B–Type Natriuretic Peptide: Pathophysiology and the Clinical Role
Objectives

1. Discuss current challenges associated with diagnosing heart failure (HF).
2. Describe the pathophysiology and clinical presentation of patients with HF and the role of the natriuretic peptide system in HF.
3. Review the use of B-type Natriuretic Peptide (BNP) as an aid in the diagnosis and assessment of disease severity in patients with HF.
4. Describe the role of BNP in risk stratification in Acute Coronary Syndromes.
5. Discuss evidence based indications of the use for BNP through review of current evidence based research.
Heart Failure

- Heart failure (HF) is a condition in which the heart loses its ability to pump enough blood.
- HF usually develops slowly over years as the heart loses its pumping ability.
- Two main categories of HF:
  - **Systolic** – occurs when the heart’s ability to contract diminishes often measure by ejection fraction.
  - **Diastolic** (or Preserved Systolic) – occurs when the heart has problems relaxing.
Heart Failure 2000 compared to 2010

- 1 million Hospitalizations for CHF in 2000 & in 2010
- Most were for those aged ≥ 65 but the proportion <65 increased significantly from 23% to 29%
- Overall rate of CHF hospitalization per 10,000 population did not change significantly (35.5/32.8) but trends were different for those under & over 65
- Hospitalizations for males under age 65 increased significantly while females decreased significantly
- A greater share of inpatients <65 compared with ≥65 were discharged to home

Heart Failure Costly in the U.S.

2007 direct and indirect HF costs: $33.2 billion

2009 direct and indirect HF costs: $37 billion

2010 direct and indirect HF costs: $34.4 billion

More Medicare dollars were spent for the diagnosis and treatment of Heart Failure than any other diagnosis

Heart Disease and Stroke Statistics – 2003 and 2007 Updates, AHA
Texas Heart Institute Journal V37(5), 2010
Heidenreich, et al; Circulation 2011;123(8):933-944 Forecasting the future of Cardiovascular Disease in the US…
Survival is poorer for men. 1-year mortality is 20%.
CHF Hospitalization Rates for Males & Females

The changes from 2000 to 2010

Yellow – Female
Purple – Male

† Change was statistically significant at the 0.05 level using a weighted least squares regression method, including data from all years, to measure linear trends over time from 2000 to 2010.

Common Risk Factors Associated with Development of HF

- Hypertension
- Coronary Artery Disease
- Diabetes
- Hyperlipidemia
- Family history of cardiomyopathy

“Only early detection and treatment is likely to stem the current epidemic of heart failure (HF).”
Heart Failure Defined

“The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return.”

E. Braunwald
Myocardial Infarction
This damage (necrosis) may cause HF
HF: How It Changes the Heart
Some Other Causes of Heart Failure

- Hypertension
- Toxin–induced from drugs, alcohol, infections, other conditions or disorders
- Idiopathic
Staging of Heart Failure

New York Heart Association Classification:
- **Class I** – No limitations of physical activity
- **Class II** – Slight limitations
- **Class III** – Marked limitations of physical activity
- **Class IV** – Inability to carry out physical activities without discomfort

- Class I: 1,680,000 (35%)
- Class II: 1,680,000 (35%)
- Class III: 1,200,000 (25%)
- Class IV: 240,000 (5%)
Heart Failure Treatment

- Medical and Surgical
  - Early to Advanced Disease
    - ACE inhibitors
    - beta blockers
    - diuretics
    - digoxin
    - Many new drugs in clinical trials/development
    - Lifestyle changes
  - Advanced Disease
    - Ventricular Assist Device (VAD)
    - Transplant

Exercise!!!
Lose weight!!!
Stop smoking!!!

Early treatment most effective
Signs and Symptoms of HF

- Weight gain
- Swelling of feet and ankles
- Swelling of the abdomen
- Pronounced neck veins
- Shortness of breath
- Difficulty sleeping
- Fatigue, weakness, faintness
- Sensation of feeling the heart beat (palpitations)
- Irregular or rapid pulse
- Decreased alertness or concentration
- Cough
Differential diagnosis may include:

- Myocardial Infarction
- Congestive Heart Failure
- Pneumonia
- COPD
- Cardiac Tamponade
- Anxiety

Diagnostic testing may include:

