January, 2005

Dear Colleagues:

It is our pleasure to provide this summary of the Brain Natriuretic Peptide (BNP) 2004 Consensus Panel recommendations. BNP represents one of the most important diagnostic and therapeutic substances to be introduced in the last decade. This peptide represents both an excellent diagnostic test for heart failure (HF) as well as a potent therapy for this condition.

Over the last decade, the incidence of HF has been rising as more patients are surviving significant myocardial infarctions. The physical examination and chest x-ray represent relatively insensitive diagnostic tests for HF. The common use of BNP for diagnosis, provided through point-of-care testing in some emergency departments, substantially improves the diagnostic accuracy for the clinician. Similarly, BNP represents a novel therapy for HF, representing a relatively unique situation where a diagnostic peptide also provides therapy for the same condition.

Dr. Frank Peacock, of the Cleveland Clinic, provides detailed summaries of the diagnostic and therapeutic approaches for HF using BNP based on the BNP Consensus Panel recommendations published in September, 2004 in Congestive Heart Failure. We hope this EMCREG-International newsletter provides useful information which helps you provide care to patients with HF.

Sincerely,

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Director, CME-EMCREG
Chairman, EMCREG

A BNP expert consensus panel (1), consisting of individuals with basic, methodologic, and clinical expertise, was convened in 2004 to create a summary document to help guide the clinician on the recent explosion of natriuretic peptide (NP) data. This document contains the information from their recommendations most applicable to the emergency physician.

Natriuretic Peptide Physiology

More than a pump, the heart is a critical endocrine organ functioning with other physiological systems to control fluid volume. Myocytes manufacture a family of peptide hormones, termed the NPs, represented by atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Release of the NPs is stimulated by volume overload (2), and physiologically, they have powerful diuretic, natriuretic, and vascular smooth muscle relaxing actions. Importantly, they also serve as antagonists to the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) (3,4). Release of NPs results from cardiac wall stretch, ventricular dilation, or increased pressures from circulatory volume overload. The effects of NPs result in lowering blood volume and pressure.

BNP is derived from a precursor, preproBNP, which undergoes several cleavages. The assay relevant products are the inert N-terminal (NT) pro-BNP fragment, and physiologically active BNP. BNP’s are preferentially produced and secreted by the cardiac ventricles (5), although fluid overload may cause rapid BNP manufacture in both heart chambers (6). The primary function of NPs is to defend against volume over-
load. After release into circulation, BNP actions are modulated at target sites by specific cell membrane receptors, termed A, B, and C, which mediate physiological actions by cyclic GMP (7). Cyclic GMP has potent vasodilatory actions. BNP also causes an intravascular fluid shift, from the capillary bed into the interstitium, which contracts intravascular volume and decreases blood pressure (8, 9, 10). In addition, BNP is a RAAS antagonist, where it counteracts sodium conservation, vasoconstriction, and volume retention. BNP also inhibits the release of renin from kidney cells and aldosterone from adrenal cells. BNP is primarily metabolized by the NPR-C receptor, although some additional degradation may occur by neutral endopeptidase (11, 12, 13). Neutral endopeptidase has a wide tissue distribution, including adipose, kidneys, lung and brain (Figure 1).

Biologic Determinants on BNP Measurements

Blood levels of NPs are affected by a variety of factors, including circadian rhythm, age, exercise, and body posture (14). Many drugs including diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists, sex and thyroid hormones, glucocorticoids, sodium intake, and other conditions impact levels. BNP increases with age and gender. Baseline and pathologic levels are higher in women (15, 16). The age induced BNP increase may be due to the decline in myocardial function (17) or to decreased clearance.

BNP Assay

It should be made clear that the BNP assay is not a stand-alone test. Its greatest value is when it is used with the physician’s clinical judgment, and with other appropriate testing. The Triage BNP assay system is the only FDA approved point-of-care assay (18). It requires 15-minutes to perform, and reports BNP levels from 5 to 5000 pg/mL. This assay is rated as moderately complex assay per Clinical Laboratory Improvement Amendments (CLIA) regulations.

