treated with bronchodilators</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

46,599 ED ADHF

Vasoactive by location

4,096 in ED 1.1 hr
3,499 inpatient 22 hr

Mortality vs. Quartiles of Diuretic Time & BNP Level

Time to Diuretic

- <1.05
- 1.05-2.22
- 2.23-4.98
- >4.98

BNP pg/mL

- <449
- 450-864
- 865-1738
- >1738

Mortality
Prediction Tool
30-day mortality
N ~ 4,000 patients

If < 70 total points,
30 day mortality is <1%.

Lee DS, et al.
ADHERE CART: Predictors of Mortality

Highest to Lowest Risk Cohort
OR 12.9 (95% CI 10.4-15.9)

Cardiac Troponin and Outcome in Acute Heart Failure

W. Frank Peacock IV, MD, Teresa De Marco, MD, Gregg C. Fonarow, MD, Deborah Diercks, MD, Janet Wynne, MS, Fred S. Apple, PhD, and Alan H.B. Wu, PhD, for the ADHERE Investigators

In-hospital Mortality According to Troponin T Quartile

<table>
<thead>
<tr>
<th>Troponin T Quartile</th>
<th>No. of Patients</th>
<th>In-Hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\leq 0.01)</td>
<td>1773</td>
<td>1.7</td>
</tr>
<tr>
<td>&gt; 0.01-0.02</td>
<td>502</td>
<td>2.8</td>
</tr>
<tr>
<td>&gt; 0.02-0.06</td>
<td>1138</td>
<td>3.3</td>
</tr>
<tr>
<td>&gt; 0.06</td>
<td>1119</td>
<td>6.3</td>
</tr>
</tbody>
</table>

\(P < 0.001\)

Mortality According to Time in Hospital and Troponin Status at Presentation

<table>
<thead>
<tr>
<th>Days in Hospital</th>
<th>Cumulative Mortality (%)</th>
<th>P &lt;0.001*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>6</td>
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<td>13</td>
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<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dashed lines show 95% CI

In-Hospital Mortality Risk by Initial BNP and Troponin Levels

48,629 (63%) out of 77,467 pt episodes had BNP assessment at initial evaluation.
42,636 (87.6%) with troponin I or T along with BNP levels Q2 2003 to Q4 2004.

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP &lt; 840, Tn Neg</td>
<td>20,439</td>
</tr>
<tr>
<td>BNP &gt; 840, Tn Neg</td>
<td>19,827</td>
</tr>
<tr>
<td>BNP &lt; 840, Tn Pos</td>
<td>7,340</td>
</tr>
<tr>
<td>BNP &gt; 840, Tn Pos</td>
<td>16,266</td>
</tr>
</tbody>
</table>

P < 0.0001
OU Risk Stratification

Analysis of the following variables:

- Gender
- Age > 70 years
- Insurance status
- Diabetes
- HTN
- CHF
- Renal insufficiency
- CAD
- Ejection fraction <40%
- Systolic BP >160 (SBP)
- No ischemic or infarction ECG change (iECG)
- Cr< 2.5 mg/dl
- BUN<60 mg/dl
- Normal initial troponin
- Hct>30 mg/dl
- Sodium > 136 mEq/dl
- No pulmonary edema on CXR
- Initial pulse oximetry >90%

Results: N=499

27% of ADHF patients defined as “low risk” by the following independent variables:

- Significant variables from univariate analysis:
  - SBP > 160
  - No iECG
  - Normal initial Troponin I

- Significant variables after multivariate analysis:
  - SBP >160 and
  - Normal initial Troponin I

Diercks et al. J Cardiac Failure 2004;10(No 4 suppl):S118
Analysis of the following variables:

- Gender
- Age
- Details of medical Hx
- Clinical course
- Initial ED Systolic BP
- Treatment
- Disposition
- Laboratory data:
  - B-type natriuretic peptide
  - Cr
  - BUN
  - Hg
  - Sodium level

Results: N=385

Univariate analysis showed the following had statistically significant association with admissions:
- Elevated Cr
- Elevated BUN

Multivariate analysis showed only BUN > 30mg/dL had a significant relation to admissions

Burkhardt  Annals Emerg Med 2004;44:S99-S100
ED Dyspnea

Age > 40y, not clearly asthma

Possible HF?: Consider BNP [creatinine & BMI]
BNP < 100, 100-500, > 500

Disposition/Risk Stratification

Low
BUN < 30<sup>a</sup>
BP > 160 mmHg<sup>b</sup>
Tn (−)<sup>b</sup>

Gestaut

High
BUN > 43 mg/dL<sup>c</sup>
BP < 115 mmHg
Cr > 2.75 mg/dL

<sup>a</sup> Burkardt. AJEM. 2005.  
<sup>b</sup> Diercks. HFSA. 2004.  
<sup>c</sup> Fonarow. JAMA. 2005.
Summary: ED Dyspnea Rules

1) There are penalties for being wrong

2) There are penalties for being slow
   • You’ve got 4 hours…period.