- Cardiac markers: TnI, CK-MB, Myoglobin, BNP
- CBC, chemistry, lipid panel
- EKG
- X-Ray
- Echocardiogram
- Stress test
B–Type Natriuretic Peptide (BNP)

- B–Type Natriuretic Peptide (BNP) is a cardiac neurohormone specifically secreted from the cardiac ventricles as a response to:
  - ventricular volume expansion
  - pressure overload
  - resultant increased wall tension

- FDA cleared the first BNP test for use as a diagnostic aid in 2000
BNP Function

- Found primarily in the cardiac ventricles
- Is strongly induced during ventricular-wall tension or stretch
- Potent natriuretic, diuretic, and vasorelaxant peptide
- Inhibits sympathetic tone, renin–angiotensin axis, and synthesis of vasoconstrictor molecules

Maisel et al, Reviews in Cardiovascular Medicine 2003
Natriuretic Peptides

ANP

$$\text{NH}_2\text{Ser Leu Arg Arg Ser Ser Cys Phe Gly Arg Met Asp Ile Gly}$$

$$\text{COOH Tyr}$$

BNP

$$\text{H}_2\text{N-Ser Pro Lys Met Val Gin Gly Arg Lys Met Asp Arg Ile}$$

$$\text{COOH His}$$

Urodilatin

$$\text{NH}_2\text{Pro Arg Ser Leu Arg Arg Ser Ser Cys Phe Gly Arg Met Asp Ile Gly}$$

$$\text{COOH Tyr}$$

CNP

$$\text{H}_2\text{N-Gly Leu Ser Lys Gly Asp Cys Phe Gly Leu Lys Leu Arg Asp}$$

$$\text{COOH Cys}$$
Heart Failure Pathophysiology

Myocardial injury → Fall in LV performance

Activation of RAAS, SNS, ET, AVP, and others

Myocardial toxicity

Peripheral vasoconstriction
Hemodynamic alterations
Remodeling and progressive worsening of LV function
Heart failure symptoms
Morbidity and mortality

BNP
The Natriuretic Peptide System is Overwhelmed in Acute Decompensated Heart Failure

Adapted from Burnett JC, J Hypertens 1999
The Cardiovascular Disease Continuum: Clinical Implications

Risk Factors:
- Obesity,
- Insulin Resistance

Endothelial Dysfunction

Vascular Disease (Atherosclerosis)

Pathological Remodeling (LVH)

Heart Attack (Myocardial Dysfunction)

Left Ventricular Enlargement

Heart Failure

Death

Source: Adapted from Dzau V et al. Am Heart J. 1991
The Cardiovascular Disease Continuum: Clinical Implications

- Risk Factors: Obesity, Insulin Resistance
- Endothelial Dysfunction
- Vascular Disease (Atherosclerosis)
- Pathological Remodeling (LVH)
- Heart Attack (Myocardial Dysfunction)
- Left Ventricular Enlargement
- Heart Failure
- Death

BNP = 0

Source: Adapted from Dzau V et al. Am Heart J. 1991
Release of BNP

Pro-BNP

- NT Pro-BNP
- BNP

Natriuresis
Vasodilatation
↓ RAAS
BNP and NT-proBNP

- **BNP:**
  - Cleared by binding to receptors, and neutral endopeptidase, kidneys
  - Active hormone promoting sodium and water excretion
  - Half Life approximately 20 minutes

- **NT-proBNP:**
  - Not a Natriuretic peptide, does not assist in decreasing fluid volume
  - Inactive protein, clearance via filtration by the kidneys
  - Half Life approximately 1–2 hours

Half-life

Clinical Impact of Half Life

- BNP: 20 min * 5 half lives = 100 min
- NT-proBNP: 120 min. * 5 half lives = 10 h
- Provides a more current assessment of hemodynamic state
- Example: If a patient presents to the ED at 6am, BNP represents the patient’s condition at around 4am and NT-pro BNP represents their condition at around 8pm the night before
- BNP more closely reflects the current condition of the patient with its 20 minute half-life
BNP Relationship to NYHA Objective Vs. Subjective Evaluation

![Bar chart showing the relationship between BNP and NYHA stages.](Triage BNP package insert.)
BNP vs. Standards
Comparative Accuracy

Accuracy (%)

N-HANES 67
Framingham 73
BNP 83

Maisel, NEJM 2002
## Endpoints

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<th>BNP (pg/ml)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
<th>Accuracy (%)</th>
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<td>85 (83–88)</td>
<td>84</td>
</tr>
</tbody>
</table>

