Use of Plasma Brain Natriuretic Peptide Concentration to Aid in the Diagnosis of Heart Failure

Heart failure (HF) is a common and highly morbid disorder. An estimated 5 million people in the United States have HF, and it is diagnosed in 500,000 new patients each year. For individuals older than 40 years, the lifetime risk of developing HF has been estimated at 20% for both men and women. The incidence of HF is highest in people older than 65 years, a rapidly growing segment of our population, ensuring an epidemic of HF that will continue to grow as the population ages.

Heart failure is a syndrome associated with perturbations in cardiac structure and function that result from various cardiovascular diseases. The diagnosis of HF is a clinical one based on symptoms, signs, chest radiographs, and response to therapy. Echocardiography is used to characterize the specific structural and functional abnormalities associated with the syndrome but does not determine the diagnosis of HF.

Diagnosing HF often can be extremely difficult, and both underdiagnosis and overdiagnosis are common. This is true especially in the elderly population, obese individuals, patients who are deconditioned, and those with an underlying lung disease. Symptoms and signs may be difficult to evaluate in patients who are in acute respiratory distress, when rapid diagnosis and therapy are needed. Many physicians attempt to confirm their suspicion of HF by obtaining an echocardiogram to detect the presence of systolic dysfunction. However, studies have shown repeatedly that 50% of patients presenting with well-established clinical HF have normal systolic function (diastolic HF [DHF]). Furthermore, 50% of patients with systolic dysfunction have no symptoms of HF (asymptomatic ventricular dysfunction). Thus, a low ejection fraction (EF) is not synonymous with the diagnosis of HF.

Finally, access to echocardiography is limited in urgent care settings. For these reasons, there has been intense interest in an inexpensive, widely available, easily interpreted diagnostic aid that reflects the physiology common to patients with systolic HF and DHF.

### Physiology of BNP

The natriuretic peptide family includes BNP, atrial natriuretic peptide (ANP), and C-type natriuretic peptide. Both BNP and ANP are of myocardial cell origin, whereas C-type natriuretic peptide is of endothelial cell origin. These hormones are important for volume homeostasis and for regulation of blood pressure. The physiological actions of the natriuretic peptide system include arterial and venous dilatation, natriuresis, and suppression of the renin-angiotensin-aldosterone system and the sympathetic nervous system. These peptides also may exert autocrine-paracrine effects, acting on the heart to inhibit fibrosis and hypertrophy and enhance diastolic function. Pressure and volume overload of the cardiac chambers stimulate enhanced production and release of natriuretic peptides. Thus, these peptides reflect the common denominator present in patients with systolic or diastolic dysfunction, volume overload, and HF, regardless of the underlying cardiovascular disease.

Other forms of natriuretic peptides, such as proBNP and N-terminal proBNP, are being evaluated currently. Although a discussion of these other peptides is beyond the scope of this article, it is notable that these new assays will soon be available to aid in the diagnosis of HF.

### Clinical Evidence of the Diagnostic Utility of BNP

Substantial evidence shows that the BNP test aids in the diagnosis of HF. In 1994, Davis et al published a study of 52 patients who required urgent admission to a hospital for evaluation of dyspnea. During initial assessment, a history, physical examination, chest radiograph, and plasma BNP concentration were obtained. Pulmonary function tests and measurement of EF using radionucleotide ventriculography were performed shortly after admission. This study showed that the BNP level was higher in patients with HF compared with patients with lung...
disease and that use of the BNP assay was 93% sensitive and 90% specific for a diagnosis of HF.

A similar study of 122 patients who were referred to a rapid access outpatient clinic for evaluation of suspected HF had a similar design with extensive clinical evaluation and an independent panel of cardiologists blinded to the natriuretic peptide data as the gold standard for the diagnosis of HF. BNP, ANP, and end-terminal ANP were evaluated. Although all peptides correlated with the diagnosis of HF, BNP had the highest sensitivity (97%) and specificity (84%) for the diagnosis of HF. This study suggested that BNP was useful in the outpatient setting, where patients who present with dyspnea are likely to have a milder form of HF than those presenting to the emergency department (ED).