3) All patients must go somewhere
   • Rules 1 & 2 still apply

4) Don’t bankrupt the house
   • Rules 1, 2 and 3 still apply
LEADIND EDGE TECHNOLOGY IN ACUTE CARE

Hear Failure Risk stratification: Who really Cares?

Prof. Salvatore Di Somma MD
Director and Chairman
Postgraduate School of Emergency Medicine

SOCIETY OF ACUTE MEDICINE, 5° INTERNATIONAL CONFERENCE
IMPERIAL COLLEGE LONDON, 29-30 SEPTEMBER 2011
**QuicK Intravascular Volume assessment: BNP + VENA CAVA INDEX**

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure SOB (n.24)</th>
<th>No Heart Failure SOB (n.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/ml)</td>
<td>675.5 ± 875.64 *</td>
<td>158.8 ± 184.28</td>
</tr>
<tr>
<td>CI (%)</td>
<td>33.81 ± 21.36 *</td>
<td>54.9 ± 34.9</td>
</tr>
</tbody>
</table>

**Graph:**
- BNP vs. Collapse
  - Correlation coefficient: R = 0.38
  - P < 0.05

**Table:**
- Diameter
  - Collapse Index
  - CVP

- **< 1.5 cm**
  - 100%
  - 0 - 5 mmHg

- **1.5 - 2.0 cm**
  - > 50%
  - 5 - 10 mmHg

- **1.5 - 2.0 cm**
  - 33 - 50%
  - 10 - 15 mmHg

- **2.0 - 2.5 cm**
  - 0 - 33%
  - 15 - 20 mmHg

- **> 2.5 cm**
  - > 20 mmHg

**Images:**
- Ultrasound images of RV and IVC.
Bio Impedance Vector Analysis: Assessment of Body fluid status

Electric alternating current flux of 800 microA and an operating frequency of 50 kHz
BIVA patterns

Major axis => tissue hydration, minor axis => soft tissue mass

Resistance

Piccoli A. Contrib. Nephrol. 2005
Levels of hydration on BIVA plot
Outcomes vs Vector Length in Hemodialysis

The multivariable RR of death

A vertical bar on the midpoint of the six vector magnitude intervals

**Shorter vector associated with greater death**

A  <200
B  200 to 250
C  250 to 300
D  300 to 350
E  350 to 400
F  ≥400 ohm/m

Solid circle = $P < 0.05$ RR
Open circle = ns

Pillon L. Kidney Int. 66, 1266–1271, 2004
Total Body Water in CHF

- 22 CHF patients
- Body composition measured by
  - Dual-energy X-ray absorptiometry (DXA)
  - Deuterium dilution
  - BIVA

• **Normally hydrated**
  – Tissue H2O 72.7% - 74.3%

• **Dehydration**
  – 72.7-71% = slight
  – 71-69% = moderate
  – <69% = severe

• **Hyperhydration**
  – 74.3 – 81% = slight
  – 81 and 87% = moderate
  – >87% = H2O overload
    • (sub clinical edema)
  – >87% = severe water overload
    • (tissue edema).
292 dyspneic patients
- 58.9% ADHF
  - BNP = 591.8 ± 501
- 41.1% Non-ADHF
  - BNP = 69.5 ± 42

BIVA + BNP best predictor of ADHF
- ROC = 0.989
  - (p<0.005)

Parrinello G,. J Cardiac Failure 14(8), 2008, 676-86
Effect of Diuretic treatment in ADHF patients: Monitoring BNP and Fluid content

BNP+BIVA variations and clinical improvement

Conclusions: “Our study confirms the hypothesis that combined BNP/BIVA sequential measurements help to achieve adequate fluid balance status in patients with ADHF and can be used to drive a “tailored therapy,” allowing clinicians to identify high-risk patients and possibly to reduce the incidence of complications secondary to fluid management strategies”.

Valle R. et al. Heart Failure Review 2011
B-Type Natriuretic Peptide and Non-Invasive Haemodynamics and Hydration Status Assessments in the Management of Patients with Acute Heart Failure in the Emergency Department

Rossella Marino,1,2 Laura Magrini,1,2 Enrico Ferri,1,2 Giulia Gagliano1,2 and Salvatore Di Somma1,2

1 Emergency Department, II Medical School University of Rome “Sapienza”, Sant’Andrea Hospital, Rome, Italy
2 Global Research on Acute Conditions Team Network Scientific Association (GREAT) Rome, Italy
Fig. 1. Mean B-type natriuretic peptide (BNP) and hydration during hospitalization. * p < 0.05.