Figure 1. BNP EFFECTS


CONSENSUS STATEMENTS: GENERAL COMMENTS

The laboratory should perform BNP testing on a continuous 24-hour basis with a turn-around-time (TAT) of 60 minutes or less. The TAT is defined as the time from blood collection to notification of result to physician or caregiver. Either central laboratory instrumentation or point of care testing systems are acceptable.

• In considering NP measurements, one needs to carefully consider laboratory and biologic variation, including gender, sex, obesity, and renal function.

• The results of natriuretic testing is dependent on the type of test you are obtaining. N terminal pro BNP and bioactive BNP are NOT interchangeable.
BNP for Diagnosis of Heart Failure

Despite advances in our understanding of heart failure (HF) pathophysiology, diagnosis is still difficult. While emergency department (ED) diagnosis needs to be rapid and accurate (19), the signs and symptoms of HF are nonspecific (20). Respiratory distress can preclude obtaining the history, and dyspnea is nonspecific in the elderly or obese (21). Routine labs, ECG, and x-rays are also not accurate enough to always make the correct diagnosis (22,23,24).

The Breathing Not Properly study (25) was a large, multinational, prospective study using BNP to evaluate dyspnea in 1586 dyspneic ED patients. BNP levels were measured on arrival, and physicians assessed the probability of the patient having HF. Two cardiologists, blinded to the BNP level, reviewed all data after hospitalization to produce a "gold standard" clinical diagnosis. BNP levels alone more accurately predicted the presence or absence of HF than any other finding. The 100 pg/mL cutpoint had a 90% sensitivity and 76% specificity for a HF diagnosis. In multivariate analysis, BNP levels always contributed to the diagnosis, even after considering features of the history and physical examination.

BNP levels may also help in disposition decisions. The Rapid Emergency Department Heart Failure Outpatient (REDHOT) Trial demonstrated a "strong disconnect" between the perceived severity of HF, and illness severity as determined by BNP. On average, patients discharged from the ED had a higher BNP than those admitted, 976 pg/mL, versus 766 pg/mL, respectively. BNP also predicted outcomes of patients discharged. Seventy-eight percent had a BNP > 400 pg/mL, however, there was no mortality at 30 days if the BNP was less than 400 pg/mL.

The Swiss BASEL Study (26) examined the cost-effectiveness of using BNP through the diagnosis and hospitalization in acute decompensated heart failure (ADHF). In 452 patients, ED measurement of BNP was associated with a 10% decrease in hospital admissions, a 3-day decline in length of stay, and an $1800 savings, with no effects on mortality or re-hospitalization rates.

CONSENSUS STATEMENT: USING BNP TO HELP TRIAGE ED PATIENTS WITH DYSPNEA

BNP is of diagnostic utility in the evaluation of patients with acute dyspnea. Thus, in new patients presenting with dyspnea to an emergency setting, a history, physical examination, chest x-ray and ECG should be undertaken together with laboratory measurements that include BNP. Current data suggest the following guidelines:

- As BNP rises with age and is affected by gender, comorbidity, and drug use, it should not be used in isolation from the clinical context.
- If the BNP is <100 pg/mL, then HF is highly unlikely (NPV = 90%).
- If the BNP is >500 pg/mL, then HF is highly likely (PPV = 90%)
- If the BNP is 100–500 pg/mL, consider the baseline BNP is elevated due to stable underlying dysfunction, right ventricular failure from cor pulmonale, acute pulmonary embolism, or renal failure
- Patients may present with HF and a normal BNP, or with levels below what is expected in the following situations: flash pulmonary edema (<1–2 hours), HF up-stream from the left ventricle (such as with acute mitral regurgitation from papillary muscle rupture and obese patients (body mass index [BMI] >35)
BNP and Renal Failure

Chronic kidney disease (CKD) influences the cut-point for BNP. In general, as CKD advances, a higher BNP cut-point is implied. An upper limit of approximately 200 pg/mL is reasonable for those with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m². Using this approach, BNP maintains a high level of diagnostic utility, with an area under the ROC curve of >0.80 across all CKD groups.

