The Dyspneic Patient in the ED
Which Biomarkers should we use and how
Diagnostic Biomarkers

BNP
Mid-region proANP
Procalcitonin
NGAL
NGAL
BIVA
Prognostic Biomarkers

Troponin
Adrenomedulin
ST-2
Acute Heart Failure
Magnitude of the Problem

• 1 million admissions annually in the U.S. (↑50% over the past 10 years)
• Most common admitting diagnosis for patients ≥ 65 years
• Hospitalization costs are considerable (>60% of amount spent on heart failure)
Dyspnea Pie
Heart Failure (45% of pie!)
Signs and Symptoms of HF

- Shortness of breath
- Edema
- Neck vein Distension
- S-3
A chest x-ray can NEVER rule out acute heart failure!

- Misses 20% of Echocardiogram proven cardiomegaly
- Even worse if done portable
- Diaphragm not well distended
“Well, Bob, it looks like a paper cut, but just to be sure. Let’s get an echo.”
How sure are we about the diagnosis of AHF?

What happens if we misdiagnose the acute breathless patient?

Dyspnea of respiratory origin

- Bronchodilators: 4%
- No therapy: 8%
- CHF Therapy: 14%

P < 0.05

Diagnostic Biomarkers

EMERGENCY PHYSICIAN

BNP
Procalcitonin
NGAL
BIVA
NT-proBNP? BNP?
Breathing Not Properly STUDY

The New England Journal of Medicine

VOLUME 347 JULY 18, 2002 NUMBER 3

RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE EMERGENCY DIAGNOSIS OF HEART FAILURE

ALAN S. MAISEL, M.D., Padma Krishnaswamy, M.D., Richard M. Nowak, MD, MBA; James McCord, MD; Judd E. Hollander, MD; Howard C. Herrmann, MD; Philippe G. Steg, MD; Philippe Duc, MD; Arne Westheim, MD, PhD; Torbjorn Omland, MD, PhD, MPH; Cathrine Wold Knudsen, MD; Alan B. Storrow, MD; William T. Abraham, MD; Sumant Lamba, MD; Alan H.B. Wu, PhD; Alberto Perez, MD; Paul Clopton, MS; Padma Krishnaswamy, MD; Radmila Kazanegra, MD; Alan S. Maisel, MD; for the BNP Multinational Study Investigators

B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure

Analysis From Breathing Not Properly (BNP) Multinational Study

Clinical Investigation and Reports
Accuracy is 90%

Optimal cut-off point determined @ 100 pg/mL

Positive predictive value = 75%

Negative predictive value = 90%

Clarification of Diagnosis & BNP

BNP reduces clinical indecision by 74%

43% Clinical

11% Clinical Evaluation
BNP levels adds to the physician’s ability
Cost-Effectiveness of BNP at ED: The BASEL Study


Biosite Triage BNP (in pg/mL)

€1,545 Savings/Patient

CLINICAL AND ECONOMIC IMPACT USING RAPID BNP TESTING

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n=227)</th>
<th>BNP Group (n=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients admitted to hospital</td>
<td>85%</td>
<td>75%</td>
</tr>
<tr>
<td>% patients in ICU</td>
<td>24%</td>
<td>15%</td>
</tr>
</tbody>
</table>

$8000

$6000

$2000

$0

11 days

8 days

$7,264

$5,410
You can’t win them all (ask R. Federer) : Caveats to NP testing

- Dry versus wet BNP
- Gray Zone
- Renal dysfunction
- Obesity
- Heart Failure with normal levels
BNP level = baseline BNP(dry) plus change due to increased volume(wet)
Obesity

- There appears to be a linear inverse relationship between BMI and NP levels.

- Patients who are obese (BMI >35kg/m²) should have their NP doubled to use the standard cut-points.