More recently, a study performed in a Veterans Administration hospital included 250 relatively young (mean age of 64 years) male patients who presented to the ED with dyspnea. Routine clinical parameters, echocardiograms, chest radiographs, and other clinical data were collected. This study revealed that the BNP level was elevated markedly in those deemed to have HF compared with those believed to have a pulmonary etiology for the dyspnea. A receiver operating characteristics (ROC) analysis showed that the area under the ROC curve for BNP for the diagnosis of HF was exceptionally high at 0.97, indicating near-perfect sensitivity and specificity.

The Breathing Not Properly Multinational Study was a prospective multicenter study of 1586 patients presenting to the ED with the chief complaint of dyspnea. The Triage BNP Test was used to measure plasma levels of BNP. The diagnosis of HF was established by an independent panel of cardiologists who had access to all clinical data obtained in the ED evaluation and in the subsequent hospital course. In this study, the ED physicians were required to designate a diagnosis of either HF or noncardiac dyspnea. The physicians were also required to provide an estimate of their confidence in the diagnosis of HF. If they were at least 80% confident in the diagnosis of HF, the ED diagnosis was considered HF. This study then compared the clinical diagnosis of HF and its accuracy to that obtained by plasma BNP concentrations. As in the single-center study, plasma BNP levels were elevated in patients with HF (Figure 1). Patients who had known systolic dysfunction but were believed to have a different etiology of their acute dyspnea had BNP levels that were intermediate, between those with HF and those with noncardiac dyspnea. Although the accuracy of the clinical diagnoses and BNP diagnoses was similar, the clinical test was more sensitive but less specific than clinical judgment (Table 1). A plasma BNP value of 100 pg/mL was deemed the best cutoff value in this study. Use of higher concentrations yielded better specificity but less sensitivity. A Bayesian-type analysis suggested that BNP was most helpful when the diagnosis of HF was intermediate. This concept is common to all diagnostic tests, particularly to the use of exercise testing in the diagnosis of coronary artery disease. Therefore, the investigators suggested that BNP is best used when the physician suspects HF but is unsure of the diagnosis.

| Table 1. Predictive Characteristics of Brain Natriuretic Peptide (BNP) and Clinical Judgment for Diagnosis of Heart Failure in the Breathing Not Properly Multinational Study |
|-----------------|--------|--------|--------|---------|--------|
| BNP (pg/mL)     | Sensitivity (%) | Specificity (%) | Accuracy (%) | Sensitivity/(1 – specificity) | (1 – sensitivity)/specificity |
| ≥50             | 97     | 62     | 79     | 2.55    | 0.048  |
| ≥100            | 90     | 76     | 81     | 3.75    | 0.13   |
| ≥150            | 85     | 83     | 83     | 5       | 0.18   |
| Clinical judgment‡ | 49     | 96     | 74     | 12.25   | 0.53   |

*Sensitivity/(1 – specificity).
†(1 – sensitivity)/specificity.
‡At >80% confidence in the presence of heart failure.
Confounding Variables

Detection of Mild HF
BNP levels increase in relation to the severity of CHF. Thus, BNP levels are highest in patients with the most severe HF. However, data in outpatients indicate that use of BNP tests enhances the diagnosis of HF, even in patients with milder HF being seen as outpatients.

Diagnosis of Diastolic Heart Failure
An important issue is whether BNP levels can be used for accurate diagnoses of diastolic heart failure (DHF). Recent studies suggest the BNP test is an excellent diagnostic tool because BNP levels are elevated in patients presenting with DHF.

Lung Disease with Cor Pulmonale
Another important issue is whether patients who have severe lung disease with cor pulmonale have elevated BNP levels related to right ventricular dysfunction. The limited data suggest that BNP levels are elevated in the presence of right ventricular dysfunction associated with severe obstructive lung disease. All studies emphasized that an elevated plasma BNP level serves to direct the initial evaluation and therapy. An abnormal BNP level should prompt an echocardiographic study to characterize the type and severity of cardiac dysfunction associated with the clinical syndrome of HF. Nonetheless, physicians using the BNP test must be aware that right HF associated with severe lung disease or pulmonary embolism can result in an elevated BNP level and that this test augments but does not replace clinical evaluation.