Cardiopulmonary Disease

Some non-HF cardiopulmonary diseases may cause BNP elevations. These include cor pulmonale, lung cancer, pulmonary embolism (PE) and primary pulmonary hypertension. In these, BNP may be elevated, but not to the extent found in ADHF. In PE, BNP may be prognostic since patients with a BNP in the upper normal range or > 100 pg/mL have a higher mortality rate (27). Although BNP is not an adequate screening test for PE, in the setting of a suspected or confirmed embolic event, a BNP elevation implies RV pressure overload and increased mortality risk. Finally, in primary pulmonary hypertension, BNP elevations parallel the extent of pulmonary hemodynamic changes and right HF (28).

CONSENSUS STATEMENT: COMORBIDITIES AND SPECIAL ISSUES THAT INFLUENCE THE INTERPRETATION OF BNP LEVELS

- BNP is altered with chronic renal insufficiency (estimated GFR < 60 mL/min), with a recalibration of the cut off value to 200 pg/mL.

- BNP is helpful in the evaluation of dyspnea when it is very low or high. NT-pro BNP has greater correlation with eGFR than BNP, hence levels can be elevated even with the normal age related decline of renal function in the eGFR 60-90 mL/min range.

- When the eGFR is below 60 mL/min, N terminal proBNP can be considerably elevated and in this setting its utility in the evaluation of HF is unknown.

- Baseline BNP levels might therefore be important in dialysis patients, as changes most likely reflect volume status. Thus a pre-dialysis BNP may help determine the amount of volume which should be removed.

CONSENSUS STATEMENT: BNP IN PULMONARY AND ASSOCIATED CARDIAC DISEASE

- In approximately 20% of patients with pulmonary disease, BNP is elevated implying combined HF and lung disease, cor pulmonale, or a misdiagnosis when the true etiology of dyspnea is HF.

- In the setting of PE, BNP is elevated in 1/3 of cases and is associated with RV pressure overload and a higher mortality. BNP is not diagnostic for acute PE.

- Pulmonary disease which results in pulmonary hypertension and RV pressure or volume overload can lead to elevated BNP levels, usually in the range of 100-500 pg/mL.
Preserved Systolic Function (PSF) Heart Failure

Diastolic myocardial dysfunction, also known as PSF, is the cause of HF in as many of 50% of cases and is also associated with high BNP \(^{(29,30)}\). BNP has been found to be approximately half as high in PSF as in cases of systolic dysfunction \(^{(31)}\).

**CONSENSUS STATEMENT: BNP IN DIASTOLIC DYSFUNCTION**

- BNP might be used to detect patients with diastolic dysfunction.
- BNP concentrations above age-adjusted cut-points may identify elderly patients with diastolic dysfunction.

Obesity

Obesity is an important risk factor for coronary artery disease and HF \(^{(32,33,34,35)}\). Physiologically, adipose tissue is related to the natriuretic clearance receptor \(^{(36,37)}\) and obesity can interfere with the usual diagnostic approach to HF. Mehra \(^{(38)}\) documented an inverse relationship between Basal Metabolic Index (BMI) and BNP. Lower levels of BNP in the obese (BMI > 30Kg/M2) were noted, despite similar severity of HF compared to a lean cohort, and nearly 40% of obese patients had BNP < 100 pg/mL.

**CONSENSUS STATEMENT: BNP IN OBESITY**

- Since obese patients (body mass index [BMI] > 30kg/m2) express lower levels of BNP for any given severity of HF, caution should be exercised in interpreting BNP levels in such patients.

BNP and Acute Coronary Syndromes (ACS)

Large studies report NP elevations in unstable angina without myocardial necrosis \(^{(39,40)}\). As ischemia may result in only small NP elevations, their sensitivity and specificity are inadequate as a "rule out" tool for myocardial ischemia. However if present, an elevation of NP in ACS is a powerful predictor of adverse events. In 2,525 patients \(^{(41)}\) grouped into BNP quartiles 40 hours after ACS onset, an increasing BNP was associated with higher 10-month mortality, and this relationship persisted even without evidence of HF or myocardial necrosis.