Fig. 2. Mean B-type natriuretic peptide (BNP) and cardiac index (CI) during hospitalization. * p < 0.05.

Fig. 3. Mean cardiac index (CI) and hydration during hospitalization. * p < 0.05.

Fig. 5. Correlation of percentage variation between cardiac index (CI) and hydration (p < 0.05).
Case report: CS ♀ 78 yrs

- Dyspnea, Fatigue,
- **severe abdominal ascites**;

Anamnestic data: **Heart Failure** with moderate tricuspidal insufficiency, moderate mitral insufficiency; **Hypertension**; **bicameral PMK**; **mild chronic kidney failure**; primary hypothyroidism

BP: 135/65 mmHg, RR: 22/min,
HR: 60 bpm, SatO2 100%.
Conscious, pink skin.

**Colonnar leg edema**
Case report: CS ♀ 78 yrs

- Dyspnea, Fatigue,
- **severe abdominal ascites**;

**Anamnestic data:** Heart Failure with moderate tricuspidal insufficiency, moderate mitral insufficiency; Hypertension; bicameral PMK; mild chronic kidney failure; primary hypothyroidism

BP: 135/65 mmHg, RR: 22/min,
HR: 60 bpm, SatO2 100%.

Conscious, pink skin.

**Colonnar leg edema**
Diagnostic exams

**Creatinine:** 1.20 mg/dL (previous creatinine 1.7 mg/dl);

**Urea:** 34 mg/dl; **BNP:** 807 pg/ml; **Na** 135 mmol/L; **K** 4.40 mmol/L;

**Echocardiogram:** dTD 57mm, EF 50%. Bi-atrial dilation. Moderate mitral and tricuspidal insufficiency. PAPs 30 mmHg.

**BIVA:**

**Hydration index:** 90.1%
Failure of Additive Therapy for ADHF

- **Furosemide** 250 mg ½ i.v. bid
- **K+ Kanreonoate** 200 mg 1 i.v. bid
- **Nitroglicerin** 100 mcgr/min i.v.
- Carvediolol 6.25 mg bid
- Losartan 50 mg day
- LWMH 4000 U fl sc
- Tiroxin 50 mcgr 1 cp
No clinical improvement! ..but.. AKI from diuretic!

Creatinine serial measurements

NGAL serial measurements

..but.. AKI from diuretic!
Evaluating treatment efficacy in AHF: BiVA+BNP+NGAL

<table>
<thead>
<tr>
<th>Tests</th>
<th>Before paracentesis</th>
<th>After paracentesis</th>
<th>Discharge (48 h after paracentesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL ng/ml</td>
<td>233</td>
<td>148</td>
<td>141</td>
</tr>
<tr>
<td>BNP pg/ml</td>
<td>776</td>
<td>654</td>
<td>356</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>1.3</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Hydration (BIVA) %</td>
<td>90.1%</td>
<td>92%</td>
<td>84.2%</td>
</tr>
</tbody>
</table>

Fig. 1. A multimarker approach and BIVA before and after paracentesis and at discharge.

BIVA Caveats

- Accurate body position (limbs short circuit)
- Cannot distinguish Trunk compartments
  - pericardial, pleural, or abdominal effusion
  - diaphoresis, excessive hair
- Standardized for Caucasians
- Poor skin-electrode interface
- Uncooperative patient
- Electrical ground or interference
  - metal bed frame
For starting.....in Heart Failure how can I do my choise?

BNP ?
NGAL ?
BNP ?
BIVA ?
BIVA+BNP+NGAL : Value in the ER?

• **Good**
  – As accurate as the gold standard (total fluid overload assessment);
  – As accurate for AHF diagnosis, prognosis and treatment efficacy monitoring;

• **Fast**
  – 2.15 minutes;
  – Data precedes all other technology;
  – Easy and non-invasive;
  – **Can immediately institute therapy with increased accuracy.**
ADHF management in Acute Care: Different MDs means: different clinical decisions? Is Biomarkers +BIVA the solution?
Traslational research from basic science to clinical application and multidisciplinary approach: The biomarkers+technology is the solution?

www.Greatnetwork.org
Biomarkers and Technology in Acute Care should be used wisely

- They should be used as a tool together with clinical experience;
- You need to know:
- clinical indications,

A fool with a tool is still a fool...
Thank You!