Discrimination Between HF and Noncardiac Dyspnea in Patients With Known Systolic Dysfunction
Patients with systolic dysfunction who are well compensated can develop dyspnea related to pulmonary disease. Determining whether dyspnea is due to an exacerbation of HF or whether it is due to pulmonary causes can be difficult. As indicated in the Breathing Not Properly Multinational Study, patients with known systolic dysfunction who present with dyspnea unrelated to HF typically have BNP levels between those seen with HF and no HF. Aggressive medical therapy can normalize BNP, even in those with severe systolic dysfunction. An extremely high or low BNP may be helpful for diagnosing these patients, but an intermediate level may not discriminate between HF and dyspnea due to a concomitant pulmonary condition.

Flash Pulmonary Edema
Of note, some patients with extremely rapid onset of pulmonary edema seen within the first hours of onset of symptoms may have a normal or low BNP level because it takes time for the production and release of BNP to be augmented in response to an acute increase in filling pressures.

Renal Insufficiency and Renal Failure
There has been some speculation that BNP levels are falsely elevated in patients with underlying renal impairment; however, this does not seem to be the case. Cataliotti et al showed that among patients with end-stage renal disease, the BNP level is elevated only in those with concurrent left ventricular hypertrophy. In the absence of left ventricular hypertrophy, the BNP level was not elevated. These data are consistent with the fact that BNP is not cleared primarily by the kidney but is degraded by endopeptidases and clearance receptors throughout the body.
BNP Level That Indicates HF

Currently, the BNP test recommends that a value of 100 pg/mL be used to indicate HF. However, data gathered from using the BNP test and other assay systems indicate clearly that even in individuals who are free of cardiovascular disease, use no cardiovascular medications, or have no detectable systolic, diastolic, or valvular dysfunction, BNP values increase with age and are higher in women (Figure 2). Indeed, in women older than 65 years, the 95th percentile value for BNP is well over 100 pg/mL and can be as high as 155 pg/mL. Furthermore, the BNP level increases with severity of symptoms, suggesting that the test should be interpreted in relation to severity of symptoms and BNP level.

Standard Care

Approved to aid in the diagnosis of HF, the BNP assay does not replace, but rather augments, clinical evaluation. Heart failure must be clinically diagnosed by using data obtained from the patient’s history, physical examination, and chest radiographs. However, the BNP test may lead to more efficient and accurate diagnoses of this syndrome and prove helpful to the physician. Of note, the strongest evidence so far for use of BNP pertains to its use in the diagnosis of HF. Therefore, it should be ordered when there is uncertainty about the proper diagnosis. For example, use of BNP testing in a patient with a known EF of 20% and a history, physical examination, and chest radiograph clearly indicative of HF adds nothing with respect to diagnosis. Conversely, a BNP test would be extremely helpful in a patient whose history, physical examination, and chest radiograph are suggestive of, but not clearly indicative of, HF. In this case, the “pretest” probability of HF is intermediate; therefore, the BNP test may help the physician make the correct diagnosis more rapidly. In this patient, if the BNP level is above normal, suspicion rises greatly with respect to the diagnosis of HF. However, if the BNP level is normal, this suggests the patient has noncardiac dyspnea.

The severity of symptoms also may influence the interpretation of the test. The more severe the symptoms, the higher the BNP level should be if the symptoms are due to HF. Thus, a minimally elevated BNP level in a patient with gradual onset of severe dyspnea at rest and an intermediate probability of HF is not as useful.

In conclusion, as with all diagnostic tests, BNP tests can be helpful for diagnosing HF in patients in whom the diagnosis is not obvious and the pretest probability is intermediate. As always, the physician must remember that the diagnosis of HF is not made solely on the basis of a laboratory test or an echocardiogram, but rather on clinical grounds; these tests are used to augment clinical judgment.

Excerpted from Mayo Clinic Proceedings 2003;78:481-486. References omitted. The complete article is available online at www.mayo.edu/proceedings.
Chromosome Analysis of POC Test Change
With the introduction of the new fluorescent in situ hybridization (FISH) test, #81081 Aneuploidy Detection, Products of Conception, FISH, if the tissue culture for #8887 Chromosome Analysis, Autopsy, Products of Conception, or Stillbirth fails, the FISH test will automatically be ordered and performed. In this situation, there will be no charge for the chromosome test #8887.