**CONSENSUS STATEMENTS: BNP IN SUDDEN DEATH, ACS, AND CAD**

When used together, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and ACS. Multimarker panels with BNP and troponin are now available, where each of these markers provide unique and independent outcome data.
BNP and Prognosis

BNP elevation is a powerful marker of HF prognosis. In 325 patients, followed for 6 months after an ED visit for dyspnea, the relative risk of 6-month HF admission or death was 24 times higher if the BNP was >230 pg/mL (Figure 2)⁴². This was confirmed by the Val-HeFT trial, where the lowest quartile of BNP (< 50 pg/mL) had the lowest all-cause mortality and the highest quartile (> 238 pg/mL) had the highest mortality, 32% at 30 months.

BNP as Therapy

When ADHF occurs, the balance between vasoconstrictors and endogenous vasodilators is disturbed. This forms the basis as to why exogenous BNP is given as therapy despite high endogenous levels. It is analogous to giving insulin for insulin resistance. In ADHF, high levels of BNP occur as a "distress hormone", where supra-normal levels are no longer effective at maintaining the balance of vasoconstriction and vasodilation. Hence giving BNP, in the form of nesiritide, can restore neurohormonal homeostasis.

Natriuretic peptides are much closer to ideal drugs for ADHF than other agents. The use of nesiritide is associated with reduced filling pressures, decreased pulmonary vascular resistance, lower central venous pressures, and reduction in systemic BP. There is also increased cardiac output due to the unloading effect of vasodilatation, but without reflex tachycardia. Moreover, reducing preload and afterload without increasing heart rate is consistent with decreased myocardial oxygen consumption and a decrease in ventricular stress - a stimulus presumed to drive the neurohormonal activation of ADHF. Lastly, tolerance to these effects does not occur, and these changes in hemodynamics are present and persistent throughout the administration of nesiritide.

To date, nesiritide is the only natriuretic peptide available in the United States for intravenous therapy. Colucci et al.⁴³, in the Efficacy Trial, showed that nesiritide causes a dose-related decrease in PCWP, systemic vascular resistance, mean right arterial pressure, dyspnea, fatigue, a significant increase in cardiac index, and an improvement in global status. The most common side effect was dose-related hypotension. The Comparative Trial⁴⁴ evaluated nesiritide versus many other cardiovascular agents, including dobutamine, milrinone, nitroglycerin, dopamine, and amrinone. Global clinical status, fatigue, and dyspnea improved in all groups, with no significant differences between nesiritide and standard therapy. The most common side-effects were bradycardia and dose-related hypotension.

![Figure 2. Relationship of B-type natriuretic peptide (BNP) to death or heart failure hospitalization. Reprinted with permission from Ann Emerg Med. 2002;39:131-138.](image-url)

Giving BNP, in the form of nesiritide, can restore neurohormonal homeostasis and is associated with reduced filling pressures, decreased pulmonary vascular resistance, lowered central venous pressures, and reduction in systemic BP.
In 1998, Burger et al. conducted the PRECEDENT study. Its primary objective was to compare heart rate and arrhythmias with two doses of nesiritide (0.015 or 0.03 µg/kg/min) to dobutamine. They concluded that although inotropic HF therapies, including dobutamine and milrinone, are associated with favorable hemodynamic and symptomatic effects, they cause arrhythmias and tachycardia which may increase myocardial oxygen demand, ischemia, and mortality. They demonstrated fewer arrhythmias and no heart rate increase with nesiritide. Furthermore, the rates of 21-day readmission and 6-month mortality were higher with dobutamine. The authors concluded that nesiritide is safer than dobutamine for short-term ADHF management.

The VMAC trial was a safety and efficacy study of intravenous nesiritide versus intravenous nitroglycerin or placebo in 489 ADHF patients with dyspnea at rest. Swan-Ganz catheterization was performed in roughly half, at the physician’s choice. Patients were randomized into four blinded groups, each receiving standard therapy and: fixed dose nesiritide, titratable nesiritide, titratable nitroglycerin, or placebo. Nesiritide had a faster onset and greater reduction in PCWP than nitroglycerin. The improvement in clinical status and dyspnea was similar in both groups (Figure 3). They concluded that when added to standard care, nesiritide improves hemodynamic function more effectively than IV nitroglycerin or placebo.

In another evaluation, a risk adjusted comparison of outcomes from the ADHERE registry of more than 100,000 ADHF patients found improved survival with vasodilators compared to inotropes. When comparing vasodilators, there are similar outcomes between nesiritide and nitroglycerin.