Maisel, NEJM 2002
BNP Multinational Study: Conclusions

- BNP independently adds diagnostic information to traditional components of the evaluation including history, physical exam, and chest x-ray

- Mean BNP values reflect functional class in those with heart failure

- BNP measured at the time of initial ED evaluation, has a high degree of sensitivity, specificity and accuracy as an aid in the diagnosis of heart failure

Maisel, NEJM 2002
“B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure”

Analysis From Breathing Not Properly (BNP) Multinational Study

Purpose: Determine the degree to which B-type natriuretic peptide (BNP) adds to clinical judgment in the diagnosis of CHF

McCullough, et al
Circulation, Vol.106, No 4, 2002
FREQUENCY HISTOGRAM

From Bayesian Analysis substudy
Clinical Probability of Heart Failure

Significant Indecision Exists

McCullough, Circulation 2002
Frequency Histogram

Pre Test Probability of CHF (Blinded to BNP)

Significant Indecision Exists
43 %
Clinical Indecision (C.I.)
with and without BNP
Conclusions

- BNP can add to clinical judgment and enhance diagnostic accuracy in patients with acute dyspnea
- BNP can clarify the diagnosis when clinical indecision exists
B.N.P. MULTINATIONAL STUDY
BAYESIAN ANALYSIS CONCLUSIONS

- Clinical Indecision Exists in the E.D. following the initial diagnosis of CHF

- In those patients which clinical indecision exists in the ED, a BNP at a cutoff of 100 pg/ml correctly classified 74% of cases

- BNP testing, when used in conjunction with existing standards, can clarify diagnostic ambiguity in this difficult population
Bedside B–type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure with Reduced or Preserved Ejection Fraction

Results from the Breathing Not Properly Multinational Study

JACC, 2003 Jun 4; 41 (11) 2010–17
B–type Natriuretic Peptide and Renal Function in the Diagnosis of Heart Failure: An Analysis From the Breathing Not Properly Multinational Study

American Journal of Kidney Diseases
2003 Mar;41(3):571–579
The Value of BNP in the setting of Chronic Renal Failure:

- BNP increases with declining kidney function but remains useful for the diagnosis of CHF
- Data from the Breathing Not Properly Study re-examined

Mean BNP Values by NKF–KDOQI Stage and Final Diagnosis of Non-Cardiac Dyspnea or CHF

BNP increases with worsening renal function but continues to differentiate CHF from non-cardiac dyspnea

A rapid test for BNP correlates with falling wedge pressures in patients treated for decompensated heart failure

Changes in BNP Levels and Pulmonary Wedge Pressure During 24 Hours of Treatment
Study Results

- Falling wedge correlated by percentage to falling BNP in the responders

- Elevated final BNP was noted in pts with fatal outcome (1078 +/- 123 vs. 701 +/- 107 pg/ml)
Statement 2 – An Algorithm

Patient presenting with dyspnea
Physical examination, chest x-ray, ECG, BNP level

BNP <100 pg/mL
- HF very improbable (2%)
  - Treatment Options (noncardiac): Consider COPD; pulmonary embolism; asthma; pneumonia; sepsis
  - Treatment Options (cardiac): Consider acute coronary syndromes

BNP 100–500 pg/mL
- Clinical suspicion of HF or past history of HF?
  - HF probable (90%)
    - Treatment Options: Diuretics as required; consider nesiritide if pulmonary congestion, or for borderline hemodynamic instability, Creat >1.5 mg/dL, CrCl <60 mL/min, BUN >40 mg/dL

BNP >500 pg/mL
- HF very probable (95%)
  - Treatment Options for HF with BP <90 or shock: Diuretics, inotropes, vasodilators and/or nesiritide to follow
  - Treatment Options for HF with BP >90: Diuretics plus nesiritide, especially with CKD and pulmonary congestion; consider adding vasodilators if hypertensive; consider adding inotropes for poor perfusion
BNP Utilization: Evidence Based

- Aid to Diagnosis of CHF in the ED
- Assessment of CHF Disease Severity
- Risk Stratification of Patients with Heart Failure and Acute Coronary Syndromes
Tools for ACS risk stratification?