Cortisol Test Changes
The blood test for cortisol, #9369 Cortisol, Serum, LC-MS/MS, was recently converted from a high-performance liquid chromatography (HPLC) method to HPLC with tandem mass spectrometry (LC-MS/MS). This change has resulted in changes to the preferred specimen requirement, test name, and reference values. This test is used as a second-order test when cortisol measurement by immunoassay (eg, #8545 Cortisol, Serum) gives results that are inconsistent with clinical symptoms or if patients are known to, or suspected of, taking exogenous synthetic steroids.

The type(s) of exogenous synthetic corticosteroid taken, and its concentration(s), can be determined by LC-MS/MS tests in urine or serum (#81035 Synthetic Glucocorticoid Screen, Urine or #81031 Synthetic Glucocorticoid Screen, Serum).

Oligoclonal Banding Test Changes
A method change has resulted in changes to the test name, reference values, and specimen requirement for oligoclonal banding. The new method requires significantly less spinal fluid (CSF) specimen-only 0.5 mL, extends the window for collection of the accompanying serum specimen to 7 days, and is easier to interpret than the previous method. The test reports the number of CSF and serum bands (the normal reference value is <4 bands seen in CSF than are seen in the serum), with an interpretation.

New Test Name
#8017 Oligoclonal Banding

Previous Test Name
Oligoclonal Banding, Spinal Fluid

New Method
Isoelectric Focusing (IEF) with IgG immunoblot detection

Previous Method
Agar Gel Electrophoresis

New Specimen Requirement
Both serum and spinal fluid are required for this test. Specimens must be obtained within 7 days of each other.

Serum
Draw blood in a plain, red-top tube(s) or a serum gel tube(s). Spin down and send 0.5 mL of serum frozen in plastic vial.

Spinal Fluid
0.5 mL of spinal fluid. Send specimen frozen in plastic vial.

New Reference Values
<4 bands

Previous Reference Values
0-1 bands
C1 Esterase Inhibitor Test Changes
The method for C1 esterase inhibitor was changed from automated immunoturbidimetry to nephelometry. Because of this change, the test name, specimen required, and reference values also have changed.

New Test Name
#8198 C1 Esterase Inhibitor Antigen, Serum
Previous Test Name
C1 Esterase Inhibitor Antigen, Plasma

New Specimen Requirement
Draw blood in a plain, red-top tube(s) or a serum gel tube(s).
Spin down and send 1.0 mL of serum frozen in plastic vial.

Previous Specimen Requirement
Draw blood in a lavender-top (EDTA) tube(s) from a fasting patient (12-hour fast preferred). Spin down and send 1.0 mL (minimum volume: 0.5 mL) of EDTA plasma frozen in plastic vial.

New Reference Values
19-37 mg/dL
Previous Reference Values
18-40 mg/dL

Lyme Test Changes
Testing for DNA of Borrelia burgdorferi has been converted to a rapid polymerase chain reaction method using LightCycler technology. The method change significantly improves the test by expanding the strains detected and reducing turnaround time for results. Previously detecting only the American Strain, Borrelia burgdorferi, the new method also detects the European strains Borrelia afzelii (central and western Europe, and Russia) and Borrelia garinii (Europe, Russia, and northern Asia). The turnaround time was reduced from 2-3 days to 1 day, and is now performed Monday through Friday. The name of the test has been changed to reflect the new methodology. There are no other changes to the test.

New Test Name
#80574 Lyme Disease by Rapid Polymerase Chain Reaction (PCR)
Previous Test Name
Borrelia burgdorferi Detection by Polymerase Chain Reaction (PCR)

Lipoprotein PLAC Test Specimen Change
Based on suggestions from the manufacturer of the PLAC assay and on the Food and Drug Administration approval of this test, the preferred specimen type was changed from serum to plasma. As a result, the test name was changed to reflect the new preferred specimen type, #81043 Lipoprotein Associated Phospholipase A2 (PLAC Test), Plasma. There were no changes to any other aspect of the test.