The current approved use of nesiritide is for ADHF. Although guideline statements are lacking, the totality of diagnostic and therapeutic data regarding nesiritide yield an intuitive rationale and a reasonable evidence-based approach for ADHF assessment and management. One of the most valuable findings is that beginning vasoactive therapy in the ED is associated with a 3.1 day reduction in hospital length of stay compared to therapies not initiated until after admission. This suggests that the choice of therapy in the ED may critically impact the course of the patient.
INTEGRATING BNP LEVELS INTO A RATIONAL USE OF NESIRITIDE

While BNP is approved by the FDA for HF diagnosis, its usefulness to monitor treatment is still under study. However, some suggestions can be made. We believe that one can stratify patients to the high-risk category in part by using BNP levels. Fonarow (48) recently analyzed the ADHERE database and found that high BUN levels provide a poor prognosis for patients in ADHF. Thus, the combination of high BNP and poor renal function identifies high-risk patients (Figure 4).

If patients are admitted with BNP levels <500 pg/mL and BUN levels are <40 (i.e., lower risk), one can often start treatment with parenteral diuretics. Subsequently, they can be reclassified into low-risk or high-risk groups based on their response over the next 6–12 hours. Those with an adequate diuresis, a fall in BNP, and no deterioration in renal function may be candidates for continued diuretics/vasodilators until euvoemia is reached. Hopefully this will lead to a BNP level <400 pg/mL in these patients. In one study, patients whose discharge BNP levels were <430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days. (49) If the BNP level was >400 pg/mL, the volume status required re-evaluation. If the patient is not yet euvoemic, nesiritide might be considered for 24 hours.

If patients after receiving 6–12 hours of intravenous diuretics have an inadequate diuresis, no change or an increase in BNP and worsening renal function, they should be considered at high risk. If their systolic BP is at least 90 mm Hg, they can be given 1–2 days of nesiritide with IV diuretics. BNP can then be checked 6 hours after cessation of nesiritide and oral vasodilators and diuretics can be used until euvoemia is achieved.

Patients with systolic BPs <90 mm Hg often need vasopressors and/or inotropes, sometimes under Swan-Ganz catheter
guidance. In our experience at the Cleveland Clinic, if these individuals show improvement in BP and symptoms, we will then transition their therapy to nesiritide. If there is no improvement on inotropes or pressors, further invasive strategies should be considered. Finally, it is conceivable that in patients who are admitted with very high BNP levels, or have impaired renal function, nesiritide might be started immediately.

Conclusion

In conclusion, the BNP Consensus Panel of 2004 has provided expert panel approaches for the use of BNP for the diagnosis and treatment of HF. Hopefully, the use of these recommendations will improve the care of your patients.

References


CME Post Test

(Please circle answers below)

1) BNP levels may be elevated in the following conditions:
   a) Acute Myocardial Infarction
   b) Pulmonary Embolus
   c) Primary Pulmonary Hypertension
   d) Acute Decompensated Heart Failure
   e) All of the above

2) In the patient presenting with a clinical picture of acute decompensated heart failure, BNP levels may be lower than predicted in the following conditions:
   a) Acute Myocardial Infarction
   b) Pulmonary Embolus
   c) Primary Pulmonary Hypertension
   d) Morbid Obesity
   e) Vegetarians

3) A patient presents to the emergency department with acute decompensated heart failure. Nesiritide is begun, and shortly there after the patient develops symptomatic hypotension. What are the appropriate treatment steps?
   a) Stop nesiritide
   b) Administer a fluid bolus
   c) Reassess the differential diagnosis
   d) all of the above

4) Early vasoactive therapy for acute decompensated heart failure has been shown to:
   a) decrease ICU length of stay
   b) decrease hospital length of stay
   c) increase mortality
   d) A and B

5) Inotropes are useful for
   a) All Acute Decompensated Heart Failure patients
   b) Only if there is symptomatic hypotension
   c) Never
   d) Only if the blood pressure is less than 100 mmHg

Evaluation Questions

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question.

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The Evolving Role of BNP in the Diagnosis and Treatment of CHF: A Summary of the BNP Consensus Panel Report

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