Maisel, Valle, Aspromente et Al EJHF 2009
Mean BNP by eGFR - you can still diagnose heart failure

McCullough PA, Maisel AS et al. For the BNP Multinational Study Investigators. American Journal of Kidney Disease 2008

cGFR, ml/min/1.73 m$^2$
Normal levels of BNP

- Heart failure
  - Flash pulmonary edema
  - Acute atrial fibrillation
  - Acute papillary muscle rupture

- Mistaken for HF
  - Cardiac Tamponade
  - Constrictive pericarditis
Mortality vs. Diuretic Time & BNP Level
N=14,900
Diagnostic Biomarkers

- BNP
- Mid-region proANP
- Procalcitonin
- NGAL
- BIVA
The Mid- regional assay detects the corresponding prohormone fragment: midregional pro-anp

- can be easily measured by standard sandwich immunoassay technology
- MR-proANP is a reliable surrogate marker of the mature hormone

Peptides are instable in vivo and ex vivo, therefore not suitable for clinical diagnosis.

Mid-Region Prohormone Markers for Diagnosis and Prognosis in Acute Dyspnea

Results From the BACH (Biomarkers in Acute Heart Failure) Trial

Alan Maisel, MD,*## Christian Mueller, MD,† Richard Nowak, MD,‡ W. Frank Peacock, MD,§ Piotr Ponikowski, MD, PHD,¶ Martin Mockel, MD,¶¶ Christopher Hogan, MD,# Alan H. B. Wu, PHD,** Mark Richards, MD, PHD,†† Paul Clopton, MS,* Gerasimos S. Filippatos, MD,‡‡ Salvatore Di Somma, MD,§§ Inder Anand, MD, DPHIL (OXON.),||| Leong Ng, MD,¶¶ Lori B. Daniels, MD, MAS,## Sean-Xavier Neath, MD, PHD,## Robert Christenson, PHD,*** Mihael Potocki, MD,† James McCord, MD,‡ Garret Terracciano, BS,††† Dimitrios Kremastinos, MD,‡‡ Oliver Hartmann,‡‡‡ Stephan von Haehling, MD,** Andreas Bergmann, PhD,¶¶¶ Nils G. Morgenthaler, MD, PHD,¶¶¶ Stefan D. Anker, MD, PHD¶¶¶ San Diego and San Francisco, California; Basel, Switzerland; Detroit, Michigan; Cleveland, Ohio; Wroclaw, Poland; Berlin, Germany; Richmond, Virginia; Christchurch, New Zealand; Athens, Greece; Rome, Italy; Minneapolis, Minnesota; Leicester, United Kingdom; Baltimore, Maryland
## Gray Area Analysis

<table>
<thead>
<tr>
<th>Subgroup Measure</th>
<th>Subgroup Criterion</th>
<th>n</th>
<th>MR-proANP adds to BNP</th>
<th>MRproANP adds to NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR per log(_{10})</td>
<td>p</td>
</tr>
<tr>
<td>BNP</td>
<td>≥ 100 and &lt; 500</td>
<td>490</td>
<td>5.7</td>
<td>0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>≥ 300 and &lt; 900</td>
<td>228</td>
<td>16.1</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>≥ 300 and &lt; 450 if age &lt; 50</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>≥ 300 and &lt; 900 if age 50-75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 300 and &lt; 1800 if age &gt; 75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine ≥ 1.6</td>
<td>563</td>
<td>2.5</td>
<td>0.135</td>
</tr>
<tr>
<td>Obese</td>
<td>BMI &gt; 30</td>
<td>518</td>
<td>6.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Elderly</td>
<td>Age ≥ 70</td>
<td>658</td>
<td>2.6</td>
<td>0.076</td>
</tr>
<tr>
<td>Edema</td>
<td>Present</td>
<td>588</td>
<td>1.7</td>
<td>0.379</td>
</tr>
</tbody>
</table>
Diagnostic Biomarkers

- BNP
- Mid-region proANP
- Procalcitonin
- NGAL
- BIVA
Infection Source in Severe Sepsis - RESPIRATORY

Heart Failure + infection

- Heart failure plus pneumonia is present about 10-15% of time
- Heart failure plus any infection may occur in up to 20% of hospitalized heart failure patients.
- Hospital Mortality may be up to 20% (versus 5%) in heart failure patients with untreated infections
In critically ill patients, **PCT levels** elevate in correlation to the severity of bacterial infection.