New Specimen Requirement
Draw blood in a lavender-top (EDTA) tube(s) from a fasting patient (12-hour fast preferred). Spin down and send 1.0 mL (minimum volume: 0.5 mL) of EDTA plasma frozen in plastic vial.

Previous Specimen Requirement
Draw blood in a plain, red-top tube(s). Spin down and send 1.0 mL of serum frozen in plastic vial.

Carcinoembryonic Antigen Body Fluid Testing Specimen Reminder
MML offers carcinoembryonic antigen (CEA) testing on body fluids as a miscellaneous chemistry test: #8921 Miscellaneous Chemistry Test. Testing of body fluids for CEA may be performed when trying to determine whether a cyst or fluid is associated with a malignancy. Recognizing the wide variety of potential specimen sources, there are no reference values for this test and each specimen must be evaluated on an individual basis. For this reason, whenever possible a serum specimen should be submitted along with the body fluid specimen. Both the serum and the body fluid samples will be tested, providing a better framework for interpretation of the individual patient's results. The serum test is performed free of charge as part of the body fluid test. Please be sure to label each specimen appropriately as either “serum” or “body fluid.” Specific information on the source/location of the body fluid also should be included with the specimen.
Q: Why do you need so much specimen for determination of cryoglobulinemia, #9052 Cryoglobulin, Plasma and Serum?

A: Small (trace) quantities of cryoprecipitate can cause serious clinical symptoms. These can easily be missed if an insufficient volume of specimen is provided. Therefore, obtaining an adequate volume (at least 5 mL of serum and 1 mL of plasma) is a critical factor in the laboratory identification and characterization of cryoglobulins.

Q: How important are the processing instructions for cryoprecipitate specimens?

A: VERY! If the specimen is not maintained at 37°C prior to separation, the cryoprecipitate may precipitate out or be bound up in the clot, causing a false-negative result. Because the time needed to cause precipitation varies from almost immediately to 7 days, the specimen must be maintained at 37°C until after separation of serum/plasma from the red cells.

Q: We ordered cryoglobulins and you also have reported cryofibrinogen. What is cryofibrinogen?

A: Cryofibrinogens are complexes of fibrin and fibrinogen that precipitate out of plasma in the cold. Some of the clinical features that are associated with cryoglobulins also may be associated with cryofibrinogenemia. It is therefore important to perform a cryoprecipitation test on plasma to identify if cryofibrinogen is present.

Q: Why do you require both a serum specimen and a plasma specimen for a cryoglobulin assay?

A: A serum specimen is necessary to detect a cryoglobulin and a plasma specimen is required to detect cryofibrinogen. Both cryoglobulin and cryofibrinogen can be responsible for similar presenting symptoms.

Q: I had a stored specimen in my lab, refrigerated, that I wanted to submit for cryoglobulin analysis. I was told, however, that I had to go back and collect a new specimen. Why is that?

A: Specimens for cryoglobulin analysis must be kept at body temperature (37°C) from the time of the draw until after the specimen has been centrifuged. Therefore, specimens that were not specifically collected under these conditions are not suitable for cryoglobulin analysis. Results on any other specimens will not be meaningful.
2003-2004 Meeting Calendar

Interactive Satellite Programs . . .

Cardiac Markers
December 2, 2003
Presenter: Allan Jaffe, MD
Moderator: Robert Kisabeth, MD

Pharmacogenomics of Antidepressant Medication
January 6, 2004
Presenters: John Black, MD, David Mrazek, MD, Elliott Richelson, MD
Moderator: Robert M. Kisabeth, MD

HIV Update
February 3, 2004
Presenter: Zelalem Temesgen, MD
Moderator: Robert M. Kisabeth, MD

Upcoming Education Conferences . . .

Integration Through Community Laboratory Insourcing: Implementing a Successful Laboratory Outreach Program
January 21-23, 2004
Scottsdale, Arizona

Quality Issues in Phlebotomy
March 18-19, 2004
Mayo Clinic, Siebens Building
Rochester, Minnesota

Practical Spirometry
March 31-April 1, 2004
Mayo Clinic, Siebens Building
Rochester, Minnesota

For a complete listing of all the courses offered throughout the year, contact the Mayo Reference Services Education Office at 1-800-533-1710 or 507-284-8742.

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