- BNP
- High Sensitivity TnI
“The Prognostic Value of B-Type Natriuretic Peptide in Patients with Acute Coronary Syndromes”

Purpose: To evaluate the utility of BNP in ACS

De Lemos, J.S. et al

*New England Journal of Medicine*

October, 2001
Study Design/Methods

- 2525 patients from the TIMI (Thrombolysis in Myocardial Infarction) 16 trial included

- Specimens obtained at 40 $^{+/-}20$ hours after onset of ischemic symptoms

- End points of death or nonfatal MI were evaluated at 30 days and 10 months
Endpoints via BNP Cut-off of 80 pg/ml

P < 0.005 for each comparison

Conclusions

- BNP provides powerful risk stratification information across a spectrum of Acute Coronary Syndromes (ACS)

- BNP of 80 pg/ml is an appropriate risk threshold among patients with ACS

- Prognosis via neurohormonal activation (BNP) are distinct from those of myocyte necrosis (TnI)

- BNP measurement should be considered after an ACS in order to identify patients at high and low risk for adverse outcomes. Treatments including increased surveillance, pharmacologic and interventional therapy should be adjusted accordingly
Recent Recommendations for ACS

- The European Society of Cardiology (ESC) & American College of Cardiology (ACC) have recommended the definition of cardiac troponin elevation to be a measurement exceeding the 99th percentile of a reference group.

- National Academy of Clinical Biochemistry (NACB) has recommended two decision limits for optimal use of sensitive and specific TnI. One abnormal low value can indicate myocardial injury and a higher value can indicate AMI.
Advantages of POC Cardiac Marker & BNP Testing

- Lower Risk of indecision
- Early risk stratification of acute coronary syndrome patients
- Initiate clinical protocols and effective treatment earlier
- Potential Cost benefit with earlier and appropriate intervention
Predischarge BNP Assay for Identifying Patients at High Risk of Re-Admission After Decompensated Heart Failure

Logeart et al. JACC. 2004 Feb 18;43(4);635-41
Methods

- Daily BNP followed for admitted CHF patients
- Both a derivation and validation study
- 100 patients enrolled in each study
- Followed for 6 mo post discharge for death or readmission
- Applied the cutoff found in the derivation study to the population in the validation study

Derivation Study Results

- Of 105 pts, 12 died and 39 were readmitted at 6 months.
- Using multivariate analysis of clinical variables BNP levels and echo findings, only d/c BNP remained significant.
- Cutoff of 350 was found to give optimal results by ROC curve analysis (best compromise of sens/spec).

Validation Study Results

- Using the cutoff of 350 from the derivation study the researchers found:
  - Event rate of 0% at 1 mo and 12.7% at 6 mo for patients below the cutoff
  - Event rate of 23.5% at 1 mo and 79.4% at 6 mo for above the cutoff.

- Cut-off level of 350ng/l predicted death/readmission with sens 80% and spec 88%

Validation Study Results

- Event free patients had a mean D/C BNP of 247 +/- 201 ng/l vs.....

- Patients with events had a mean D/C BNP of 908 +/- 809 ng/l

Predischarge BNP

Logeart D. et al. J Am Coll Cardiol. 2004

Death or readmission (%)

Follow-up (days)

P = 0.0001

Predischarge BNP > 350 pg/l

Predischarge BNP < 350 pg/l
Predischarge BNP

- Predischarge BNP >700ng/l
  - n = 41, events = 38
  - Hazard ratio vs 1st BNP range: 15.2
  - p < 0.0001

- Predischarge BNP 350 – 700ng/l
  - n = 50, events = 30
  - Hazard ratio vs 1st BNP range: 5.1
  - p < 0.0001

- Predischarge BNP <350ng/l
  - n = 111, events = 18

Follow-up (days)

Death or readmission (%)
Predischarge BNP
Conclusions

- Predischarge BNP was the strongest predictor of all the variables for death or re-admission
  - AUC 0.80 in the derivation study
  - AUC 0.83 in the validation study

- Discharge BNP outperformed ejection fraction and clinical variables for predicting the outcome measures

Logeart D. et al. J Am Coll Cardiol. 2004
Application to Clinical Practice

- D/C BNP > 750 was associated with a HR (hazard ratio) of 15, compared to the <350 group

- D/C BNP < 350 was associated with significantly lower rate of readmission and death at follow up

Thank you

Questions?