- **In healthy people**, PCT concentration are found below 0.05ng/ml.
- **Concentrations exceeding** 0.5ng/ml can be interpreted as abnormal.
AHF, no Pneumonia (n=539)
AHF and Pneumonia (n=29)
no AHF, no Pneumonia (n=947)

BNP [ng/mL]
PCT [ng/mL]
BNP
Mid-region proANP
Procalcitonin
NGAL
BIVA

Diagnostic Biomarkers
Time Course of Development of Increasing Creatinine in Hospitalized HF Patients

“Cardiorenal Syndrome”

Cr, serum creatinine.
What can NGAL detect?

- Marker of Renal Injury
- High Sensitivity for Injury
- Moderate Specificity for underlying nephropathy
NGAL Predicts WRF in ADHF

Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Predicting Worsening Renal Function in Acute Decompensated Heart Failure

ARASH AGHEL, MD, KEVIN SHRESTHA, AB, WILFRIED MULLENS, MD, ALLEN BOROWSKI, RDHCS, AND W. H. WILSON TANG, MD

Cleveland, Ohio; Genk, Belgium

N=91
38% dev AKI/WRF

Aghel et al, J Cardiac Failure, Vol. 16 No. 1 2010
GALLANT-CHF

- n GAL evaluation
  Along with NaTiuretic peptides in CHF
Days
0 5 10 15 20 25 30
Event Free Survival
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00

NG AL < 100, BNP < 330
NG AL > 100, BNP < 330
NG AL < 100, BNP > 330
NG AL > 100, BNP > 330
AKINESIS: Acute Kidney Injury N-gal Evaluation of Symptomatic heart failure Study
NGAL = 400!!
Stop aminoglycosides
No contrast!
Do you really need more lasix?
BNP
Troponin
Procalcitonin
Adrenomedullin
NGAL
BIVA
How it works....
Ohm’s Law

• The flow of an electrical current (I) is equal to a voltage drop (E) between the two ends of a circuit divided by the resistance or impedance (Z) to current flow.

\[ I = \frac{E}{Z} \quad \text{or} \quad Z = \frac{E}{I} \]
Correct Body Position
Vector BIVA patterns for clinical use

From Kg & Liters to the distance from the mean

**Major axis** => tissue hydration, **minor axis** => soft tissue mass
BIVA patterns

Major axis => tissue hydration, minor axis => soft tissue mass
• **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)
Total Body Water in CHF

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

Begin diuretics

BNP and NGAL to aid in euvolemic balance and prevent renal dysfunction

BNP level

Creatinine

Stop diuretics or add vasodilators

N-GAL

Begin diuretics

BIVA for guidance
Prognostic Biomarkers

EMERGENCY PHYSICIAN

BREAK GLASS

Troponin
Adrenomedulin
ST-2
Risk Stratification is of Limited Value to Individual Patients

Great news! I can predict you will live 4.5 months with a p value of 0.04!
Prognostic Biomarkers

Troponin
Adrenomedulin
ST-2
Potential Mechanisms for Cardiac Troponin Elevations in HF

- Neurohormones
- Myocardial Stretch
- Inflammatory Cytokines
- Myocardial Ischemia
- Oxidative Stress
- Abnormal Calcium Cycling

- Reversible Injury with Altered Cell Permeability
- Myocardial Cell Necrosis
- Apoptosis
- Troponin Degradation Products

Cardiac Troponin I or T Detected
Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure

Yang Xue¹*, Paul Clopton², William F. Peacock³, and Alan S. Maisel¹

¹Division of Cardiology, Department of Medicine, University of California at San Diego, 200 West Arbor Drive, San Diego, CA 92103, USA; ²Veteran’s Affairs San Diego Healthcare System, La Jolla, CA, USA; and ³Department of Emergency Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA

Received 18 June 2010; revised 24 August 2010; accepted 20 September 2010
Changes in hscTnl (Nanosphere) and Mortality in Acute Heart Failure

Mortality and readmission (38 subjects)

Event free (106 subjects)

Euro J Hrt Failure, January 2011
Changing hscTnl (Nanosphere) and Mortality in Acute Heart Failure

Euro J Hrt Failure, Jan 2011
Prognostic Biomarkers

- Troponin
- Adrenomedulalin
- ST-2
Adrenomedullin:

- Peptide hormone consisting of 52 amino acids
- Vasodilator, important for microcirculation & endothelial (dys)function
- ADM measurement is not suitable for clinical routine diagnosis assessment due to its \textit{ex vivo} instability (immediate binding to receptors, 22min half-life time)
- Mid regional pro-ADM (MR-proADM) is a stable and reliable surrogate marker for ADM release

Struck J et al., Peptides. 2004; Morgenthaler NG et al., Clin Chem. 2005
Survival in AHF

Results of multivariable Cox regression:

MR-proADM is more important than either BNP or NT-proBNP in survival models using Cox Regression.

<table>
<thead>
<tr>
<th>Predictor (multivariable)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>log MR-proADM</td>
<td>14.0</td>
<td>5.0-39.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>log BNP</td>
<td>1.0</td>
<td>0.5-2.0</td>
<td>0.906</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Predictor (multivariable)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>log MR-proADM</td>
<td>10.4</td>
<td>3.3-32.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>log NT-proBNP</td>
<td>1.4</td>
<td>0.7-2.6</td>
<td>0.295</td>
</tr>
</tbody>
</table>
Survival in AHF

Risk is great in the highest quartile of MR-proADM

### Quartile HR 95% CI p

<table>
<thead>
<tr>
<th>Quartile</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>0.8</td>
<td>0.3-2.0</td>
<td>0.640</td>
</tr>
<tr>
<td>3rd</td>
<td>1.1</td>
<td>0.5-2.5</td>
<td>0.822</td>
</tr>
<tr>
<td>4th</td>
<td>3.2</td>
<td>1.6-6.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Quartile HR 95% CI p

<table>
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<tr>
<th>Quartile</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-3rd</td>
<td>1</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>3.3</td>
<td>2.0-5.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MR-proADM predicts short term (30 day) survival exceptionally well.

<table>
<thead>
<tr>
<th></th>
<th>AUC 30 days</th>
<th>AUC 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR-proADM</td>
<td>0.739</td>
<td>0.674</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.641</td>
<td>0.664</td>
</tr>
<tr>
<td>BNP</td>
<td>0.555</td>
<td>0.606</td>
</tr>
</tbody>
</table>
Prognostic Biomarkers

Troponin Adrenomedulin ST-2
ST2 Concentrations as a Function of One Year Mortality in Acute HF

% Mortality

Decile

Presage ST2 (%)
MBL ST2 (%)
Value of sST2 for prognosis in acute dyspnea

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST2</td>
<td>0.80</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.76</td>
</tr>
<tr>
<td>CRP</td>
<td>0.76</td>
</tr>
<tr>
<td>BUN</td>
<td>0.73</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.70</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.69</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>0.69</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.67</td>
</tr>
<tr>
<td>cTnT</td>
<td>0.65</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>0.54</td>
</tr>
<tr>
<td>Apelin-1</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Additive Value of ST2 to NP’s in Acute HF

The combination of an elevated ST2 and natriuretic peptide was a considerably stronger predictor of death than either alone....
ST2 Trends as a Function of Mortality

Thank You